EPA United States
Environmental Protection
Agency

October 2004
EPA/600/P-99/002bF

Air Quality Criteria for Particulate Matter

Volume II of II

EPA/600/P-99/002bF
October 2004

Air Quality Criteria for Particulate Matter

Volume II

National Center for Environmental Assessment-RTP Office
Office of Research and Development
U.S. Environmental Protection Agency
Research Triangle Park, NC

DISCLAIMER

This document has been reviewed in accordance with U.S. Environmental Protection Agency policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

National Ambient Air Quality Standards (NAAQS) are promulgated by the United States Environmental Protection Agency (EPA) to meet requirements set forth in Sections 108 and 109 of the U.S. Clean Air Act (CAA). Sections 108 and 109 require the EPA Administrator (1) to list widespread air pollutants that reasonably may be expected to endanger public health or welfare; (2) to issue air quality criteria for them that assess the latest available scientific information on nature and effects of ambient exposure to them; (3) to set "primary" NAAQS to protect human health with adequate margin of safety; (4) to set "secondary" NAAQS to protect against welfare effects (e.g., effects on vegetation, ecosystems, visibility, climate, manmade materials, etc.); and (5) to periodically (every 5 years) review and revise, as appropriate, the criteria and NAAQS for a given listed pollutant or class of pollutants.

The original NAAQS for particulate matter (PM), issued in 1971 as "total suspended particulate" (TSP) standards, were revised in 1987 to focus on protecting against human health effects associated with exposure to ambient PM less than 10 microns ($\leq$10 μm) that are capable of being deposited in thoracic (tracheobronchial and alveolar) portions of the lower respiratory tract. Later periodic reevaluation of newly available scientific information, as presented in the last previous version of this "*Air Quality Criteria for Particulate Matter*" document published in 1996, provided key scientific bases for PM NAAQS decisions published in July 1997. More specifically, the PM_{10} NAAQS set in 1987 (150 $\mu g/m^3$, 24-h; 50 $\mu g/m^3$, annual average) were retained in modified form and new standards (65 $\mu g/m^3$, 24-h; 15 $\mu g/m^3$, annual average) for particles $\leq$ 2.5 μm ($PM_{2.5}$) were promulgated in July 1997.

This final version of revised *Air Quality Criteria for Particulate Matter* assesses new scientific information that has become available (published or accepted for publication) mainly

between early 1996 through April 2002, although a few important new studies published through 2003 are also considered. Several previous successive drafts of this document were released for public comment and review by the Clean Air Scientific Advisory Committee (CASAC), to obtain comments on the organization and structure of the document, the issues addressed, the approaches employed in assessing and interpreting the newly available information on PM exposures and effects, and the key findings and conclusions arrived at by this assessment. Public comments and CASAC review recommendations were taken into account in making revisions to this document for incorporation into this final draft. Evaluations contained in this document will be drawn on to provide inputs to associated PM Staff Paper analyses prepared by EPA's Office of Air Quality Planning and Standards (OAQPS) to pose alternatives for consideration by the EPA Administrator with regard to proposal and, ultimately, promulgation of decisions on potential retention or revision of the current PM NAAQS.

The document describes the nature, sources, distribution, measurement, and concentrations of PM in outdoor (ambient) environments. It also evaluates the latest data on human exposures to ambient PM and consequent health effects in exposed human populations, to support decision making regarding primary, health-related PM NAAQS. The document also evaluates ambient PM environmental effects on vegetation and ecosystems, visibility, and man-made materials, as well as atmospheric PM effects on climate change processes, to support decision making on secondary PM NAAQS.

Preparation of this document was coordinated by EPA's National Center for Environmental Assessment in Research Triangle Park (NCEA-RTP). NCEA-RTP scientific staff, together with experts from other EPA/ORD laboratories and academia, contributed to writing of document chapters. The NCEA of EPA acknowledges the contributions provided by authors, contributors, and reviewers and the diligence of its staff and contractors in the preparation of this document.

Air Quality Criteria for Particulate Matter

VOLUME I

Air Quality Criteria for Particulate Matter

VOLUME II

Table of Contents

Table of Contents
(cont'd)

Table of Contents
(cont'd)

Table of Contents
(cont'd)

Table of Contents
(cont'd)

Table of Contents
(cont'd)

Table of Contents
(cont'd)

Table of Contents
(cont'd)

Table of Contents
(cont'd)

Table of Contents
(cont'd)

Table of Contents
(cont'd)

List of Tables

List of Tables
(cont'd)

List of Tables
(cont'd)

List of Tables
(cont'd)

List of Tables
(cont'd)

List of Tables
(cont'd)

List of Tables
(cont'd)

List of Figures

List of Figures
(cont'd)

List of Figures
(cont'd)

List of Figures
(cont'd)

List of Figures
(cont'd)

List of Figures
(cont'd)

List of Figures
(cont'd)

Authors, Contributors, and Reviewers

CHAPTER 6. DOSIMETRY OF PARTICULATE MATTER

Principal Authors

Dr. Ramesh Sarangapani—ICF Consulting, 3200 NC-54, Suite 101, P.O. Box 14348, Research Triangle Park, NC 27709

Dr. Richard Schlesinger—New York University School of Medicine, Department of Environmental Medicine, 57 Old Forge Road, Tuxedo, NY 10987

Dr. James Brown—Health Scientist, National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. William Wilson—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Contributing Authors

Dr. Lester D. Grant—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Chong Kim—National Health and Environmental Effects Research Laboratory (MD-58B), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. James McGrath—Chapel Hill, NC 27517

Contributors and Reviewers

Dr. William Bennett—University of North Carolina at Chapel Hill, Campus Box 7310, Chapel Hill, NC 37599

Dr. Dan Costa—National Health and Environmental Effects Research Laboratory (B143-02), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Robert Devlin—National Health and Environmental Effects Research Laboratory (MD-58), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Kevin Dreher—National Health and Environmental Effects Research Laboratory (B143-02), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Mark Frampton—University of Rochester, 601 Elmwood Avenue, Box 692, Rochester, NY 14642

Contributors and Reviewers
(cont' d)

Dr. Andrew Ghio—National Health and Environmental Effects Research Laboratory (MD-58D), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. John Godleski—Weston, MA 02493

Dr. Judith Graham—American Chemistry Council, 1300 Wilson Boulevard, Arlington, VA 22207

Dr. Hillel Koren—National Health and Environmental Effects Research Laboratory (MD-58C), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Ted Martonen—National Health and Environmental Effects Research Laboratory (B143-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Kent Pinkerton—University of California, ITEH, One Shields Avenue, Davis, CA 95616

Dr. Peter J.A. Rombout—National Institute of Public Health and Environmental Hygiene, Department of Inhalation Toxicology, P.O. Box 1, NL-3720 BA Bilthoven, The Netherlands

Dr. Jim Samet—National Health and Environmental Effects Research Laboratory (MD-58D), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. John Stanek—National Center for Environmental Assessment (B243-0l), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Ravi Subramaniam—National Center for Environmental Assessment (8623D), U.S. Environmental Protection Agency, Washington, DC 20460

Dr. John J. Vandenberg—National Center for Environmental Assessment (8601 D), U.S. Environmental Protection Agency, 1200 Pennsylvania Avenue, NW, Washington, DC 20460

Dr. William Watkinson—National Health and Environmental Effects Research Laboratory (B143-02), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Authors, Contributors, and Reviewers
(cont' d)

CHAPTER 7. TOXICOLOGY OF PARTICULATE MATTER IN HUMANS AND LABORATORY ANIMALS

Principal Authors

Dr. Lung Chi Chen—New York University School of Medicine, Nelson Institute of Environmental Medicine, 57 Old Forge Road, Tuxedo, NY 10987

Dr. Terry Gordon—New York University Medical Center, Department of Environmental Medicine, 57 Old Forge Road, Tuxedo, NY 10987

Dr. James McGrath—Chapel Hill, NC 27517

Dr. Christine Nadziejko—Department of Environmental Medicine, New York University School of Medicine, Tuxedo, NY

Dr. Lester D. Grant—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Lori White—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. James Brown—Health Scientist, National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. William E. Wilson—National Center for Environmental Assessment (B143-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Contributing Authors

Dr. Dan Costa—National Health and Environmental Effects Research Laboratory (B143-02), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Robert Devlin—National Health and Environmental Effects Research Laboratory (MD-58), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Mr. James Raub—National Center for Environmental Assessment (B143-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Contributors and Reviewers

Dr. Susanne Becker—National Health and Environmental Effects Research Laboratory (MD-58D), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. William Bennett—University of North Carolina at Chapel Hill, Campus Box 7310, Chapel Hill, NC 37599

Dr. Kevin Dreher—National Health and Environmental Effects Research Laboratory (B143-02), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Janice Dye—National Health and Environmental Effects Research Laboratory (B143-02), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Mark Frampton—University of Rochester, 601 Elmwood Avenue, Box 692, Rochester, NY 14642

Dr. Stephen Gavett—National Health and Environmental Effects Research Laboratory (B143-02), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Andrew Ghio—National Health and Environmental Effects Research Laboratory (MD-58D), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Ian Gilmour—National Health and Environmental Effects Research Laboratory (B143-04), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. John Godleski—Weston, MA 02493

Dr. Tony Huang—National Health and Environmental Effects Research Laboratory (MD-58D), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Chong Kim—National Health and Environmental Effects Research Laboratory (MD-58B), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Urmila Kodavanti—National Health and Environmental Effects Research Laboratory (B143-02), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Hillel Koren—National Health and Environmental Effects Research Laboratory (MD-58C), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Michael Madden—National Health and Environmental Effects Research Laboratory (MD-58B), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Contributors and Reviewers
(cont'd)

Dr. Ted Martonen—National Health and Environmental Effects Research Laboratory (B143-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Kent Pinkerton—University of California, ITEH, One Shields Avenue, Davis, CA 95616

Mr. William Russo—National Health and Environmental Effects Research Laboratory (B305-02), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Peter J.A. Rombout—National Institute of Public Health and Environmental Hygiene, Department of Inhalation Toxicology, P.O. Box 1, NL-3720 BA Bilthoven, The Netherlands

Dr. Jim Samet—National Health and Environmental Effects Research Laboratory (MD-58D), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. John J. Vandenberg—National Center for Environmental Assessment (8601D), U.S. Environmental Protection Agency, 1200 Pennsylvania Avenue, NW, Washington, DC 20460

Dr. Bellina Veronesi—National Health and Environmental Effects Research Laboratory (B105-06), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. William Watkinson—National Health and Environmental Effects Research Laboratory (B143-02), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

CHAPTER 8. EPIDEMIOLOGY OF HUMAN HEALTH EFFECTS FROM AMBIENT PARTICULATE MATTER

Principal Authors

Dr. Kazuhiko Ito—New York University Medical Center, Institute of Environmental Medicine, Long Meadow Road, Tuxedo, NY 10987

Dr. George Thurston—New York University Medical Center, Institute of Environmental Medicine, Long Meadow Road, Tuxedo, NY 10987

Authors, Contributors, and Reviewers
(cont'd)

Principal Authors
(cont'd)

Dr. Patrick Kinney—Columbia University, 60 Haven Avenue, B-l, Room 119, New York, NY 10032

Dr. Vic Hasselblad—Durham, NC 27713

Dr. Lester D. Grant—National Center for Environmental Assessment (B243-0l), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Dennis J. Kotchmar—National Center for Environmental Assessment (B243-02), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Contributing Authors

Dr. David Svendsgaard —Statistician, National Caucus and Center on Black Aged, Inc., Senior Environmental Employment Program, Washington, DC 20005

Dr. Robert Chapman—Retired, formerly at the National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Contributors and Reviewers

Dr. Burt Brunekreef—Agricultural University, Environmental and Occupational Health, P.O. Box 238, NL 6700 AE, Wageningen, The Netherlands

Dr. Richard Burnett—Health Canada, 200 Environmental Health Centre, Tunney's Pasture, Ottawa, Canada K1A 0L2

Dr. Raymond Carroll—Texas A & M University, Department of Statistics, College Station, TX 77843-3143

Dr. Wayne E. Casio—University of North Carolina School of Medicine, Chapel Hill, NC 27517

Dr. Steven Colome—Integrated Environmental Services, 5319 University Drive, #430, Irvine, CA 92612

Dr. Ralph Delfino—University of California at Irvine, Epidemiology Division, Department of Medicine, University of California at Irvine, Irvine, CA 92717

Dr. Douglas Dockery—Harvard School of Public Health, 665 Huntington Avenue, I-1414, Boston, MA 02115

Contributors and Reviewers
(cont'd)

Dr. Peter Guttorp—University of Washington, Department of Statistics, Box 354322, Seattle, WA 98195

Dr. Fred Lipfert—Northport, NY 11768

Dr. Lee-Jane Sally Liu—University of Washington, Department of Environmental Health, Box 357234, Seattle, WA 98195

Dr. Suresh Moolgavakar—Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue, N-MP 665, Seattle, WA 98109

Dr. Robert D. Morris—Tufts University, 136 Harrison Avenue, Boston, MA 02111

Dr. Lucas Neas—National Health and Environmental Effects Research Laboratory (MD-58), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. James Robins—Harvard School of Public Health, Department of Epidemiology, Boston, MA 02115

Dr. Mary Ross—Office of Air Quality Planning and Standards (C539-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Lianne Sheppard—University of Washington, Box 357232, Seattle, WA 98195-7232

Dr. Leonard Stefanski—North Carolina State University, Department of Statistics, Box 8203, Raleigh, NC 27695

Dr. John Vandenberg—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. William Wilson—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Authors, Contributors, and Reviewers
(cont' d)

CHAPTER 9. INTEGRATIVE SYNTHESIS: PARTICULATE MATTER ATMOSPHERIC SCIENCE, AIR QUALITY, HUMAN EXPOSURE, DOSIMETRY, AND HEALTH RISKS

Principal Authors

Dr. William E. Wilson—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Lester D. Grant—National Center for Environmental Assessment (B243-0l), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Contributing Authors

Dr. James Brown—Health Scientist, National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Ms. Beverly Comfort—National Center for Environmental Assessment (B243-0l), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. J.H.B. Garner—National Center for Environmental Assessment (B243-0l), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Brooke Hemming—National Center for Environmental Assessment (B243-0l), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Dennis J. Kotchmar—National Center for Environmental Assessment (B243-0l), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Joseph P. Pinto—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Lori White—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Contributors and Reviewers

Dr. Dan Costa—National Health and Environmental Effects Research Laboratory (B305-02), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Robert Devlin—National Health and Environmental Effects Research Laboratory (MD-58), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Contributors and Reviewers
(cont'd)

Dr. Mary Ross—Office of Air Quality Planning and Standards (C539-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Mr. William Russo—National Health and Environmental Effects Research Laboratory (B305-02), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. John J. Vandenberg—National Center for Environmental Assessment (8601 D), U.S. Environmental Protection Agency, 1200 Pennsylvania Avenue, NW, Washington, DC 20460

U.S. ENVIRONMENTAL PROTECTION AGENCY
PROJECT TEAM FOR DEVELOPMENT OF AIR QUALITY CRITERIA FOR PARTICULATE MATTER

Executive Direction

Dr. Lester D. Grant—Director, National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Scientific Staff

Dr. Robert W. Elias—PM Team Leader, Health Scientist, National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. William E. Wilson—Air Quality Coordinator, Physical Scientist, National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. James Brown—Health Scientist, National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Ms. Beverly Comfort—Health Scientist, National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. J.H.B. Garner—Ecological Scientist, National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Brooke L. Hemming—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Dennis J. Kotchmar—Medical Officer, National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Joseph P. Pinto—Physical Scientist, National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Lori White—National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

U.S. ENVIRONMENTAL PROTECTION AGENCY
PROJECT TEAM FOR DEVELOPMENT OF AIR QUALITY CRITERIA FOR PARTICULATE MATTER
(cont'd)

Technical Support Staff

Ms. Nancy Broom—Information Technology Manager, National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Mr. Douglas B. Fennell—Technical Information Specialist, National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Ms. Emily R. Lee—Management Analyst, National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Ms. Diane H. Ray—Program Specialist, National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Ms. Donna Wicker—Administrative Officer, National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Mr. Richard Wilson—Clerk, National Center for Environmental Assessment (B243-01), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Document Production Staff

Ms. Carolyn T. Perry—Manager/Word Processor, Computer Sciences Corporation, 2803 Slater Road, Suite 220, Morrisville, NC 27560

Dr. Barbara Liljequist—Technical Editor, Computer Sciences Corporation, 2803 Slater Road, Suite 220, Morrisville, NC 27560

Dr. Carol A. Seagle—Technical Editor, Computer Sciences Corporation, 2803 Slater Road, Suite 220, Morrisville, NC 27560

Ms. Jessica Long—Graphic Artist, Computer Sciences Corporation, 2803 Slater Road, Suite 220, Morrisville, NC 27560

Mr. Matthew Kirk—Graphic Artist, Computer Sciences Corporation, 2803 Slater Road, Suite 220, Morrisville, NC 27560

U.S. ENVIRONMENTAL PROTECTION AGENCY
PROJECT TEAM FOR DEVELOPMENT OF AIR QUALITY CRITERIA FOR PARTICULATE MATTER
(cont'd)

Document Production Staff
(cont'd)

Mr. John A. Bennett—Technical Information Specialist, Library Associates of Maryland, 11820 Parklawn Drive, Suite 400, Rockville, MD 20852

Ms. Sandra L. Hughey—Technical Information Specialist, Library Associates of Maryland, 11820 Parklawn Drive, Suite 400, Rockville, MD 20852

Ms. Rebecca Caffey—Records Management Technician, Reference Retrieval and Database Entry Clerk, InfoPro, Inc., 8200 Greensboro Drive, Suite 1450, McLean, VA 22102

U.S. ENVIRONMENTAL PROTECTION AGENCY
SCIENCE ADVISORY BOARD (SAB) STAFF OFFICE
CLEAN AIR SCIENTIFIC ADVISORY COMMITTEE (CASAC)
PARTICULATE MATTER REVIEW PANEL*

CASAC Chair

Dr. Philip Hopke—Bayard D. Clarkson Distinguished Professor, Department of Chemical Engineering, Clarkson University, Box 5708, Potsdam, NY 13699-5708

CASAC Members

Dr. Ellis Cowling—University Distinguished Professor At-Large, North Carolina State University, Colleges of Natural Resources and Agriculture and Life Sciences, North Carolina State University, 1509 Varsity Drive, Raleigh, NC 27695-7632

Dr. James D. Crapo—Chairman, Department of Medicine, National Jewish Medical and Research Center, 1400 Jackson Street, Denver, CO, 80206, and Chief Executive Officer (CEO) of Aeolus Pharmaceuticals, Inc.

Dr. Frederick J. Miller—Vice President for Research, CIIT Centers for Health Research, 6 Davis Drive, P.O. Box 12137, Research Triangle Park, NC 27709

Mr. Richard L. Poirot—Environmental Analyst, Air Pollution Control Division, Department of Environmental Conservation, Vermont Agency of Natural Resources, Bldg. 3 South, 103 South Main Street, Waterbury, VT 05671-0402

Dr. Frank Speizer—Edward Kass Professor of Medicine, Channing Laboratory, Harvard Medical School, 181 Longwood Avenue, Boston, MA 02115-5804

Dr. Barbara Zielinska—Research Professor , Division of Atmospheric Science, Desert Research Institute, 2215 Raggio Parkway, Reno, NV 89512-1095

---

* Members of this CASAC Panel consist of:

a. CASAC Members: Experts appointed to the statutory Clean Air Scientific Advisory Committee by the EPA Administrator; and

b. CASAC Consultants: Experts appointed by the SAB Staff Director to serve on one of the CASAC's National Ambient Air Quality Standards (NAAQS) Panels for a particular criteria air pollutant.

U.S. ENVIRONMENTAL PROTECTION AGENCY
SCIENCE ADVISORY BOARD (SAB) STAFF OFFICE
CLEAN AIR SCIENTIFIC ADVISORY COMMITTEE (CASAC)
PARTICULATE MATTER REVIEW PANEL*
(cont'd)

CASAC Consultants

Dr. Jane Q. Koenig—Professor, Department of Environmental Health, School of Public Health and Community Medicine, University of Washington, Box 357234, Seattle, WA 98195-7234

Dr. Petros Koutrakis—Professor of Environmental Science, Environmental Health , School of Public Health, Harvard University, HSPH, 401 Park Dr., Room 410 West, Boston, MA 02215

Dr. Allan Legge—President, Biosphere Solutions, 1601 11th Avenue NW, Calgary, Alberta, CANADA T2N 1H1

Dr. Paul J. Lioy—Associate Director and Professor, Environmental and Occupational Health Sciences Institute, UMDNJ - Robert Wood Johnson Medical School, 170 Frelinghuysen Road, Rm 301, Piscataway, NJ 08854

Dr. Morton Lippmann—Professor, Nelson Institute of Environmental Medicine, New York University School of Medicine, 57 Old Forge Road, Tuxedo, NY 10987

Dr. Joe Mauderly—Vice President, Senior Scientist, and Director, National Environmental Respiratory Center, Lovelace Respiratory Research Institute, 2425 Ridgecrest Drive SE, Albuquerque, NM, 87108

Dr. Roger O. McClellan—Consultant, 1370 Quaking Aspen Pine, Albuquerque, NM, 87111

Dr. Gunter Oberdorster—Professor of Toxicology, Department of Environmental Medicine, School of Medicine and Dentistry, University of Rochester, 575 Elmwood Avenue, Box 850, Rochester, NY 14642

Dr. Robert D. Rowe—President, Stratus Consulting, Inc., , PO Box 4059, Boulder, CO 80306-4059

Dr. Jonathan M. Samet—Professor and Chair, Department of Epidemiology, Bloomberg School of Public Health, Johns Hopkins University, 615 N. Wolfe Street, Suite W6041, Baltimore, MD 21205-2179

Dr. Sverre Vedal—Professor of Medicine, School of Public Health and Community Medicine Department of Environmental and Occupational Health Sciences, University of Washington, 4225 Roosevelt Way NE, Suite 100, Seattle, WA 98105-6099

U.S. ENVIRONMENTAL PROTECTION AGENCY
SCIENCE ADVISORY BOARD (SAB) STAFF OFFICE
CLEAN AIR SCIENTIFIC ADVISORY COMMITTEE (CASAC)
PARTICULATE MATTER REVIEW PANEL*
(cont'd)

CASAC Consultants
(cont'd)

Mr. Ronald White—Research Scientist, Epidemiology, Bloomberg School of Public Health, Room W6035, The Johns Hopkins University, 615 N. Wolfe St., Rm W6035, Baltimore, MD 21205

Dr. Warren H. White—Visiting Professor, Crocker Nuclear Laboratory, University of California-Davis, , Davis, CA 95616-8569

Dr. George T. Wolff—Principal Scientist, General Motors Corporation, 300 Renaissance Center (MC482-C27-B76), Detroit, MI 48265-3000

EPA Science Advisory Board Staff

Dr. Vanessa Vu—SAB Staff Office Director, EPA Science Advisory Board Staff Office (Mail Code 1400F), 1200 Pennsylvania Avenue, N.W., Washington DC, 20460

Mr. Fred Butterfield—CASAC Designated Federal Officer, EPA Science Advisory Board Staff Office (Mail Code 1400F), 1200 Pennsylvania Avenue, N.W., Washington, DC 20460

Abbreviations and Acronyms

A	alveolar
AC	air conditioning
ACE	angiotensin-converting enzyme
ACS	American Cancer Society
ADP	platelet aggregation
ADS	anatomic dead space
AED	aerodynamic equivalent diameter
AHSMOG	Adventist Health Study on Smog
AI	alveolar-interstitial region
AIC	Akaike Information Criterion
AM	alveolar macrophage
AOR	adjusted odds ratio
APHEA	Air Pollution and Health: a European Approach
AQCD	Air Quality Criteria Document
ASOS	Automated Surface Observing System
BAD	brachial artery diameter
BAL	bronchoalveolar lavage
BALF	brochoalveglar lavage fluid
BaP	benzo[a]pyrene
BAUS	brachial artery ultrasonography
BB	bronchial region
bb	bronchiolar region
BIC	Bayes Information Criterion
BMI	body mass index
BN	Brown Norway
BNF	biological nitrogen fixation

BP	blood pressure
BrdU	5'-bromo-2'deoxyuridine
BS	black smoke
BW	bronchial wash
CAPs	concentrated ambient particles
CARB	California Air Resources Board
CAT	computer-aided tomography
CB	carbon black
CB	chronic bronchitis
CC	conventional combustion
CESAR	Central European Air Quality and Respiratory Health
CF	cystic fibrosis
CFA	coal fly ash
CFC	chlorofluorocarbon
CFD	computational fluid dynamics
CHF	congestive heart failure
CHO	Chinese hamster ovary
CI	confidence interval
CL	chemiluminescence
CMD	count mean diameter
CMP	copper smelter dust
COD	coefficient of determination
CoH, COH	coefficient of haze
COPD	chronic obstructive pulmonary disease
CP	coarse particle
CPC	condensation particle counter
CPZ	capsazepine
CRC	contributing respiratory causes

CrD	cerebrovascular disease
CRV	cerebrovascular disease
CVD	cardiovascular disease
CVDRESP	cardiorespiratory
CVM	cardiovascular mortality
DBP	diastolic blood pressure
DCFH	dichlorofluorescin
DCM	dichloromethane
DE	diesel exhaust
DE	deposition efficiency
DEF	deferoxamine
DEP	diesel exhaust particles
df	degrees of freedom
DF	deposition fraction
DFPSS	dual fine particle sequential sampler
DHR	dihydrorhodamine-123
DMTU	dimethylthiourea
DOFA	domestic oil fly ash
DPL	dipalmitoyl lecithin
DPM	diesel particulate matter; diesel soot
DRG	dorsal root ganglia
DTPA	techetium-diethylenetriamine-pentaacetic acid
DYS	dysrhythmias
EC	elemental carbon
ECG	electrocardiogram; electrocardiographic
ED	emergency department
EGF	epidermal growth factor
ELF	epithelial lining fluid

EOC	equivalent organic carbon
EqER	equivalent exposure ratio
ER	excess risk
ERK	extracellular receptor kinase; extracellular signal-regulated kinase
ESR	electron spin resonance
ET	endothelin
ET	extrathoracic
EU	endotoxin units
FA	filtered air
FBC	fluidized-bed combustion
FEF	forced expiratory flow
FEV_1	forced expiratory volume in 1 second
FMD	flow-mediated dilation
FP	fine particle
FRC	functional reserve capacity
FVC	forced vital capacity
GAM	Generalized Additive Model
GEE	generalized estimating equations
GJIC	gap-junctional intercellular communications
GLM	Generalized Linear Model
GM	gestation month
GMCSF	granulocyte macrophage colony stimulating factor
GMPD	geometric mean particle diameter
GP	general practice
GSF	Gessellschaft fur Strahlenforschung
GSH	glutathione
HA	hospital admission
HC	hydrocarbon

HD	heavy duty
HDM	house dust mite
HEI	Health Effects Institute
HF	high frequency
HPLC	high-pressure liquid chromatography
HR	heart rate
HRV	heart rate variability
HULIS	humic-like substances
IκBα	inhibitory kappa B alpha
ICAM-1	intercellular adhesion molecule-1
ICD9	International Classification of Disease
ICRP	International Commission on Radiological Protection
IDF	intrathoracic deposition fraction
IgE	immunoglobin E
IgG	immunoglobin G
IHD	ischemic heart disease
IL	interleukin
IMF	induced mutant fraction
IMPROVE	Interagency Monitoring of Protected Visual Environments
iNOS	inducible nitric oxide synthase
IP	intraperitoneal
IP	inhalable particle
IPM	inhalable particle mass
IPN	inhalable particle network
IQR	interquartile range
IT	intratracheal
IUGR	intrauterine growth retardation
IV	intravenous

JNK	c-jun N-terminal kinase
KS	soil-corrected potassium
LBW	low birth weight
LCL	lower 95th% confidence limit
LDH	lactate dehydrogenase
LF	low frequency
LFA-1	leukocyte function-associated antigen-1
LN	lymph nodes
LOEL	lowest observed effect level
LOESS	local regression smoothers
LPS	lipopolysaccharide
LRD	lower respiratory disease
LRI	lower respiratory illness
LUDEP	Lung Dose Evaluation Program
MAPK	mitogen-activated protein kinase
MAS	Mobile Aerosol Spectrometer
MC	mass concentration
MCh	methylcholine
MCT	monocrotaline
MEK	mitogen-activated protein kinase/ERK kinase
MI	myocardial infarction
MIP	macrophage inflammatory protein
MMAD	mean median aerodynamic diameter
MMD	mass median diameter
MMPs	matrix metalloproteinases
MO	monocyte
MONICA	monitoring of trends and determinants in cardiovascular disease
MPL	multipath lung

MPO	myeloperoxidase
MPPD	multiple path particle dosimetry
MSA	Metropolitan Statistical Area
MSH	Mount St. Helens
MVRD	motor vehicle and resuspended dust
n, N	number
NAAQS	National Ambient Air Quality Standards
NAC	N-acetylcysteine (antioxidant)
NAL	nasal lavage fluid
NC	number concentration
NCEA-RTP	National Center for Environmental Assessment-Research Triangle Park
NCRP	National Council on Radiation Protection and Measurement
NF	nuclear factor
NF-κB	nuclear factor kappa B
NHANES	National Health and Nutrition Examination Surveys
NHBE	normal human bronchial epithelial
NIST	National Institutes of Standards Technology
NLCS	Netherlands Cohort Study on Diet and Cancer
NMD	nitroglycerine-mediated dilation
NMMAPS	National Morbidity, Mortality, and Air Pollution Study
NMRI	Naval Medical Research Institute
N-N	normal-to-normal
NO_X	nitrogen oxide
NOEL	no observed effect level
NOPL	nasa-oro-pharyngo-laryngeal
NS	natural splines
n.s.	statistically nonsignificant
nspline	natural splines

OAA	Ottawa ambient air
OAQPS	Office of Air Quality Planning and Standards
OC	organic carbon
OR	odds ratio
OLS	ordinary least squares
OVA	ovalbumin
P90	90th percentile value
P	pulmonary
PAC	polyaromatic compound
PAH	polycyclic aromatic hydrocarbon
PB	polymyxin-B
PBW	particle-bound water
PDGF	platelet-derived growth factor
PDL	polynomial distributed lag
PEF	peak expiratory flow
PEFR	peak expiratory flow rate
PFT	pulmonary function tests
PHS-2	prostaglandin H synthase-2
PM	particulate matter
PMN	polymorphonuclear leukocyte
PN	penalized splines
p^o	equilibrium vapor pressure
poly I:C	polyinosinic-polycytidilic acid
post-MI	post-myocardial infarction
PTEAM	Particle Total Exposure Assessment Methodology
PTFE	polytetrafluoroethylene (Teflon)
PVCs	premature ventricular complexes
Q	respiratory flow rate

QHIP	Quebec Health Insurance Plan
RBCs	red blood cells
rENP	recombinant endotoxin-neutralizing protein
r-MSSD	root mean squared differences between adjacent normal-to-normal heartbeat intervals
RCAL	Regression Calibration
RIVM	Dutch National Institute of Public Health and the Environment
RME	rapeseed oil methyl ester
ROFA	residual oil fly ash
ROI	reactive oxygen intermediates
ROS	reactive oxygen species
RR	relative risk
RTD	road tunnel dust
RTE	rat tracheal epithelial
RWC	residential wood combustion
SAD	small airway disease
SBP	systolic blood pressure
SCD	sudden cardiac death
SCE	sister chromatid exchanges
SD	Sprague-Dawley
SDANN	standard deviation of the average of normal-to-normal heartbeat intervals
SDNN	standard deviation of normal-to-normal heartbeat intervals
SH	spontaneously hypertensive
SIMEX	Simulation Extrapolation
SL	stochastic lung
SOD	superoxide dismutase
SP-A	surfactant protein A
SPM	synthetic polymer microspheres
SpO_2	oxygen saturation

SoCARB	South Coast Air Basin
SSC	spatial synoptic category
SVOC	semivolatile organic compound
TC	total carbon
TC	tungstan carbide
$T_{[CO]}$	core temperature
TB	tracheabronchial
TDF	total deposition fraction
TEOM	tapered element oscillating microbalance
TIMP	tissue inhibitor of metalloproteinase
TK	thymidine kinase
TLC	total lung capacity
TLR	Toll-like receptors
TNF	tumor necrosis factor
TPA	tissue plasminogen activator
TSI	Temporal Synoptic Index
TSP	total suspended particulate
TV	tidal volume
UAP	urban air particles
UCL	upper 95th% confidence limit
UDS	unscheduled DNA synthesis
ufCB, UCB	ultrafine carbon black
UFP	ultrafine fluorospheres
URT	upper respiratory tract
UV-B	ultraviolet-B radiation
UVD	Utah Valley dust
VA	Veterans' Administration
VAPS	Versatile Air Pollution Samplers

VCAM-1	vascular cell adhesion molecule-1
VLBW	very low body weight
V_t	tidal volume
WBC	white blood cell
WINS	Well Impactor Ninety-Six
WIS	Wistar
WKY	Wistar-Kyoto
XRF	X-ray fluororescence

6. DOSIMETRY OF PARTICULATE MATTER

6.1 INTRODUCTION

The proximal cause of a biological response to particulate matter (PM) is due to the dose deposited at the target site rather than the external exposure. Characterization of the exposure-dose-response continuum for PM requires an understanding of the mechanistic determinants of inhaled particle dose. Furthermore, dosimetric information is critical for extrapolating human health effects based on animal toxicological studies and for comparing results from controlled clinical studies involving healthy human subjects or those with preexisting disease.

Dose to a target tissue depends on the initial deposition and subsequent retention of particles within the respiratory tract. Once particles have deposited onto the surfaces of the respiratory tract, they are subsequently subjected to either absorptive or nonabsorptive particulate removal processes, which may result in their removal or translocation from airway surfaces, as well as their removal from the respiratory tract itself. Clearance of deposited particles depends upon the initial site of deposition and upon the physicochemical properties of the particles, both of which affect specific translocation pathways. Retained particle burdens are determined by the dynamic relationship between deposition and clearance rates.

This chapter discusses particle dosimetry, the study of the deposition, translocation, clearance, and retention of particles within the respiratory tract and extrapulmonary tissues. It summarizes basic concepts as presented in Chapter 10 of the 1996 EPA document, Air Quality Criteria for Particulate Matter or (1996 PM AQCD) (U.S. Environmental Protection Agency, 1996a); and it updates the state of the science based upon new literature appearing since publication of the 1996 PM AQCD. Although our understanding of the basic mechanisms governing deposition and clearance of inhaled particles has not changed, there has been significant additional information on the role of certain biological determinants of the deposition/clearance processes, such as gender, age and lung disease. Additionally, the understanding of regional dosimetry within the respiratory tract and the particle size range over which this has been evaluated has been expanded.

The dose of inhaled particles to the respiratory tract is governed by a number of factors. These include exposure concentration, exposure duration, respiratory tract anatomy, ventilatory

parameters, and particle properties (e.g., particle size, hygroscopicity, and solubility in airway fluids and cellular components). The basic characteristics of particles as they relate to deposition and retention, as well as anatomical and physiological factors influencing particle deposition and retention, were discussed in depth in the 1996 PM AQCD. Thus, in this chapter, only an overview of basic information related to one critical factor in deposition, namely particle size, is provided (Section 6.1.1) to allow the reader to understand the different terms used in the remainder of this and subsequent chapters dealing with health effects. Section 6.1.2 provides a basic overview of respiratory tract structure as it relates to particle deposition and clearance. The ensuing major sections of this chapter provide updated information on particle deposition, clearance, and retention in the respiratory tract of humans, as well as laboratory animals, that are useful in evaluating of PM health effects. Issues related to the phenomenon of particle overload as it may apply to human exposure and the use of instillation of particle suspensions as an exposure technique to evaluate PM health effects also are discussed. The final sections of the chapter deal with mathematical models of particle deposition and clearance in the respiratory tract.

It must be emphasized that any dissection into discrete topics or factors that control dose from inhaled particles tends to mask the dynamic and interdependent nature of the intact respiratory system. For example, although deposition is discussed separately from clearance mechanisms, retention (i.e., the actual amount of particles found in component regions of the respiratory tract at any point in time) is, as noted previously, determined by the relative rates of both deposition and clearance. Thus, an overall dosimetric assessment requires integration of these various components of the overall process. In summarizing the literature on particle dosimetry, when applicable, changes from control are described if they were statistically significant at a p-value of less than 0.05 (i.e., $p < 0.05$). When trends are described, actual p values given in the published reports will be provided if possible.

6.1.1 Size Characterization of Inhaled Particles

Particle size is an important determinant of the fraction of inhaled particles deposited in the various regions of the respiratory tract. Particle attributes, as well as some general definitions important in understanding particle fate within the respiratory tract, are described in Chapter 2.

Most aerosols present in natural and work environments are polydisperse. This means that the constituent particles within an aerosol have a range of sizes and are more appropriately described in terms of size distribution parameters. The lognormal distribution (i.e., the situation in which the logarithms of particle diameter [d_p] are distributed normally) can be used for describing size distributions of most aerosols. The geometric mean is the median of the distribution, and the metric of variability around this central tendency is the geometric standard deviation (σ_g). The σ_g, a dimensionless term, is the ratio of the 84th (or 16th) percentile particle size to the 50th percentile size. Thus, the only two parameters needed to describe a lognormal distribution of particle sizes for a specific aerosol are the median diameter and the geometric standard deviation. However, the actual size distribution may be obtained in various ways. When a distribution is described by counting particles, the median is called the count median diameter (CMD). On the other hand, the median of a distribution based on particle mass in an aerosol is the mass median diameter (MMD). When using aerodynamic diameters, a term that is encountered frequently is mass median aerodynamic diameter (MMAD), which is the median of the distribution of mass with respect to aerodynamic equivalent diameter (AED). Most of the present discussion will focus on MMAD because it is the most commonly used measure of aerosol distribution. However, alternative descriptions should be used for particles with actual physical sizes below ≈0.5 μm because, for these, aerodynamic properties become less important. One such metric is thermodynamic-equivalent size, i.e., the diameter of a spherical particle that has the same diffusion coefficient in air as the particle of interest.

6.1.2 Structure of the Respiratory Tract

A detailed discussion of respiratory tract structure was provided in the 1996 PM AQCD (U.S. Environmental Protection Agency, 1996a), and only a brief synopsis is presented here. For dosimetry purposes, the respiratory tract can be divided into three regions (Figure 6-1): (1) extrathoracic (ET), (2) tracheobronchial (TB), and (3) alveolar (A). The ET region consists of airways within the head (i.e., nasal and oral passages) through the larynx and represents the areas through which inhaled air first passes. In humans, inhalation can occur through the nose or mouth (or both, known as oronasal breathing). However, most laboratory animals commonly used in respiratory toxicological studies are obligate nose breathers.

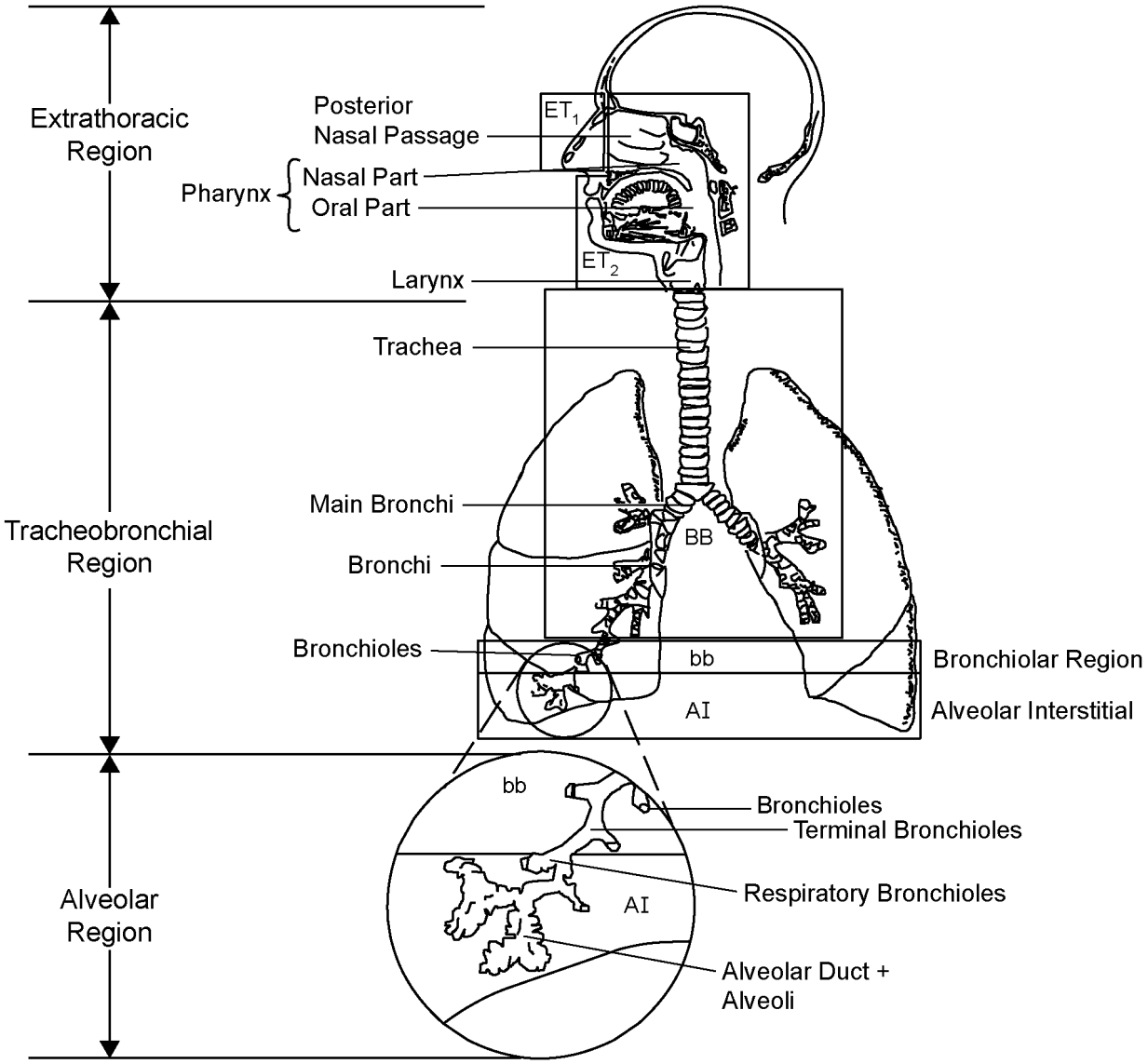

Figure 6-1. Diagrammatic representation of respiratory tract regions in humans.

Source: Based on International Commission on Radiological Protection (1994) and U.S. Environmental Protection Agency (1996a).

From the ET region, inspired air enters the TB region at the trachea. From the level of the trachea, the conducting airways then undergo dichotomous branching for a number of generations. The terminal bronchiole is the most peripheral of the distal conducting airways and, in humans, leads to the gas-exchange region, which consists of respiratory bronchioles, alveolar

ducts, alveolar sacs, and alveoli (all of which comprise the A region). All of the conducting airways, except the trachea and portions of the mainstem bronchi, are surrounded by parenchymal tissue composed primarily of the alveolated structures of the A region and associated blood and lymphatic vessels. It should be noted that the respiratory tract regions are comprised of various cell types and that there are distinct differences in the distribution of cells lining the airway surfaces in the ET, TB, and A regions. Although a discussion of cellular structure of the respiratory tract is beyond the scope of this section, details may be found in a number of sources (e.g., Crystal et al., 1997).

6.2 PARTICLE DEPOSITION

This section discusses the deposition of particles in the respiratory tract. It begins with an overview of the basic physical mechanisms that govern deposition. This is followed by an update on both total respiratory tract and regional deposition patterns in humans. Some critical biological factors that may modulate deposition are then presented. The section ends with a discussion of issues related to interspecies patterns of particle deposition.

6.2.1 Mechanisms of Deposition

Particles may deposit within the respiratory tract by five mechanisms: (1) inertial impaction, (2) sedimentation, (3) diffusion, (4) interception, and (5) electrostatic precipitation.

Sudden changes in airstream direction and velocity may cause some particles to fail to follow the streamlines of airflow. As a consequence, the particles contact, or impact, airway surfaces. The ET and upper TB airways are characterized by high air velocities and sharp directional changes and, thus, dominate as sites of inertial impaction. Impaction is a significant deposition mechanism for particles larger than 2 μm AED.

All aerosol particles are continuously influenced by gravity, but particles with an AED > 1 μm are affected to the greatest extent. A particle will acquire a terminal settling velocity when a balance is achieved between the acceleration of gravity acting on the particle and the viscous resistance of the air, and this settling out of the airstream may bring it into contact with airway surfaces. Both sedimentation and inertial impaction can influence the deposition of particles within the same size range. These deposition processes act together in the

ET and TB regions: inertial impaction dominates in the upper airways, and gravitational settling becomes increasingly dominant in the smaller conducting airways.

Particles having actual physical diameters < 1 μm are increasingly subjected to diffusive deposition because of random bombardment by air molecules, resulting in contact with airway surfaces. The root mean square displacement that a particle experiences in a unit of time along a given cartesian coordinate is a measure of its diffusivity. The density of a particle is unimportant in determining its diffusivity. Thus, instead of having an aerodynamic equivalent size, diffusive particles of different shapes can be related to the diffusivity of a thermodynamic equivalent size based on spherical particles.

The particle size range around 0.2 to 1.0 μm is frequently described as consisting of particles that are small enough to be minimally influenced by impaction or sedimentation and large enough to be minimally influenced by diffusion. Such particles are the most persistent in inhaled air and undergo the lowest degree of deposition in the respiratory tract.

Interception is deposition by physical contact with airway surfaces. The interception potential of any particle depends on its physical size. Fibers are of chief concern in relation to the interception process. Their aerodynamic size is determined predominantly by their diameter, but their length is the factor that influences probability of interception deposition.

Electrostatic precipitation is deposition related to particle charge. The minimum charge an aerosol particle can have is zero. This condition rarely is achieved because of the random charging of aerosol particles by ions in the air. Particles acquire charges by collisions with air ions because of their random thermal motion. Many laboratory-generated aerosols are highly charged, but methods such as passage of the particle-containing airstream through a Kr-85 charge neutralizer can neutralize charge. In addition, these charged aerosols will generally lose their initial charge as they attract oppositely charged ions, and an equilibrium state is eventually achieved. This Boltzmann equilibrium represents the charge distribution of an aerosol in charge equilibrium with bipolar ions. The minimum amount of charge is very small: there is a statistical probability that some particles within the aerosol will have no charge and that others will have one or more positive and negative charges.

The electrical charge on some particles will result in an enhanced deposition over what would be expected from size alone. This increase in deposition is thought to result from image charges induced on the surface of the airway by charged particles and possibly space-charge

effects whereby repulsion of particles with like charges results in increased migration toward the airway wall. The effect of charge on deposition is inversely proportional to particle size and airflow rate. This type of deposition is often small compared to the effects of turbulence and other deposition mechanisms, and it generally has been considered to be a minor contributor to overall particle deposition. However, a study by Cohen et al. (1998), employing hollow airway casts of the human tracheobronchial tree to assess deposition of ultrafine (0.02 μm) and fine (0.125 μm) particles, found the deposition of singly charged particles to be 5 to 6 times that of particles having no charge and 2 to 3 times that of particles at Boltzmann equilibrium. This suggests that electrostatic precipitation may, in certain situations such as workplace exposures or indoor tobacco smoke, be a significant deposition mechanism for ultrafine and some fine particles within the TB region. However, the influence of charge on the deposition of urban aerosols should be minimal.

6.2.2 Deposition Patterns in the Human Respiratory Tract

Knowledge of sites where particles of different sizes deposit in the respiratory tract and the amount of deposition therein is necessary for understanding and interpreting the health effects associated with exposure to particles. Particles deposited in the various respiratory tract regions are subjected to large differences in clearance mechanisms and pathways and, consequently, retention times. This section summarizes concepts of particle deposition in humans and laboratory animals as reported in the 1996 PM AQCD (U.S. Environmental Protection Agency, 1996a) and provides additional information based on studies published since that earlier document.

Ambient air often contains particles too massive to be inhaled. The term "inhalability" is used to denote the overall spectrum of particle sizes that are potentially capable of entering the respiratory tract. Inhalability is defined as the ratio of the number concentration of particles of a certain aerodynamic diameter that are inspired through the nose or mouth to the number concentration of the same diameter particle present in ambient air (International Commission on Radiological Protection, 1994). In general, for humans, unit density particles > 100 μm diameter have a low probability of entering the mouth or nose in still air, but there is no sharp cutoff to zero probability. Additionally, there is no lower limit to inhalability, so long as the particle

exceeds a critical size where the aggregation of atomic or molecular units is stable enough to endow it with "particulate" properties in contrast to those of free ions or gas molecules.

6.2.2.1 Total Respiratory Tract Deposition

Total human respiratory tract deposition, as a function of particle size, is depicted in Figure 6-2. These data were obtained by various investigators using different sizes of spherical test particles in healthy male adults under different ventilation conditions; the large standard deviations reflect inter-individual variability in airway dimensions and airway branching and breathing-pattern related variability of deposition efficiencies. Deposition in the ET region with nose breathing is generally higher than that with mouth breathing because the superior filtration capabilities of the nasal passages results in somewhat higher total deposition with nasal breathing for particles > 1 μm AED. For particles greater than 1 μm AED, deposition is governed by impaction and sedimentation, and it increases with increasing AED. For AED > 10 μm, almost all inhaled particles are deposited. As the particle size decreases from ≈0.5 μm, diffusional deposition becomes dominant and total deposition depends more on the actual physical diameter of the particle. Decreasing particle diameter below 0.1 μm leads to an increase in total deposition. Total deposition shows a minimum for particle diameters in the range of 0.2 to 1.0 μm where, as noted above, neither sedimentation, impaction, or diffusion deposition are very effective. Deposition never reaches zero because of mixing between particle-rich tidal air and nearly particle-free residual lung air. The particles in the tidal air remaining in the deep lung are gradually deposited.

Besides particle size, breathing pattern (tidal volume, breathing frequency, route of breathing) is the most important factor affecting lung deposition. Kim (2000) reported total lung deposition values in healthy adults for a wide range of breathing patterns: tidal volumes (375 to 1500 mL), flow rates (150 to 1000 mL/s), and respiratory times (2 to 12 s). Total lung deposition increased with increasing tidal volume at a given flow rate and with increasing flow rate at a given respiratory time. Various deposition values were correlated with a single composite parameter consisting of particle size, flow rate, and tidal volume.

Ultrafine particles (d_p < 0.1 μm) are being specifically evaluated for determination of their potential toxicity. There is, however, little information on total respiratory tract deposition of such particles. Frampton et al. (2000) exposed healthy adult human males and females,

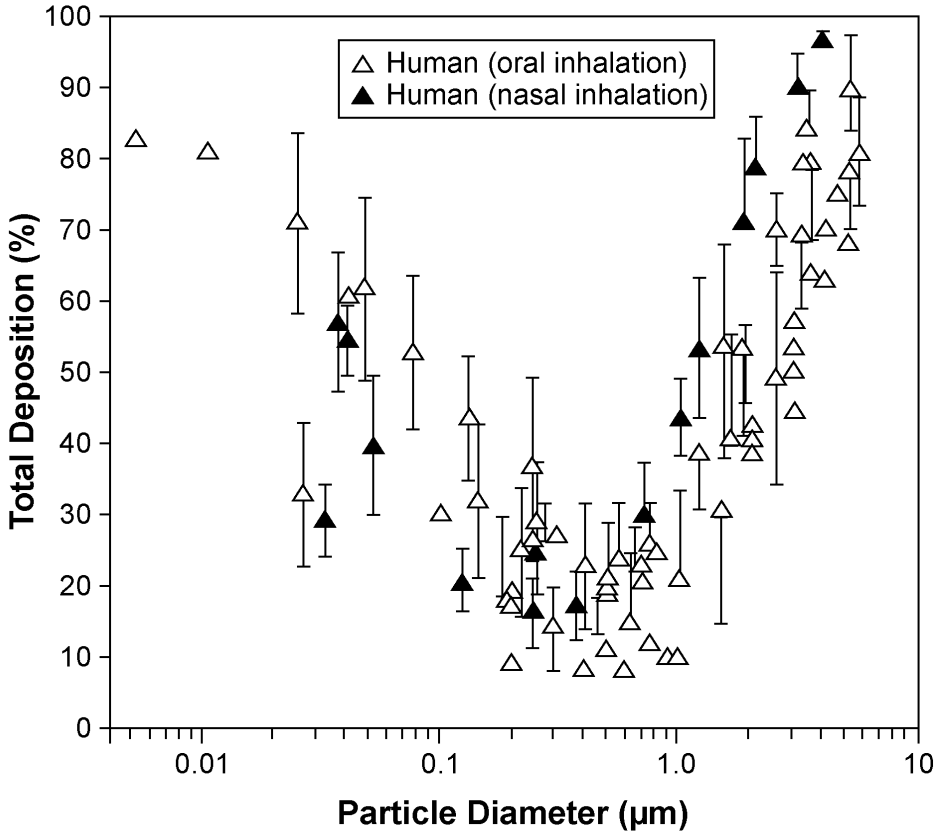

Figure 6-2. Total respiratory tract deposition (as percentage deposition of amount inhaled) in humans as a function of particle size. All values are means with standard deviations when available. Particle diameters are aerodynamic (MMAD) for those ≥ 0.5 µm and geometric (or diffusion equivalent) for those < 0.5 µm.

Source: Modified from Schlesinger (1989).

via mouthpiece, to 0.0267 µm diameter carbon particles (at 10 µg/m^3) for 2 h at rest. The inspired and expired particle number concentration and size distributions were evaluated. Total respiratory tract deposition fraction was determined for six particle size fractions ranging from 0.0075 to 0.1334 µm. They found an overall total lung deposition fraction of 0.66 (by particle number) or 0.58 (by particle mass), indicating that exhaled mean particle diameter was slightly larger than inhaled diameter. There was no gender difference. The deposition fraction decreased with increasing particle size within the ultrafine range, from 0.76 at the smallest size to 0.47 at the largest.

Jaques and Kim (2000) measured total deposition fraction (TDF) of ultrafine particles (number median diameter CMD = 0.04 to 0.1 μm and σ_g = 1.3) in 22 healthy adults (men and women in equal number) under a variety of breathing conditions. The study was designed to obtain a rigorous data set for ultrafine particles that could be applied to health risk assessment. TDF was measured for six different breathing patterns: tidal volume (V_t) of 500 mL at respiratory flow rates (Q) of 150 and 250 mL/s; V_t = 750 mL at Q of 250 and 375 mL/s; V_t = 1 L at Q of 250 and 500 mL/s. Aerosols were monitored continuously by a modified condensation nuclei counter during mouthpiece inhalation with the prescribed breathing patterns. For a given breathing pattern, TDF increased as particle size decreased, regardless of the breathing pattern used. For example, at V_t = 500 mL and Q = 250 mL/s, TDF was 0.26, 0.30, 0.35, and 0.44 for CMD = 0.10, 0.08, 0.06, and 0.04 μm, respectively (see Figure 6-3). For a given particle size, TDF increased with an increase in V_t and a decrease in Q, indicating the importance of breathing pattern in assessing respiratory dose. The study also found that TDF was somewhat greater for women than men at CMD = 0.04 μm and 0.06 μm with all breathing patterns used, but the difference was smaller or negligible for larger-sized ultrafine particles. The results clearly demonstrate that the TDF of ultrafine particles increases with a decrease of particle size and with breathing patterns of longer respiratory time, a pattern that is consistent with deposition by diffusion. These data are the only systematic human experimental data for ultrafine particles reported since the 1996 PM AQCD.

A property of some ambient particulate species that affects deposition is hygroscopicity, the propensity of a material for taking up and retaining moisture under certain conditions of humidity and temperature. Ambient fine particles (sulfate, nitrate, and possibly organics) tend to be hygroscopic (see Chapter 2). Such particles can increase in size in the humid air within the respiratory tract and, when inhaled, will deposit according to their hydrated size rather than their initial size. The implications of hygroscopic growth on deposition have been reviewed extensively by Morrow (1986) and Hiller (1991) and the difficulties of studying lung deposition of hygroscopic aerosols have been reviewed by Kim (2000). In general, compared to nonhygroscopic particles of the same initial size, the deposition of hygroscopic aerosols in different regions of the lung may be higher or lower, depending on the initial size. For particles with initial sizes larger than ≈0.5 μm, the influence of hygroscopicity would be to increase total deposition with a shift from peripheral to central or ET region; whereas for smaller ones total

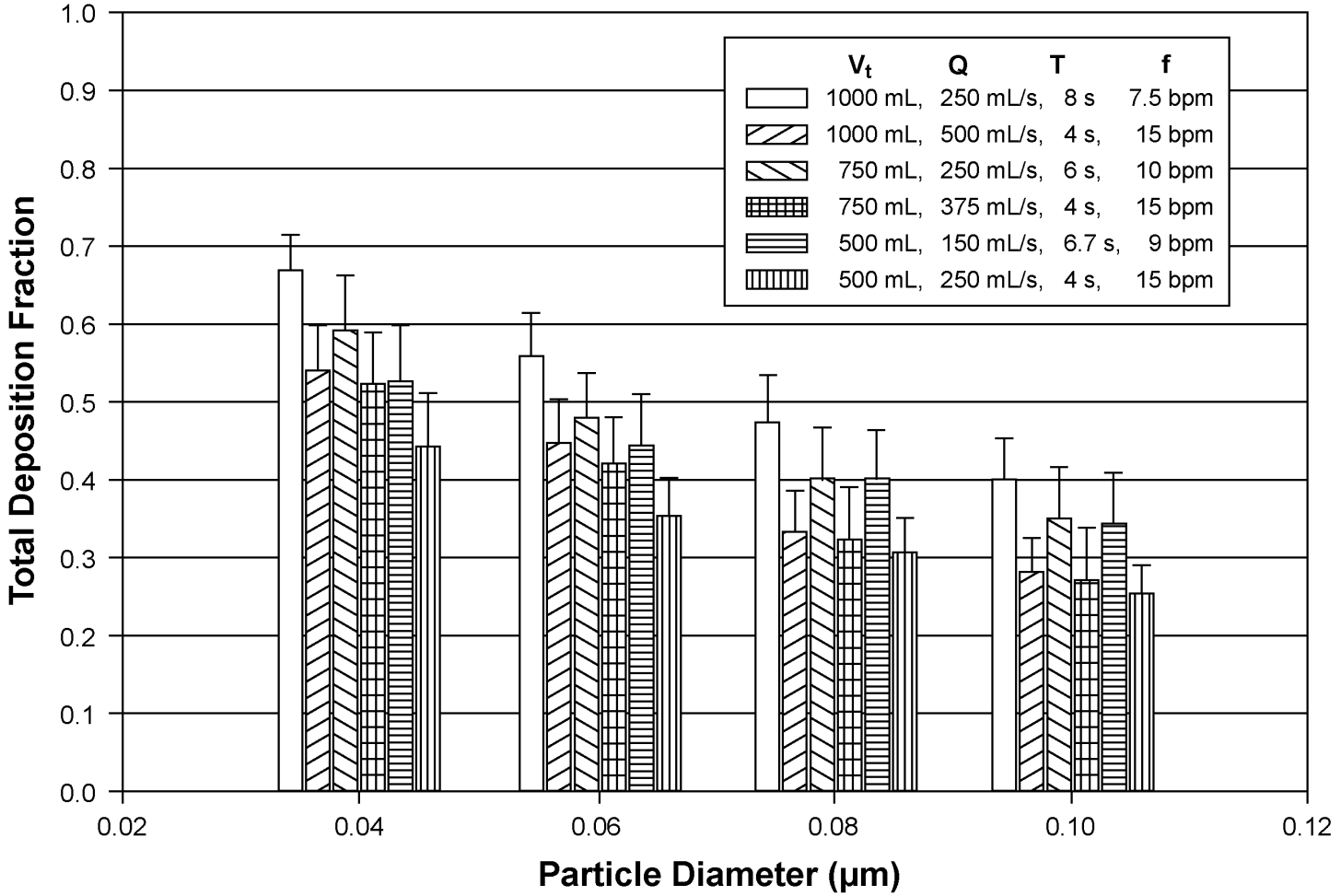

Figure 6-3. Total deposition fraction as a function of particle size in 22 healthy men and women under six different breathing patterns. For each breathing pattern, the total deposition fraction is different ($p < 0.05$) for two successive particle sizes. V_t is tidal volume (mL); Q is respiratory flow rate (mL/s); T is respiratory time (s); and f is breathing frequency in breaths/min (bpm).

Source: Jacques and Kim (2000).

deposition would tend to be decreased. See Chapter 2 for a detailed description of particle hygroscopicity.

6.2.2.2 Deposition in the Extrathoracic Region

The fraction of inhaled particles depositing in the ET region is quite variable and dependent on particle size, flow rate, breathing frequency, whether breathing is through the nose or the mouth (Figure 6-4), and the cross-sectional area of the flow path. Mouth breathing bypasses much of the filtration capabilities of the nasal airways and leads to increased deposition in the lungs (TB and A regions). The ET region is clearly the site of first contact with particles in the inhaled air and essentially acts as a "prefilter" for the lungs.

Since release of the 1996 PM AQCD, a number of studies have explored ET deposition with in vivo studies, as well as in both physical and mathematical model systems. In one study, the relative distribution of particle deposition between the oral and nasal passages was assessed during "inhalation" by use of a physical model (silicone rubber) of the human upper respiratory tract, which extended from the nostrils and mouth through the main bronchi (Lennon et al., 1998). Monodisperse particles ranging in size from 0.3 to 2.5 μm were evaluated at flow rates ranging from 15 to 50 L/min. Regional deposition in the oral passages, the lower oropharynx-trachea, nasal passages, and nasopharynx-trachea, as well as total deposition in the model, were assessed. Deposition within the nasal passages was found to agree with available data obtained from a human inhalation study (Heyder and Rudolf, 1977), being proportional to particle size, density, and inspiratory flow rate. It also was found that for oral inhalation, the relative distribution of particle deposition between the oral cavity and the oropharynx-trachea was similar; whereas for nasal inhalation, the nasal passages contained most of the particles deposited in the model, with only about 10% deposited in the nasopharynx-trachea region. Furthermore, the deposition efficiency of the nasopharynx-trachea region was greater than that of the oropharynx-trachea region. For simulated oronasal breathing, deposition in the ET region depended primarily on particle size rather than flow rate. For all flows and for all breathing modes, total deposition in the ET region increased as particle diameter increased. Such information on deposition patterns in the ET region is useful in refining empirical deposition models.

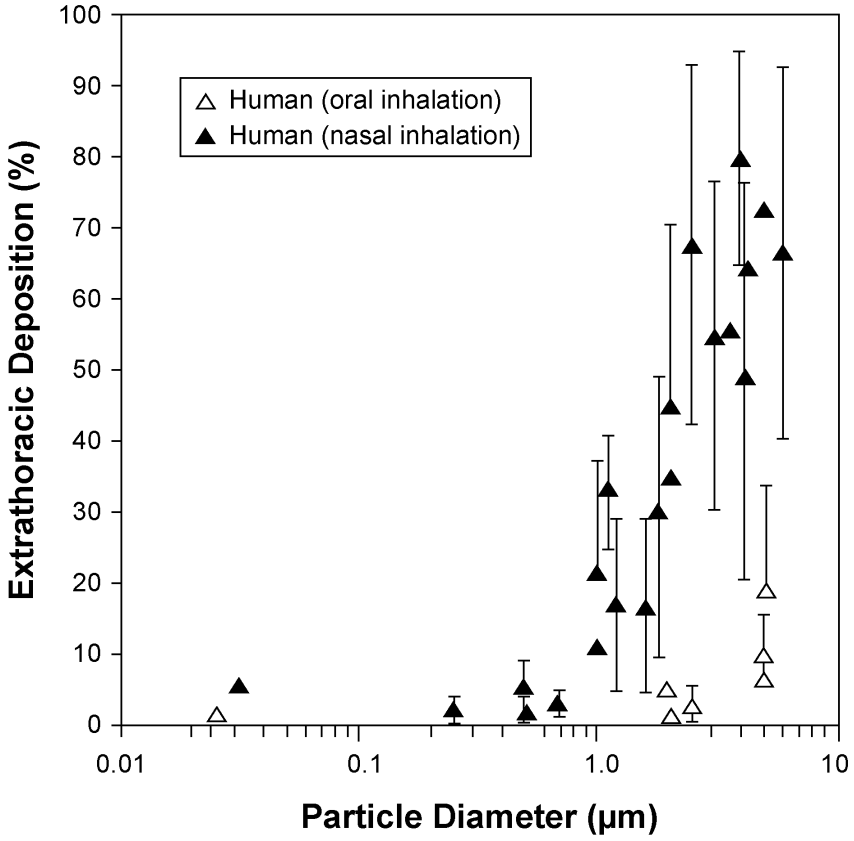

Figure 6-4. Extrathoracic deposition (as percentage deposition of the amount inhaled) in humans as a function of particle size. All values are means with standard deviations, when available. Particle diameters are aerodynamic (MMAD) for those ≥ 0.5 µm and geometric (or diffusion equivalent) for those < 0.5 µm.

Source: Modified from Schlesinger (1989).

Deposition within the nasal passages was further evaluated by Kesavanathan and Swift (1998), who examined the deposition of 1- to 10-µm particles in the nasal passages of normal adults under an inhalation regime in which the particles were drawn through the nose and out through the mouth at flow rates ranging from 15 to 35 L/min. At any particle size, deposition increased with increasing flow rate; whereas deposition increased with increasing particle size at any flow rate. In addition, as shown experimentally by Lennon et al. (1998) under oronasal breathing conditions, deposition of 0.3- to 2.5-µm particles within the nasal passages was significantly greater than within the oral passages, and nasal inhalation resulted in greater total deposition in the model than did oral inhalation. These results are consistent with other studies

discussed in the 1996 PM AQCD and with the known dominance of deposition by impaction within the ET region.

Rasmussen et al. (2000) measured deposition of 0.7 μm particles consisting of sodium chloride and radioactively-labeled technetium-diethylenetriamine-pentaacetic acid (DTPA) in the nasal cavity of normal adult humans. Each subject inhaled one liter for each inspiration at flow rates ranging from 10 to 30 L/min. They found that the deposition fraction in the nasal passages increased as flow rate increased and that an estimate of maximum linear air velocity was the best single predictor of nasal deposition fraction.

For ultrafine particles ($d_p < 0.1$ μm), deposition in the ET region is controlled by diffusion, which depends only on the particle's geometric diameter. Prior to 1996, ET deposition for this particle size range had not been studied extensively in humans, and this remains the case. In the 1996 PM AQCD, the only data available for ET deposition of ultrafine particles were from hollow airway cast studies. More recently, deposition in the ET region has been examined using mathematical modeling. Three-dimensional numerical simulations of flow and particle diffusion in the human upper respiratory tract, which included the nasal region, oral region, larynx, and first two generations of bronchi, were performed by Yu et al. (1998). Deposition of 0.001- and 0.01-μm particles in these different regions was calculated under inspiratory and expiratory flow conditions. Deposition efficiencies in the total model were lower on expiration than inspiration, although values for the former were quite high. During inspiration, about 75% of the 0.001-μm particles were deposited compared to only 31% of the 0.01-μm particles. Deposition in the nose accounted for 74 to 81% of total deposition in the model system during nasal inspiration. With oral inhalation, deposition in the mouth was 60 to 67% of total deposition in the model (Yu et al., 1998).

Swift and Strong (1996) examined the deposition of ultrafine particles, ranging in size from 0.00053 to 0.00062 μm (0.53 to 0.62 nm), in the nasal passages of normal adults during constant inspiratory flows of 6 to 22 L/min. In this case, deposition ranged from 94 to 99% (of amount inhaled). These results are consistent with results noted in studies above, namely that the nasal passages are highly efficient collectors for ultrafine particles. Only a weak dependence of deposition on flow rate was found, which contrasts with results noted above (i.e., Lennon et al., 1998) for particles > 0.3 μm, but is consistent with diffusion being the main deposition mechanism. This report has important implications for assessing the toxicity of PM because the

filtration efficiency of the nasal passages will lessen the deposition probability of ultrafine particles, particularly smaller-size ultrafines, in the lungs.

Cheng et al. (1997) examined oral airway deposition in a replicate cast of the human nasal cavity, oral cavity, and laryngeal-tracheal sections. For particle sizes of 0.005 to 0.150 μm, using constant inspiratory and expiratory flow rates of 7.5 to 30 L/min, they noted that the deposition fractions within the oral cavity were essentially the same as that in the laryngeal-tracheal sections for all particle sizes and flow rates. They ascribed this to the balance between flow turbulence and residence time in these two regions. Svartengren et al. (1995) examined the effect of changes in external resistance on oropharyngeal deposition of 3.6-μm particles in asthmatics. Under controlled mouthpiece breathing conditions (flow rate = 0.5 L/s), the median deposition as a percentage of inhaled particles in the mouth and throat was 20% (mean = 33%; range 12 to 84%). Although the mean deposition fell to 22% with added resistance, the median value remained at 20% (range = 13 to 47%). Fiberoptic examination of the larynx revealed a trend for increased mouth and throat deposition which was associated with laryngeal narrowing. On the basis of mathematical model calculations, Katz et al. (1999) found that turbulence plays a key role in enhancing particle deposition in the larynx and trachea.

The results of all of the above studies support the previously known ability of the ET region, especially the nasal passages, to act as an efficient filter for small ultrafine particles (< 0.01 μm) as well as for larger ones (> 2 μm), potentially reducing the amount of particles within a wide size range that are available for deposition in the TB and A regions (for nasal breathing, head deposition would be about 20% for 0.01 μm particles).

6.2.2.3 Deposition in the Tracheobronchial and Alveolar Regions

Particles that do not deposit in the ET region of the respiratory tract enter the lungs; however, their regional deposition within the lungs cannot be precisely measured. Much of the available deposition data for the TB and A regions have been obtained from experiments with radioactively labeled, poorly soluble particles (Figures 6-5 and 6-6, respectively). These have been described previously (U.S. Environmental Protection Agency, 1996a).

Since the publication of that document, a novel serial bolus delivery method has been introduced. Using this bolus technique, regional deposition has been estimated for fine and coarse aerosols (Kim et al., 1996; Kim and Hu, 1998) and for ultrafine aerosols (Kim and Jaques,

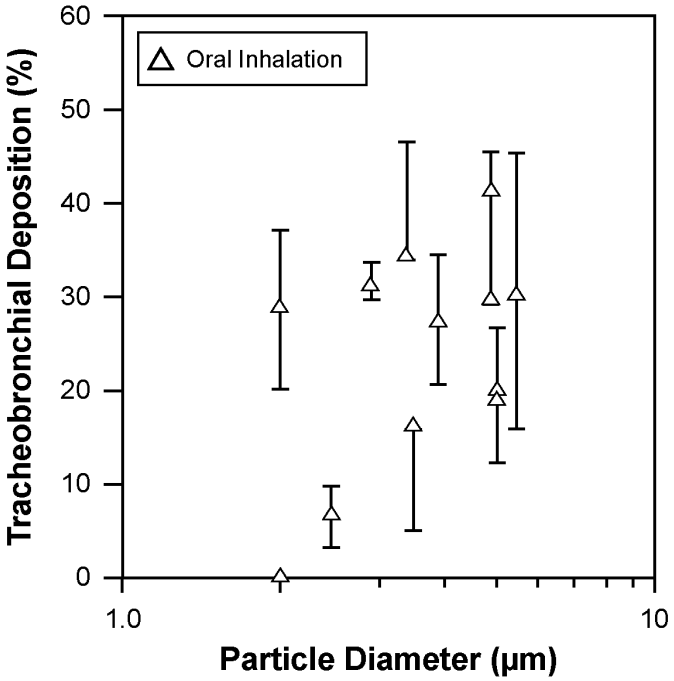

Figure 6-5.
Tracheobronchial deposition (as percentage of the amount inhaled) in humans as a function of particle size. All values are means with standard deviations, when available. Particle diameters are aerodynamic (MMAD).

Source: Modified from Schlesinger (1989).

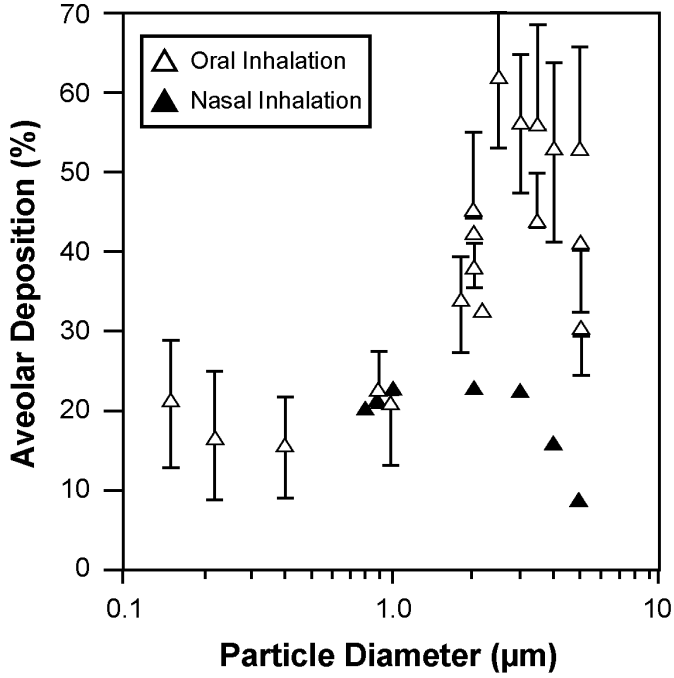

Figure 6-6.
Alveolar deposition (as percentage of the amount inhaled) in humans as a function of particle size. All values are means with standard deviations, when available. Particle diameters are aerodynamic (MMAD) for those ≥ 0.5 µm and geometric (or diffusion equivalent) for those < 0.5 µm.

Source: Modified from Schlesinger (1989).

2000). The serial bolus method uses nonradioactive aerosols and can estimate regional deposition in a virtually unlimited number of lung compartments. Because of experimental limitations of the technique, the investigators estimated regional lung deposition in ten serial, 50-mL increments from the mouth to the end of a typical 500-mL tidal volume. Deposition estimates in the TB and A regions were obtained for both men and women for particles ranging from 0.04 to 5.0 μm in diameter. It should be noted that particle deposition in the TB and A regions was based on volumetric compartments of 50 to 150 mL and > 150 mL, respectively. Deposition in the ET region was based on the 0 to 50 mL compartment. However, their estimates of TB deposition may artificially increase with decreasing anatomical dead space, i.e., the TB region of 50 to 150 mL includes more anatomically distal airways in the smaller lungs of women relative to men. Lung deposition fractions are shown in Figure 6-7. In men, 24 to 32% of total particle deposition (0.04-, 0.06-, 0.08-, and 0.10-μm particles) was deposited in the TB region and 67 to 76% was deposited in the A region. In women, compared to men, the deposition of these particles was consistently greater in the TB region (21-48%; $p < 0.05$ for 0.04 and 0.06 μm), but was comparable or slightly smaller in the A region. As a result, total lung deposition of ultrafine particles was slightly greater (~5-14%) in women than men, particularly for 0.04 and 0.06 μm ($p < 0.05$). For 1-, 3-, and 5-μm particles in men, 16 to 37% of total particle deposition was in the TB region and 57 to 83% was in the A region. Deposition of these size particles, in women was consistently greater in the TB region, particularly for 3 and 5 μm (56 to 68%, $p < 0.05$), but was comparable or slightly smaller in the A region as compared to men. As a result, total lung deposition was slightly greater (~20%) in women than men for 3 and 5 μm ($p < 0.5$). Thus, deposition of ultrafine and coarse particles in the TB region was somewhat greater for women than men, but there were no differences in either total or regional deposition of 0.08, 0.10, or 1.0 μm particles in men vs. women. The potential biological significance of the relatively small absolute magnitude (versus percentage) differences, if any, remains to be elucidated.

Fine particles that penetrate to the gas exchange airways are deposited on airway bifurcations at higher concentrations. The deposition diminishes rapidly with airway generation, consistent with the concentration of streamlines near the bifurcations and the penetration depth of convective tidal flow.

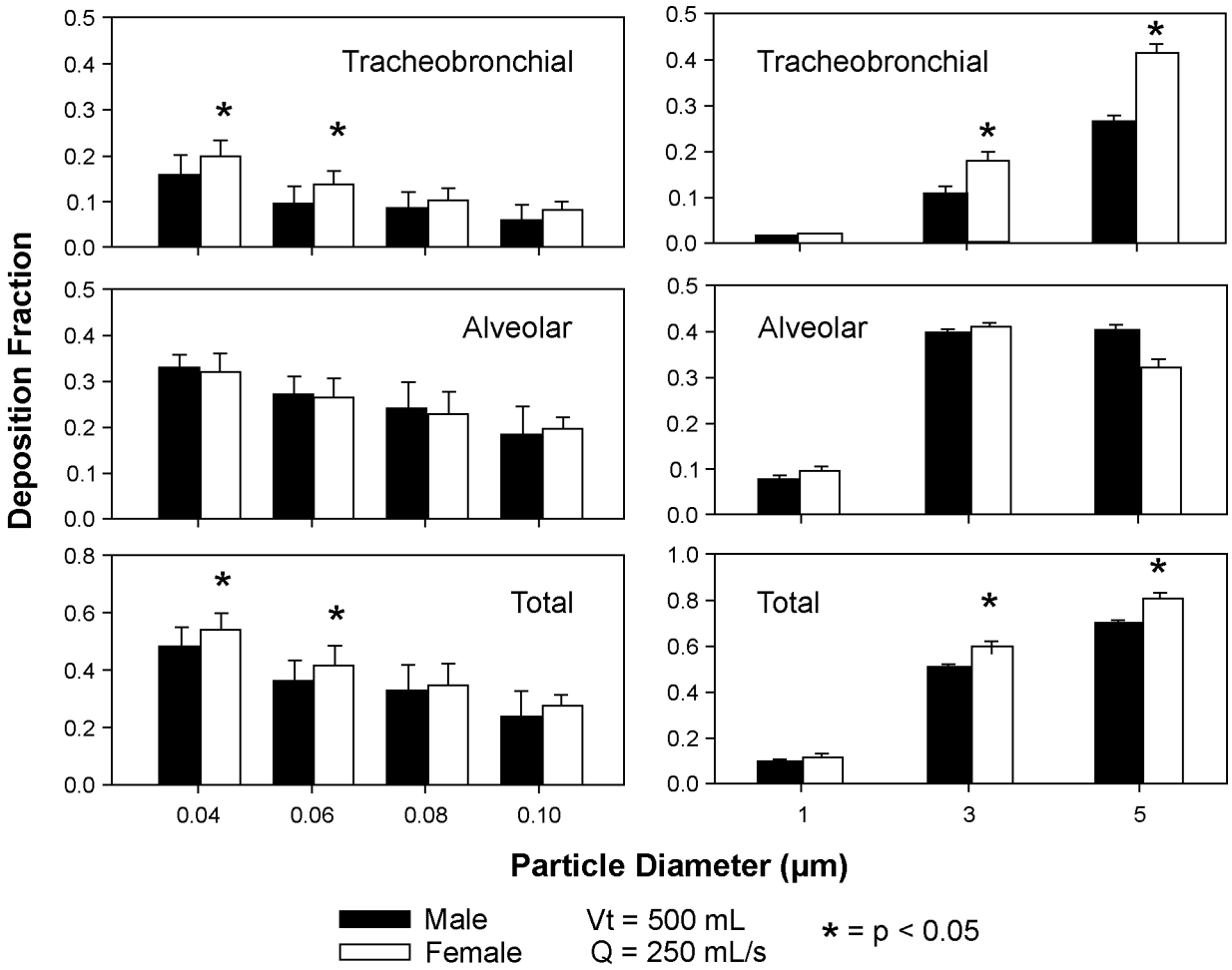

Figure 6-7. Lung deposition fractions in the tracheobronchial (TB) and alveolar (A) regions estimated by the bolus technique. Using a breathing pattern of 500 mL at 15 breaths per min, TB deposition was 1.5, 10.6, and 26.1% and A deposition was 7.7, 39.4, and 39.8% for particles of 1, 3, and 5 µm in diameter, respectively, for men. In comparison to men, TB deposition in women was 68% and 50% greater for 3 and 5 µm respectively (both $p < 0.05$), whereas A deposition was comparable. For ultrafine particles of 0.04 to 0.1 µm diameter, TB and A deposition in men ranged from 5.7 to 15.6% and 18.2 to 33.1%, respectively. In comparison to men, TB deposition in women was 27% and 48% greater for 0.04 and 0.06 µm respectively (both $p < 0.05$), whereas A deposition was comparable. There was no difference for 0.08, 0.1, and 1 µm between men and women. Both TB and A deposition decreased with increasing particle size within the ultrafine range, which is consistent with deposition theory.

Source: Kim and Hu (1998); Kim and Jaques (2000).

6.2.2.4 Local Distribution of Deposition

Airway structure and its associated air flow patterns are exceedingly complex, and ventilation distribution of air in different parts of the lung is uneven. Thus, it is expected that particle deposition patterns within the ET, TB, and A regions would be highly nonuniform, with some sites exhibiting deposition that is much greater than average levels within these regions. This was discussed in detail in the 1996 PM AQCD. Basically, using deposition data from living subjects as well as from mathematical and physical models, enhanced deposition has been shown to occur in the nasal passages and trachea and at branching points in the TB and A regions (see Chapter 10 of U.S. Environmental Protection Agency, 1996a). Churg and Vedal (1996) examined retention of particles on carinal ridges and tubular sections of airways from lungs obtained at necropsy. Results indicated significant enhancement of particle retention on carinal ridges through the segmental bronchi; the ratios were similar in all airway generations examined.

Kim and Fisher (1999) studied local deposition efficiencies and deposition patterns of aerosol particles (2.9 to 6.7 μm) in sequential double-bifurcation tube-models with two different branching geometries: one with in-plane (Model-A) and another with out-of-plane (Model-B) bifurcation. The deposition efficiencies (DE) in each bifurcation increased with increasing Stokes number (ratio of the stopping distance of a particle to a characteristic dimension of an obstacle). The Stokes number is used to characterize the ability of a particle to follow a streamline in curvilinear motion. As the Stokes number increases, particles tend to become less able to follow a streamline around an obstacle and more likely to impact the obstacle (Hinds, 1999). With symmetric flow conditions, DE was somewhat smaller in the second than the first bifurcation in both models. DE was greater in the second bifurcation in Model-B than in Model-A. With asymmetric flows, DE was greater in the low-flow side compared to the high-flow side; this was consistent in both models. Deposition pattern analysis showed highly localized deposition on and in the immediate vicinity of each bifurcation ridge, regardless of branching and flow patterns.

Comer et al. (2000) used a three-dimensional computer simulation technique to investigate local deposition patterns in sequentially bifurcating airway models that were previously used in experiments by Kim and Fisher (1999). The simulation was for 3-, 5-, and 7-μm particles and assumed steady, laminar, constant air flow with symmetry about the first bifurcation. The overall trend of the particle deposition efficiency, i.e., an exponential increase with Stokes

number, was similar for all bifurcations; and deposition efficiencies in the bifurcation regions agreed very well with experimental data. Local deposition patterns consistently showed that the majority of the deposition occurred within the carinal region.

Deposition "hot spots" at airway bifurcations have undergone additional analyses using mathematical modeling techniques. Using calculated deposition sites, a strong correlation has been demonstrated between secondary flow patterns and deposition sites and density both for large (10 μm) particles and for ultrafine (0.01 μm) particles (Heistracher and Hofmann, 1997; Hofmann et al., 1996). This supports experimental work, noted in U.S. Environmental Protection Agency (1996a), indicating that, like larger particles, ultrafine particles show enhanced deposition at airway branch points — even in the upper tracheobronchial tree.

The pattern of particle distribution on a more regional scale was evaluated by Kim et al. (1996) and Kim and Hu (1998). Deposition patterns were measured in situ in nonsmoking healthy young adult males using an aerosol bolus technique that delivered 1-, 3-, or 5-μm particles into specific volumetric depths within the lungs. The distribution of particle deposition shifted from distal to proximal regions of the lungs with increasing particle size (Figure 6-8). Furthermore, the surface dose was found to be greater in the conducting airways than in the alveolar region for all of the particle sizes evaluated. Within the conducting airways, the largest airway regions (i.e., 50 to 100 mL volume distal to the larynx) received the greatest surface doses.

Bennett et al. (1998) studied the effect of variable anatomic dead space (ADS) on particle deposition using an aerosol bolus technique in healthy subjects inhaling radiolabeled (^{99m}Tc) iron oxide particles (3.5 μm MMAD). The subjects inhaled 40 mL aerosol boluses to a volumetric front depth of 70 mL into the lung at a lung volume of 70% total lung capacity end-inhalation and estimated the fraction of the inhaled boluses deposited in intrathoracic airways. ADS was also measured from 70% total lung capacity. The intrathoracic deposition fraction (IDF) varied from 0.04 to 0.43 and increased with decreasing ADS. The IDF was lower in subjects with large ADS (> 250 mL). Hence, women had twice the IDF due to their smaller ADS and smaller airspace dimensions. They observed significantly greater deposition in the left (L) versus right (R) lung; mean L/R (ratio of deposition in L lung to R lung, normalized to ratio of L-to-R lung volume) was 1.58 ± 0.42. Retention of deposited particles at 2 h was independent of ADS or IDF. There was significant retention of particles in the whole lung at 24 h post deposition and

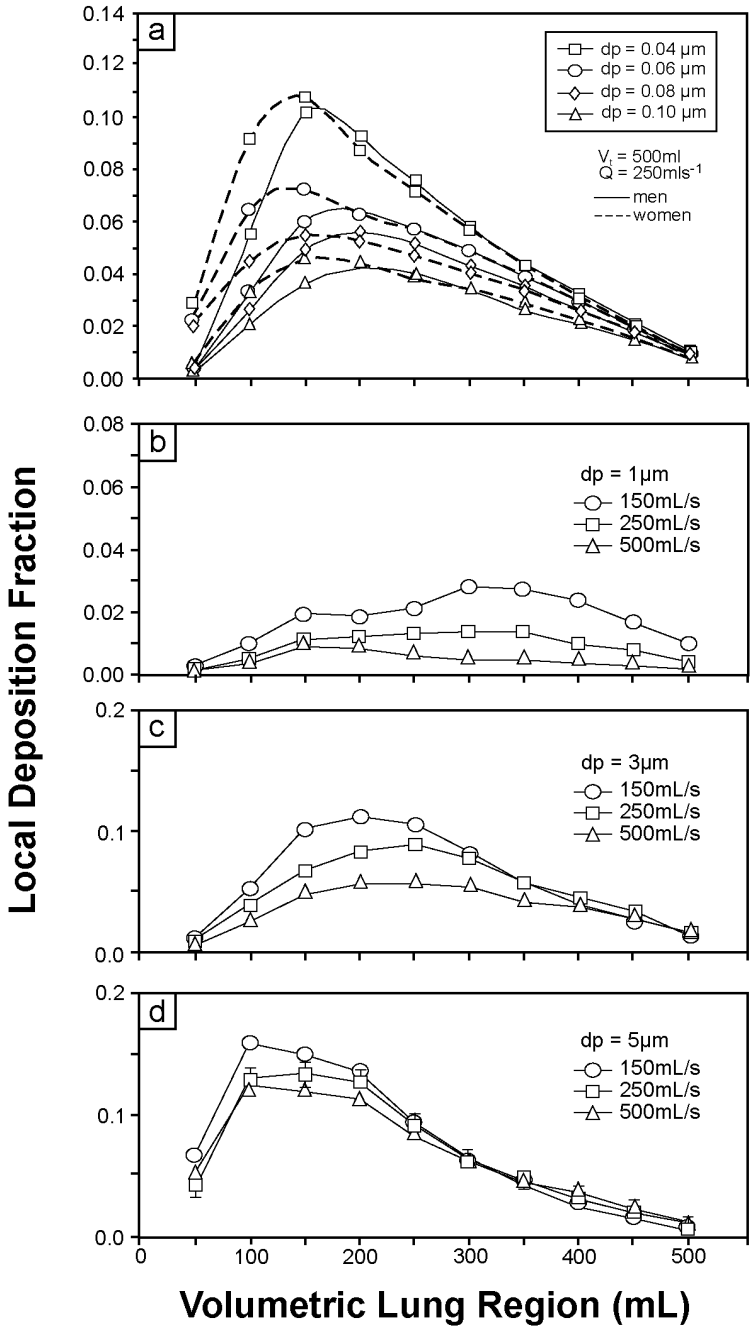

Figure 6-8. Estimated lung deposition fractions in ten volumetric regions for particle sizes ranging from ultrafine particle diameter (d_p) of 0.04 to 0.01 µm (Panel A) to fine (d_p = 1.0 µm MMAD; Panel B) and coarse (d_p = 3 and 5 µm MMAD; Panels C and D). Healthy young adults inhaled a small bolus of monodisperse aerosols under a range of normal breathing conditions (ie., tidal volume of 500 mL at breathing frequencies of 9, 15, and 30 breaths per min.).

Source: Kim et al. (1996); Kim and Jaques (2000).

slow clearance of these particles continued through 48 h post deposition. There was significant retention of insoluble particles in large bronchial airways at 24 h post deposition (i.e., 24 h central-to-peripheral ratio of 1.40 and 1.82 in the R and L lung, respectively).

Kim and Jaques (2000) used the respiratory bolus technique to estimate the deposition distribution of ultrafine particles (0.04, 0.06, 0.08, and 0.1 μm) in young adults. Under normal breathing conditions (V_t, tidal volume 500 mL; Q, 250 mL/s), bolus aerosols were delivered sequentially to a lung depth ranging from 50 to 500 mL in 50-mL increments. The results indicate that regional deposition of ultrafine particles (0.04 to 0.10 μm) varies widely along the depth of the lung (Figure 6-8). Regional deposition of these particles is approximately bounded by those of larger particles (1.0 to 5.0 μm). The variability with depth is small for 1 μm particles but large for 5 μm particles. (Note the difference in y-axis values.) The deposition patterns for ultrafine particles, especially for very small ultrafine particles, were similar to those for coarse particles. Peak deposition occurred in the lung regions situated between 150 and 200 mL from the mouth, and sites of peak deposition shifted proximally with decreasing particle size. Deposition dose per unit average surface area was greatest in the proximal lung regions and decreased rapidly with increased lung depth. Peak surface dose was 5 to 7 times greater than average lung dose. These results indicate that local enhancement of dose occurs in healthy lungs, which could be an important factor in eliciting pathophysiological effects.

6.2.2.5 Deposition of Specific Size Modes of Ambient Aerosol

Several recent modeling studies provide estimates of the deposition profiles for "real world" particle size fractions. One such study using a lung-anatomical model (Venkataraman and Kao, 1999) examined the contribution of two specific size modes of the PM_{10} ambient aerosol, namely the fine mode (defined as particles with diameters up to 2.5 μm) and the thoracic fraction of the coarse mode (defined as particles with diameters between 2.5 and 10 μm) to total lung and regional lung doses (i.e., a daily dose expressed as μg/day, and a surface dose expressed as $\mu g/cm^2$/day) resulting from a 24-h exposure to a particle concentration of 150 $\mu g/m^3$. The study also evaluated deposition in terms of two metrics, namely mass dose and number dose. Deposition was calculated using a mathematical model for a healthy human lung under both simulated moderate exertion (V_t = 1 L at 15 breaths/min) and vigorous exertion (V_t = 1.5 L at 15 breaths/min) and for a compromised lung (V_t 0.5 L at 30 breaths/min).

Regional deposition values were obtained for the ET, TB, and A regions. Because the exposure scenario was is quite unrealistic, only general trends should be inferred from this study rather than actual deposition values. These estimates would also be highly uncertain for the compromised lung.

The daily modeled mass dose for the fine particles peaked in the A region for all breathing patterns, whereas the mass dose for coarse particles was comparable in the TB and A regions. The mass per unit surface area of various airways from the fine and coarse fractions was larger in the trachea and first few generations of bronchi. Venkataraman and Kao (1999) suggested that these large surface doses may be related to aggravation of upper respiratory tract illness. The modeled daily number dose was different for fine and coarse fractions in all lung airways: the dose from the fine fraction was higher by about 100 times in the ET and about 10^5 times in internal lung airways. The surface number dose (particles/cm^2/day) was 10^3 to 10^5 times higher for fine than for coarse particles in all lung airways, indicating the larger number of fine particles depositing. Particle number doses did not follow trends in mass doses and were much higher for fine than coarse particles. It also was concluded that the fine fraction contributes 10,000 times greater particle number per alveolar macrophage than the coarse fraction particles. As noted, these results must be viewed with caution because they were obtained using a pure mathematical model that remains to be validated in terms of realistic physiologic conditions.

Another evaluation of deposition that included consideration of size mode of the ambient aerosol was that of Broday and Georgopoulos (2001). In this study, a mathematical model was used to account for particle hygroscopic growth, transport, and deposition. It was concluded that different rates of particle growth in the inspired air resulted in a change in the aerosol size distribution such that the initially inspired ultrafine particles (< 0.1 μm) grew into the size range between 0.1 to 1 μm. Due to their growth, particles deposited to a lesser extent than expected for ultrafine particles due to a decrease in diffusive deposition. On the other hand, particles that were originally in the 0.1- to 1-μm size range when inhaled will undergo enhanced deposition because as they increase in size due to hygroscopic growth. Hence, the initial size distribution of the inhaled polydisperse aerosol affects the evolution of size distribution once inhaled and, thus, its deposition profile in the respiratory tract. Hygroscopicity of respirable particles must be considered for accurate predictions of deposition. Because different size fractions likely have

different chemical composition, such changes in deposition patterns could affect biological responses.

6.2.3 Biological Factors Modulating Deposition

Experimental deposition data in humans have been commonly derived using healthy adult Caucasian males. Various factors can act to alter deposition patterns from those obtained in this group. Evaluation of these factors is important to help understand potentially susceptible subpopulations because differences in biological response following pollutant exposure may be caused by dosimetry differences as well as by differences in innate sensitivity. The effects of different biological factors on deposition were discussed in the 1996 PM AQCD (U.S. Environmental Protection Agency, 1996a) and are summarized below together with additional information obtained from more recent studies.

6.2.3.1 Gender

Males and females differ in body size, conductive airway size, and ventilatory parameter distributions; therefore, gender differences in deposition should be expected. In some of the controlled studies, however, the men and women were constrained to breathe at the same tidal volume and frequency. Since women are generally smaller than the men, the increased minute ventilation compared to their normal ventilation could affect deposition patterns. This may help to explain some of the differing results discussed below.

Using particles in the 2.5- to 7.5-μm size range, Pritchard et al. (1986) indicated that, for comparable particle sizes and inspiratory flow rates, females had higher ET and TB deposition and smaller A deposition than did males. The ratio of A deposition to total thoracic deposition in females also was found to be smaller. These differences were attributed to gender differences in airway size.

In another study (Bennett et al., 1996), the total respiratory tract deposition of 2-μm particles was examined in adult males and females aged 18 to 80 years who breathed with a normal resting pattern. Deposition was assessed in terms of a deposition fraction, the difference between the amount of particles inhaled and exhaled during oral breathing. Although there was a tendency for a greater deposition fraction in females compared to males, because males had

greater minute ventilation, the deposition rate (i.e., deposition per unit time) was greater in males than in females.

Kim and Hu (1998) assessed the regional deposition patterns of 1-, 3-, and 5-μm MMAD particles in healthy adult males and females using an aerosol bolus technique and controlled breathing. The total fractional deposition in the lungs was similar for both genders with the 1-μm particle size, but was greater in women for the 3- and 5-μm particles regardless of the inhalation flow rate used; this difference ranged from 9 to 31% ($p < 0.05$), with higher values associated with higher flow rates. The pattern of deposition was similar for both genders, although females showed enhanced deposition peaks for all three particle sizes. The volumetric depth location of these peaks was found to shift from peripheral (i.e., increased volumetric depth) to proximal (i.e., shallow volumetric depth) regions of the lung with increasing particle size, with the shift being greater in females than in males. Thus, deposition appeared to be more localized in the lungs of females compared to those of males. These differences were attributed to the smaller size of the upper airways, particularly of the laryngeal structure, in females. Local deposition of 1-μm particles was somewhat flow dependent but, for larger (5-μm) particles, was largely independent of flow (flows did not include those that would be typical of exercise).

In a related study, Kim (2000) evaluated differences in deposition between males and females under varying breathing patterns (simulating breathing conditions of sleep, resting, and mild exercise). Using particles at the same size noted above and a number of breathing conditions, total fractional lung deposition was comparable between men and women for l-μm particles, but was slightly greater in women than men for 3- and 5-μm particles with all breathing patterns. The gender difference was about 15% at rest and variable during exercise depending on particle size. However, total lung deposition rate (i.e., deposition per unit time) was found to be 3 to 4 times greater during moderate exercise than at rest for all particle sizes. Thus, it was concluded that exercise may increase the health risk from particles because of increased large airway deposition and that women may be more susceptible to these exercise-induced changes.

Jaques and Kim (2000) and Kim and Jaques (2000) expanded the evaluation of deposition in males and females to particles < 1 μm. They measured total fractional lung deposition in healthy adults using sizes in the ultrafine mode (0.04 to 0.1 μm). Total fractional lung deposition was greater in females than in males for 0.04- and 0.06-μm particles ($p < 0.05$). The

difference was negligible for 0.08- and 0.1-μm particles. Therefore, the gender effect was particle-size dependent, showing a greater fractional deposition in females for very small ultrafine and large coarse particles, but not for particles ranging from 0.08 to 0.1 μm. A local deposition fraction was determined in each volumetric compartment of the lung to which particles were injected based on the inhalation procedure (Kim and Jaques, 2000). The fractional deposition was found to increase with increasing lung depth from the mouth, reach a peak value, and then decrease with further increase in lung volumetric depth. Figure 6-8 shows these ultrafine data along with fine and coarse particle data from Kim et al. (1996). The height of the peak and its depth varied with particle size and breathing pattern. Peak fractional deposition for the 5-μm particles was more proximal than that for the 1-μm particles, whereas that for the ultrafine particles occurred between these two peaks. For the ultrafine particles, the peak fractional deposition became more proximal as particle size decreased. Although this pattern of deposition distribution was similar for both men and women, the region of peak fractional deposition was shifted closer to the mouth and peak height was slightly greater for women than for men for all exposure conditions.

6.2.3.2 Age

Airway structure and respiratory conditions vary with age, and these variations may alter the deposition pattern of inhaled particles (Table 6-1). The limited experimental studies reported in the 1996 PM AQCD (U. S. Environmental Protection Agency, 1996a) indicated results ranging from no clear dependence of total deposition on age to slightly higher deposition in children than adults. However, children have a different resting ventilation than do adults. Experimental studies must adjust for different breathing patterns and the higher minute ventilation per unit body weight in children when comparing deposition results to those obtained in adults.

Inhaled Deposition Patterns

Bennett et al. (1997a) analyzed the regional deposition of poorly soluble 4.5-μm particles inhaled via mouthpiece. The subjects were children and adults with mild cystic fibrosis (CF), but who likely had normal upper airway anatomy such that intra- and ET deposition would be similar to that in healthy people. The mean age of the children was 13.8 years and 29.1 years for

TABLE 6-1. EFFECTS OF AGE ON PARTICLE DEPOSITION IN RESPIRATORY TRACT

Type study	Particles (MMAD)	Summary	Author
Inhalation	2 μm	Measured deposition of particles in children, adolescents, and adults. No differences in deposition among three groups. Breath-to-breath fractional deposition in children increased with increasing tidal volume. Rate of deposition normalized to lung surface area tended to be 35% greater in children compared to adolescents and adults.	Bennett and Zeman (1998)
Inhalation	4.5 μm	Particles inhaled via mouthpiece by children and adults with mild CF, but normal airway anatomy. Extrathoracic deposition of particles 50% greater in children and tended to be higher for younger ages. No significant difference in lung or total respiratory tract deposition.	Bennett et al. (1997a)
Inhalation	2 μm	Examined deposition of particles in subjects aged 18-80 yrs. Fractional deposition not found to be age-related but more dependant on airway resistance and breathing patterns.	Bennett et al. (1996)
Inhalation	1, 2.05, 2.8 μm	For same flow rate, children had higher nasal resistance then adults. Nasal deposition increased with particle size, ventilation flow rate, and nasal resistance. Average nasal deposition percentages lower in children than in adults; differences increased with exercise. Average nasal deposition percentages best correlated with airflow rate.	Becquemin et al. (1991)
Airway models	1, 5, 10, 15 μm	Airway models of trachea and first few generations of bronchial airways of children and adult; total deposition in child model greater than in adult.	Oldham et al. (1997)
Nasal casts	0.0046-0.2 μm	Nasal casts of children's airways; deposition efficiency for particles decreased with increasing age.	Cheng et al. (1995)
Model	0.1-10 μm	Total fractional lung deposition comparable between children and adults for all sizes. TB-deposition fraction greater in children; A deposition fraction reduced in children.	Phalen and Oldham (2001)
Model	1.95 μm	Mass-based deposition of ROFA decreased with age from 7 mo to adulthood; mass deposition per unit surface area greater in children.	Musante and Martonen (2000a)
Model	0.25-5 μm	A fractional deposition highest in children for all particle sizes; TB fractional deposition decreased as function of age for all sizes; total fractional lung deposition higher in children than adults.	Musante and Martonen (1999)
Model		ET deposition in children higher; TB and A may be lower or higher depending on particle size; enhanced deposition for particles < 5 μm in children.	Xu and Yu (1986)

CF = Cystic fibrosis.

the adults. Extrathoracic deposition of the 4.5-μm particles, as a percentage of total respiratory tract deposition, was higher by about 50% in children compared to adults. There was an age dependence of ET deposition for the 4.5-μm particles in the children in that the percentage ET deposition tended to be higher at a younger age ($p = 0.08$). The younger group (< 14 years; $p = 0.05$) had almost twice the percentage ET deposition of the older group (> 14 years). Additional analyses showed an inverse correlation of ET deposition with body height. These results are consistent with the predicted increase in head deposition of particle greater than 2 μm with decreasing age reported by Xu and Yu (1986).

Becquemin et al. (1991) compared nasal filtering efficiency in children and adults; two groups of children (12 children, aged 5.5 to 11.5 years; 8 children, aged 12 to 15 years) were studied along with 10 adults. The deposition of polystyrene beads (1, 2.05, and 2.8 μm MMAD) was measured for both nose and mouth breathing. Ventilation was controlled to scale breathing patterns appropriate for each age either at rest or during moderate exercise. Anterior nasal resistance and standard lung function were measured for each subject. For the same inhalation flow rate, children had much higher nasal resistances than adults. Individually, nasal deposition increased with particle size, ventilation flow rate, and nasal resistance from rest to exercise. The average for these particle sizes were better correlated with inspiratory airflow rate than with resistances or pressure drops at rest and during moderate exercise. Although the nasal airways of children are narrower, they are also shorter and the inhalation flow rate is reduced. The authors conclude that while the nasal deposition percentages were lower in children than in adults at rest, these differences were even greater during exercise. This would mean that the thoracic airways of children are protected to a lesser degree than those of adults.

Bennett and Zeman (1998) measured the deposition of monodisperse 2-μm (MMAD) particles in children (aged 7 to 14 years) and adolescents (aged 14 to 18 years) for comparison to that in adults (19 to 35 years). Each subject inhaled the particles by following their previously determined individual spontaneous resting breathing pattern. Deposition was assessed by measuring the amount of particles inhaled and exhaled. There was no age-related difference in deposition within the children group. There was also no significant difference in deposition between the children and adolescents, between the children and adults, nor between the adolescents and adults. However, the investigators noted that, because the children had smaller

lungs and higher minute ventilation relative to lung size, they likely would receive greater doses of particles per lung surface area compared to adults. Furthermore, breath-to-breath fractional deposition in children varied with tidal volume, increasing with increasing tidal volume. The rate of deposition normalized to lung surface area tended ($p = 0.07$) to be greater (35%) in children when compared to the combined group of adolescents and adults. These additional studies still do not provide unequivocal evidence for significant differences in deposition between adults and children, even when considering differences in lung surface area. However, it should be noted that differences in levels of activity between adults and children are likely to play a fairly large role in age-related differences in deposition patterns of ambient particles. Children generally have higher activity levels during the day and higher associated minute ventilation per lung size, which can contribute to a greater size-specific dose of particles. Activity levels in relationship to exposure are discussed more fully in Chapter 5.

Another subpopulation of potential concern related to susceptibility to inhaled particles is the elderly. In the study of Bennett et al. (1996), the total respiratory tract deposition of 2-μm particles was examined in people aged 18 to 80 years, the deposition fraction in the lungs of people with normal lung function was found to be independent of age, however, depending solely on breathing pattern and airway resistance.

Modeled Deposition Patterns

Differences in regional deposition between children and adults have been assessed to a greater extent using mathematical models than experimentally. These models indicate that, if the entire respiratory tract and a complete breathing cycle at normal rate are considered, then ET deposition in children would be generally higher than in adults. However, TB and A regional deposition in children may be either higher or lower than that in adults, depending on particle size (Xu and Yu, 1986). There is enhanced TB deposition in children for particles < 5 μm (Xu and Yu, 1986; Hofmann et al., 1989a).

An age-dependent theoretical model to predict regional particle deposition in children's lungs that incorporates breathing parameters and morphology of the growing lung was developed by Musante and Martonen (1999). The model was used to compare deposition of monodisperse aerosols, ranging from 0.25 to 5 μm, in the lungs of children (ages 7, 22, 48, and 98 months) at

rest to that in adults (age 30 years) at rest. Compared to adults, the fractional deposition was highest in the 48- and 98-month subjects for all particle sizes. Total fractional lung deposition (i.e., TB + A) was generally higher in children than adults, with children of all ages showing similar total deposition fractions. The TB fractional deposition was reported to monotonically decrease as a function of age for all sizes. This apparent linear relationship may arise due to the way the investigators scaled the anatomical data for the adult down to the lung size for children. Still, the key point is that children may have greater deposition of mass per unit area than adults, even if this relationship may not be a linear function of age.

The model was later used by Musante and Martonen (2000a) to evaluate the deposition of a residual oil fly ash (ROFA) having an MMAD of 1.95 μm, a σ_g of 2.19, and a CMD of 0.53 (assuming a particle density of 0.34 g/cm^2). Deposition was evaluated under resting breathing conditions. The mass-based deposition fraction of the particles was found to decrease with age from 7 months to adulthood, and the mass deposition per unit surface area in the lungs of children could be significantly greater than in adults.

Phalen and Oldham (2001) calculated the respiratory deposition of particles with sizes ranging from 0.1 to 10 μm in diameter for 20 year-old adults and 2 year-old children. Total fractional lung deposition was comparable between adults and children for all particle sizes tested; however, TB deposition fraction was much greater in children than in adults (from 13 to 81%, depending on particle size). Particle deposition fraction in the A region was significantly reduced in children.

Cheng et al. (1995) examined the deposition of ultrafine particles in replica casts of the nasal airways of children aged 1.5 to 4 years. Particle sizes ranged from 0.0046 to 0.2 μm, and both inspiratory and expiratory flow rates were used (3 to 16 L/min). Deposition efficiency was found to decrease with increasing age for a given particle size and flow rate.

Oldham et al. (1997) examined the deposition of monodisperse particles having diameters of 1, 5, 10, and 15 μm in hollow airway models that were designed to represent the trachea and the first few bronchial airway generations of an adult, a 7-year-old child, and a 4-year-old child. They noted that, in most cases, the total deposition efficiency was greater in the child-size models than in the adult model.

6.2.3.3 Respiratory Tract Disease

The presence of respiratory tract disease can affect airway structure and ventilatory parameters, thus altering deposition compared to that occurring in healthy individuals. The effect of airway diseases on deposition has been studied extensively, as described in the 1996 PM AQCD (U.S. Environmental Protection Agency, 1996a). Studies described therein showed that people with chronic obstructive pulmonary disease (COPD) had very heterogeneous deposition patterns and differences in regional deposition compared to healthy individuals. People with obstructive pulmonary diseases tended to have greater deposition in the TB region than did healthy people. Furthermore, there tended to be an inverse relationship between bronchoconstriction and the extent of deposition in the A region, whereas total respiratory tract deposition generally increased with increasing degrees of airway obstruction. The described studies were performed during controlled breathing, i.e., all subjects breathed with the same tidal volume and respiratory rate. However, although resting tidal volume is similar or elevated in people with COPD compared to healthy individuals, the former tend to breathe at a faster rate, resulting in higher than normal tidal peak flow and resting minute ventilation. Thus, given that breathing patterns differ between healthy and obstructed individuals, particle deposition data for controlled breathing may not be appropriate for estimating respiratory doses from ambient PM exposures. Although the extent to which lung deposition may change with respect to particle size, breathing pattern, and disease status in people with COPD is still unclear, some recent studies have attempted to provide additional insight into this issue.

Bennett et al. (1997b) measured the fractional deposition of insoluble 2-μm particles in people with severe to moderate COPD (mix of emphysema and chronic bronchitis, mean age 62 years) and compared this to healthy older adults (mean age 67 years) under conditions where the subjects breathed using their individual resting breathing pattern as well as a controlled breathing pattern. People with COPD tended to have an elevated tidal volume and a faster breathing rate than people with healthy lungs, resulting in about 50% higher resting minute ventilation. Total respiratory tract deposition was assessed in terms of deposition fraction (determined from measures of the amount of aerosol inhaled and exhaled) and deposition rate (the amount of particulate deposited per unit time). Under typical breathing conditions, people with COPD had about 50% greater deposition fraction than did age-matched healthy adults. Because of the elevation in minute ventilation, people with COPD had average deposition rates

about 2.5 times that of healthy adults. Similar to previously reviewed studies (U.S. Environmental Protection Agency, 1996a), these investigators observed an increase in deposition with an increase in airway resistance, suggesting that, at rest, COPD resulted in increased deposition of fine particles in proportion to the severity of airway disease. The investigators also reported a decrease in deposition with increasing mean effective airspace diameter; this suggested that the enhanced deposition was associated more with the chronic bronchitic component of COPD than with the emphysematous component. Greater deposition was noted with natural breathing compared to the fixed pattern.

Brown et al. (2002) measured the deposition of an ultrafine aerosol (CMD = 0.033 μm) in 10 patients with moderate-to-severe COPD (mean age 61 years) and 9 healthy adults (mean age 53 years). The COPD group consisted of 7 patients with chronic bronchitis and 3 patients with emphysema. All subjects respired aerosol at their individual resting breathing pattern, which had been previously measured. The aerosol deposition fraction in the bronchitic patients (0.67) was significantly ($p < 0.02$) greater than in either the patients with emphysema (0.48) or the healthy subjects (0.54). Minute ventilation increased with disease severity (healthy, 5.8 L/min; chronic bronchitic, 6.9 L/min; emphysema, 11 L/min). For an aerosol exposure of 10 $\mu g/m^3$, the dose rates for the healthy, bronchitic, and emphysemic subjects were 1.9 μg/h, 2.8 μg/h (different from healthy, $p < 0.05$), and 3.2 μg/h, respectively. Hence, relative to the healthy subjects, the average dose rate was significantly ($p < 0.05$) increased by 54% in the COPD patients, whereas the deposition fraction only tended to be increased by 15%. Consistent with Bennett et al. (1997b), these data demonstrate the need to consider dose rates (which depend on minute ventilation) rather than just deposition fractions when evaluating the effect of respiratory disease on particle deposition and dose.

Kim and Kang (1997) measured lung deposition of 1-μm particles inhaled via the mouth by healthy adults (mean age 27 years) and by those with various degrees of airway obstruction, namely smokers (mean age 27 years), smokers with small airway disease (SAD; mean age 37 years), asthmatics (mean age 48 years), and patients with COPD (mean age 61 years) breathing under the same controlled pattern. Deposition fraction was obtained by measuring the number of particles inhaled and exhaled, breath by breath. There was a marked increase in deposition in people with COPD. Deposition was 16%, 49%, 59%, and 103% greater in smokers, smokers with SAD, asthmatics, and people with COPD, respectively, than in healthy

adults. Deposition in COPD patients was significantly greater than that associated with either SAD or asthma; there was no significant difference in deposition between people with SAD and asthma. Deposition fraction was found to be correlated with percent predicted forced expiratory volume (FEV_1) and forced expiratory flow ($FEF_{25-75\%}$). Airway resistance was not correlated strongly with total lung deposition. Kohlhäufl et al. (1999) showed increased deposition of fine particles (0.9 μm) in women with bronchial hyperresponsiveness.

Brown et al. (2001) examined the relationship between regional lung deposition for coarse particles (5 μm) and ventilation distribution in healthy adults and in patients with CF. They found that deposition in the TB region was positively associated with regional ventilation in healthy subjects, but negatively associated in CF patients. The relationships were reversed for deposition in the A region. These data suggest that significant coarse particle deposition may occur in the TB region of poorly ventilated lungs, as occurs in CF; whereas TB deposition follows ventilation in healthy subjects. This study demonstrated that there can be large differences in regional particle deposition within the diseased lung and that these differences are at least partially due to ventilation distribution.

Segal et al. (2000a) developed a mathematical model for airflow and particle motion in the lung that was used to evaluate how lung cancer affects deposition patterns in the lungs of children. It was noted that the presence of airway tumors could affect deposition by increasing the probability of inertial deposition and diffusion. The former would occur on upstream surfaces of tumors and the latter on downstream surfaces. It was concluded that particle deposition is affected by the presence of airway disease, that effects may be systematic and predictable, and that, therefore, they could be incorporated into dosimetry models. Segal et al. (2002) used a computer model to calculate the deposition fractions of PM within the lungs of COPD patients. The original model was for a healthy lung with a total volume of 4800 mL. The chronic bronchitis component of COPD was modeled by reducing airway diameters based on airway resistance measurements in vivo. The emphysema component was modeled by increasing alveolar volumes by 10 to 30%. The calculated results were compared with experimental data obtained from COPD patients for controlled breathing trials (tidal volume of 500 mL, respiratory time of 1 s) with a particle size of 1 μm. The model successfully depicts PM deposition patterns and their dependence on the severity of disease and indicates that airway obstructions are the main cause for increased deposition in the COPD lung.

Thus, the database related to particle deposition and lung disease suggests that total lung deposition generally is increased with obstructed airways, regardless of deposition distribution between the TB and A regions. Airflow distribution is very uneven in diseased lungs because of the irregular pattern of obstruction, and there can be closure of small airways. In this situation, a part of the lung is inaccessible, and particles can penetrate deeper into other, better ventilated regions. Thus, deposition can be enhanced locally in regions of active ventilation, particularly in the A region.

6.2.3.4 Anatomical Variability

As indicated above, variations in anatomical parameters between genders and between healthy people and those with obstructive lung disease can affect deposition patterns. However, previous analyses generally have overlooked the effect on deposition of normal inter-individual variability in airway structure in healthy individuals. This is an important consideration in dosimetry modeling, which often is based on a single idealized structure. Studies that have become available since the 1996 PM AQCD have attempted to assess the influence of such variation in respiratory tract structure on deposition patterns.

The ET region is the first to contact inhaled particles and, therefore, deposition within this region would reduce the amount of particles available for deposition in the lungs. Variations in relative deposition within the ET region will, therefore, propagate through the rest of the respiratory tract, creating differences in calculated doses from individual to individual. A number of studies have examined the influence of variations in airway geometry on deposition in the ET region.

Cheng et al. (1996) examined nasal airway deposition in healthy adults using particles ranging in size from 0.004 to 0.15 μm and at two constant inspiratory flow rates, 167 and 333 mL/s. Deposition was evaluated in relation to measures of nasal geometry as determined by magnetic resonance imaging and acoustic rhinometry. They noted that inter-individual variability in deposition was correlated with the wide variation of nasal dimensions, in that greater surface area, smaller cross-sectional area, and increasing complexity of airway shape were all associated with enhanced deposition.

Using a regression analysis of data on nasal airway deposition derived from Cheng et al. (1996), Guilmette et al. (1997) noted that the deposition efficiency within this region was highly

correlated with both nasal airway surface area and volume. This indicated that airway size and shape factors were important in explaining intra-individual variability observed in experimental studies of human nasal airway aerosol deposition. Thus, much of the variability in measured deposition among people arose from differences in the size and shape of specific airway regions.

As described in Section 6.2.2.4, Bennett et al. (1998) investigated the effects of ADS on particle deposition and retention in bronchial airways, using an aerosol bolus technique. They found that the fractional deposition was dependant on the subject's ADS and that a significant number of particles was retained beyond 24 h. This finding of prolonged retention of insoluble particles in the airways is consistent with the findings of Scheuch et al. (1995) and Stahlhofen et al. (1986a) and with the predictions of asymmetric stochastic human lung models (Asgharian et al., 2001). Bennett et al. (1999) also found a lung volume-dependent asymmetric distribution of particles between the left and right lung; the left:right ratio was increased at increased percentage of total lung capacity (e.g., at 70% TLC, L:R was 1.60).

From the analysis of detailed deposition patterns measured by a serial-bolus mouth-delivery method, Kim and Hu (1998) and Kim and Jaques (2000) found a marked enhancement in deposition in the very shallow region (lung penetration depth < 150 mL) of the lungs in females. The enhanced local deposition for both ultrafine and coarse particles was attributed to a smaller size of the upper airways, particularly of the laryngeal area.

Kesavanathan and Swift (1998) also evaluated the influence of geometry in affecting deposition in the nasal passages of normal adults from two ethnic groups. Mathematical modeling of the results indicated that the shape of the nostril affected particle deposition in the nasal passages, but that there still remained large inter-subject variations in deposition when this was accounted for, and which was likely caused by geometric variability in the mid and posterior regions of the nasal passages.

Hofmann et al. (2000) examined the role of heterogeneity of airway structure in the rat acinar region in affecting deposition patterns within this area of the lungs. Using different morphometric models, they showed a substantial variability in predicted particle deposition and concluded that the heterogeneity of acinar airway structure is primarily responsible for the heterogeneity of acinar particle deposition.

6.2.3.5 Inhaled Irritants

As noted above (Section 6.2.3.3), the narrowing of bronchial airways due to certain chronic disease states (e.g., bronchoconstriction associated with asthma) tends to increase TB region deposition, but decreases A region deposition. Bronchoconstriction induced by inhaled irritants, as discussed by Schlesinger (1995), would analogously be expected to increase TB deposition. Bronchoconstrictive effects are among the more notable effects associated with acute exposures to both SO_2 and O_3 as discussed in detail in respective EPA criteria documents for those pollutants (U.S. Environmental Protection Agency, 1994, 1996b). Thus, co-exposures to either SO_2 or O_3 sufficient to induce bronchoconstriction could potentially enhance particle deposition in the TB region, but reduce in the deposition A region.

6.2.4 Interspecies Patterns of Deposition

The primary purpose of this document is to assess the health effects of particles in humans. As such, human dosimetry studies have been stressed in this chapter. Such studies avoid the uncertainties associated with the extrapolation of dosimetric data from laboratory animals to humans. However, animal models have been and continue to be used in evaluating PM health effects because of ethical limits on the types of studies that can be performed with human subjects. Thus, there is a considerable need to understand dosimetry in animals and dosimetric differences between animals and humans. In this regard, there are a number of newly published studies that assess particle dosimetry in commonly used animals and attempt to relate this to dosimetry in humans.

The various species used in inhalation toxicologic studies that serve as the basis for dose-response assessment may not receive identical doses in a comparable respiratory tract region (i.e., ET, TB, or A) when exposed to the same aerosol at the same inhaled concentration. Such interspecies differences are important because toxic effects are potentially related to the quantitative pattern of deposition within the respiratory tract as well as to the exposure concentration. The pattern of deposition determines not only the initial respiratory tract tissue dose, but also the specific pathways by which deposited material is cleared and redistributed (Schlesinger, 1985). Differences in patterns of deposition between humans and animals were assessed previously in the 1996 PM AQCD (U.S. Environmental Protection Agency, 1996a) and

by others (Schlesinger et al., 1997). Such differences in initial deposition must be considered when relating biological responses obtained in laboratory animal studies to effects in humans.

It is difficult to systematically compare interspecies deposition patterns obtained from various reported studies because of variations in experimental protocols, measurement techniques, definitions of specific respiratory tract regions, and so on. For example, tests with humans are generally conducted under protocols that standardize the breathing pattern; whereas those using laboratory animals involve a wider variation in respiratory exposure conditions (e.g., spontaneous breathing versus ventilated breathing or varying degrees of sedation). Much of the variability in the reported data for individual species may be due to the lack of normalization for specific respiratory parameters during exposure. In addition, the various studies have used different exposure techniques, such as nasal mask, oral mask, oral tube, or tracheal intubation. Regional deposition is affected by the exposure route and delivery technique employed.

Figure 6-9 shows the regional deposition data versus particle diameter in commonly used laboratory animals obtained by various investigators as compiled by Schlesinger (1988, 1989). The results are described in detail in the 1996 PM AQCD (U.S. Environmental Protection Agency, 1996a). In general, there is much variability in the data; however, it is possible to make some generalizations concerning comparative deposition patterns. The relationship between total respiratory tract deposition and particle size is approximately the same in humans and most of these animals: deposition increases on both sides of a minimum that occurs for particles of 0.2 to 1 μm. Interspecies differences in regional deposition occur due to anatomical and physiological factors. In most laboratory animal species, deposition in the ET region is near 100% percent for particles greater than 5 μm AED (Raabe et al., 1988), indicating greater efficiency than that seen in humans. In the TB region, there is a relatively constant, but lower, deposition fraction for particles greater than 1 μm AED in all species compared to humans. Finally, in the A region, deposition fraction peaks at a lower particle size (about 1 μm AED) in laboratory animals than in humans.

One of the issues that must be considered in interspecies comparisons of hazards from inhaled particles is inhalability of the aerosol in the atmosphere of concern. Inhalability is the fraction of suspended PM in ambient air that actually enters the nose or mouth with the volume of air inhaled and is a function of a particle's AED, inspiratory flow rate, wind speed, and wind direction. Although inhalability may not be an issue for humans per se as far as exposure to

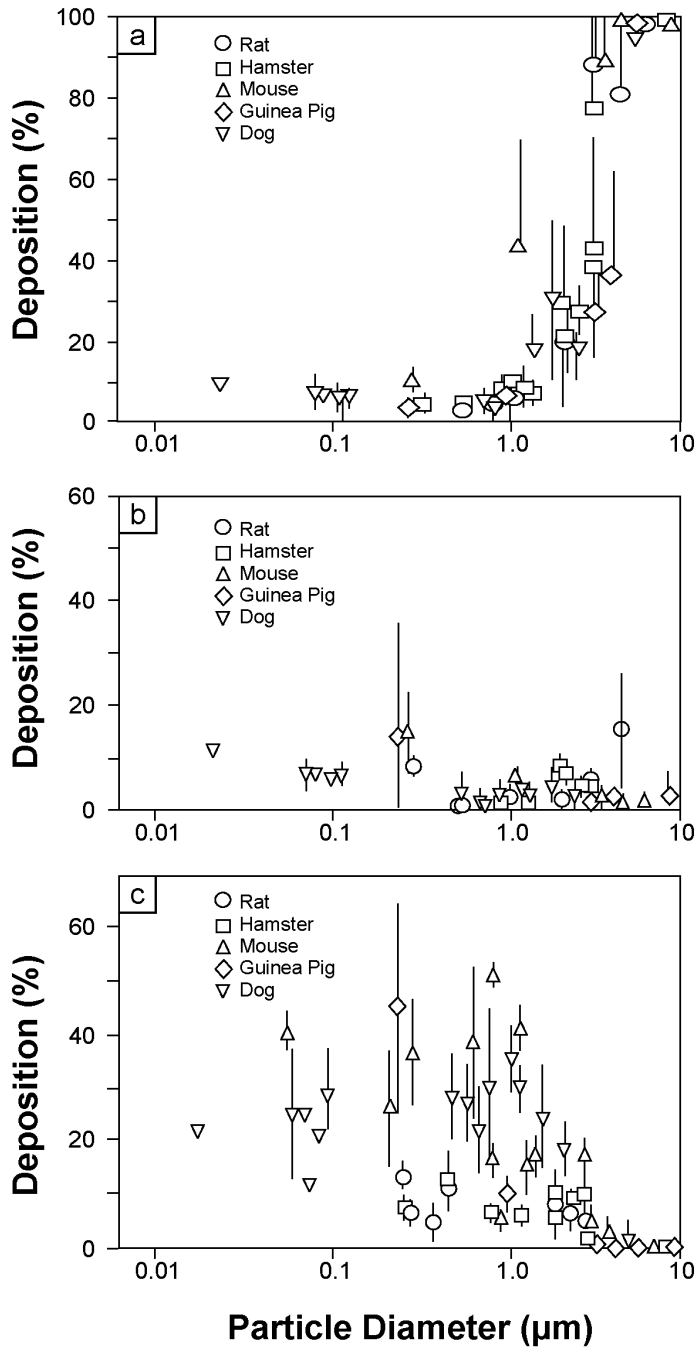

Figure 6-9. Regional deposition fraction measured in laboratory animals as a function of particle size for (a) upper respiratory tract, (b) tracheobronchial region, and (c) pulmonary region. Particle diameters are aerodynamic (MMAD) for those ≥ 0.5 µm and geometric (or diffusion equivalent) for those < 0.5 µm.

Source: Schlesinger (1988).

ambient particles is concerned, it can be important when attempting to extrapolate to humans the results of studies using animal species commonly employed in inhalation toxicological studies (Miller et al., 1995). For example, differences between rat and human become very pronounced for particles > 5 μm AED, and some differences are also evident for particles as small as l μm AED (Figure 6-10). Ménache et al. (1995) developed equations that can be used to determine the inhalability adjustments needed as a function of particle size to compare laboratory animal and human studies.

A number of studies have addressed various aspects of interspecies differences in respiratory tract deposition using mathematical modeling approaches. Hofmann et al. (1996) compared deposition between rat and human lungs using three-dimensional asymmetric bifurcation models and mathematical procedures for obtaining air flow and particle trajectories. Deposition in segmental bronchi and terminal bronchioles was evaluated under both inspiration and expiration at particle sizes of 0.01, 1.0, and 10 μm, which covers the range of deposition mechanisms from diffusion to impaction. Total deposition efficiencies of all particles in the upper and lower airway bifurcations were comparable in magnitude for both rat and human. However, the investigators noted that penetration probabilities from preceding airways must be considered. When considering the higher penetration probability in the human lung, the resulting bronchial deposition fractions were generally higher than in the rat. For all particle sizes, deposition at rat bronchial bifurcations was less enhanced on the carinas compared to that found in human airways.

Hofmann et al. (1996) attempted to account for interspecies differences in branching patterns in deposition analyses. Numerical simulations of three-dimensional particle deposition patterns within selected (species-specific) bronchial bifurcations indicated that morphologic asymmetry was a major determinant of the heterogeneity of local deposition patterns. They noted that many interspecies deposition calculations used morphometry that was described by deterministic lung models (i.e., the number of airways in each airway generation is constant, and all airways in a given generation have identical lengths and diameters). Such models cannot account for variability and branching asymmetry of airways in the lungs. Thus, their study employed computations that used stochastic morphometric models of human and rat lungs (Koblinger and Hofmann, 1985, 1988; Hofmann et al., 1989b) and evaluated regional and local particle deposition. Stochastic models of lung structure describe, in mathematical terms, the

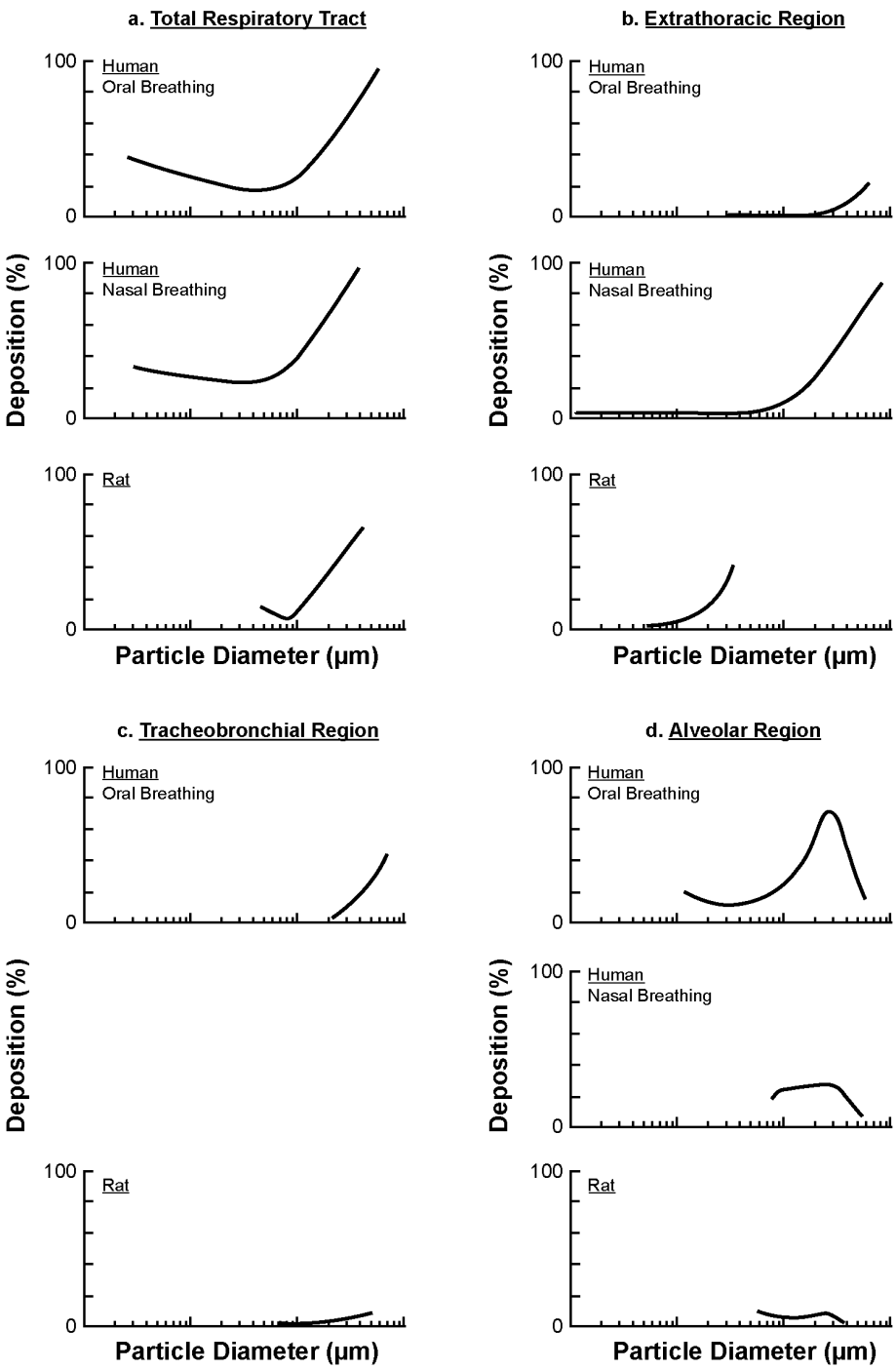

Figure 6-10. Particle deposition efficiency in rats and humans as a function of particle size for (a) total respiratory tract, (b) extrathoracic region, (c) tracheobronchial region, and (d) alveolar region. Each curve represents an eye fit through mean values (or centers of ranges) for the data compiled by Schlesinger (1985). Particle diameters are aerodynamic (MMAD) for those ≥ 0.5 μm and geometric (or diffusion equivalent) for those < 0.5 μm.

Source: Modified from Schlesinger (1989).

inherent asymmetry and variability of the airway system, including diameter, length, and angle. They are based on statistical analyses of actual morphometric analyses of lungs. The model also incorporated breathing patterns for humans and rats.

In a later analysis (Hofmann and Bergmann, 1998), the dependence of deposition on particle size was found to be qualitatively similar in both rats and humans. Deposition minima were found for total deposition as well as deposition within the TB and A regions in the size range of 0.1 to 1 μm. In addition, a deposition maximum occurred at about 0.02 to 0.03 μm and between 3 and 5 μm in both species. The deposition decrease in the A region at the smallest and largest sizes resulted from the filtering efficiency of upstream airways. Although deposition patterns were qualitatively similar in rat and human, deposition in the human lung appeared to be consistently higher than in the rat in all regions of the lung (TB and A) over the entire size range. Both species showed a similar pattern of dependence of deposition on flow rate. In both human and rat, deposition of 0.001-μm particles was highest in the upper bronchial airways; whereas 0.1- and 1-μm particles showed higher deposition in more peripheral airways, namely the bronchiolar airways in rat and the respiratory bronchioles in humans. Deposition was variable within any branching generation because of differences in airway dimensions, and regional and total deposition also exhibited intrasubject variations. Airway geometric differences between rats and humans were reflected in deposition. Because of the greater branching asymmetry in rats prior to about generation 12, each generation showed deposition maxima at two particle sizes, reflecting deposition in major and minor daughters. These geometric differences became reduced with depth into the lung; beyond generation 12, these two maxima were no longer seen.

Another comparison of deposition in lungs of humans and rats was performed by Musante and Martonen (2000b). An interspecies mathematical dosimetry model was used to determine the deposition of ROFA (MMAD, 1.95 μm; σ_g, 2.19)in the lungs under sedentary and light activity breathing patterns. This latter condition was mimicked in the rat by increasing the CO_2 level in the exposure system. They noted that physiologically comparable respiratory intensity levels did not necessarily correspond to comparable dose distribution in the lungs. Because of this, the investigators speculated that the resting rat may not be a good model for the resting human. The ratio of aerosol mass deposited in the TB region to that in the A region for the human at rest was 0.961, indicating fairly uniform deposition throughout the lungs. On the other hand, in the resting rat, the ratio was 2.24, indicating greater deposition in the TB region than in

the A region. However, by mimicking light activity in the rat, the ratio was reduced to 0.97, similar to the human. These data underscore the need for dose-response studies and for models that are capable of adjusting for the dosimetric differences between species.

The relative distribution of particles deposited within the bronchial and alveolar regions of the airways may differ in the lungs of animals and humans for the same total amount of deposited matter because of structural differences. The effect of such structural differences between rat and human airways on particle deposition patterns was examined by Hofmann et al. (1999, 2000) in an attempt to find the most appropriate morphometric parameter to characterize local particle deposition for extrapolation modeling purposes. Particle deposition patterns were evaluated as functions of three morphometric parameters, namely (1) airway generation, (2) airway diameter, and (3) cumulative path length. It was noted that airway diameter was a more appropriate morphometric parameter for comparison of particle deposition patterns in human and rat lungs than was airway generation.

The manner in which particle dose is expressed, that is, the specific dose metric, may affect relative differences in deposition between humans and other animal species. For example, although deposition when expressed on a mass per unit alveolar surface area basis may not be different between rats and humans, dose metrics based on particle number per various anatomical parameters (e.g., per alveolus or alveolar macrophage) can differ between rats and humans, especially for particles around 0.1 to 0.3 μm (Miller et al., 1995). Furthermore, in humans with lung disease (e.g., asthma or COPD), rat and human differences can be even more pronounced.

The probability of any biological effect occurring in humans or animals depends on deposition and retention of particles, as well as the underlying tissue sensitivity. Interspecies dosimetric extrapolation must consider these differences in evaluating dose-response relationships. Thus, even similar deposition patterns may not result in similar effects in different species because dose is also affected by clearance mechanisms. In addition, the total number of particles deposited in the lung may not be the most relevant dose metric for interspecies comparisons. For example, it may be the number of deposited particles per unit surface area or dose to a specific cell (e.g., alveolar macrophage) that determines response for specific regions. More specifically, even if fractional deposition is similar in the rat and human, there would be differences in deposition density because of the higher metabolic rate in the rat. Thus, species-

specific differences in deposition density should be considered when health effects observed in laboratory animals are being evaluated for potential effects occurring in humans.

6.3 PARTICLE CLEARANCE

This section discusses the clearance and translocation of particles that have deposited in the respiratory tract. Here, clearance refers to the processes by which deposited particles are removed from the surface of the respiratory tract. Translocation refers to specific clearance processes emphasizing movement of particles from one specific location to another either within the lung or to extrapulmonary organs. First, a basic overview of biological mechanisms and pathways of clearance in the various region of the respiratory tract is presented. This is followed by an update on regional kinetics of particle clearance. Interspecies patterns of clearance are then addressed, followed by new information on biological factors that may modulate clearance.

6.3.1 Mechanisms and Pathways of Clearance

Particles that deposit on airway surfaces may be either cleared from the respiratory tract completely or translocated to other sites within this system by various regionally distinct processes. These clearance mechanisms, outlined in Table 6-2, can be categorized as either absorptive (i.e., dissolution) or nonabsorptive (i.e., transport of intact particles) and may occur simultaneously or with temporal variations. It should be mentioned that particle solubility in terms of clearance refers to solubility within the respiratory tract fluids and cells. Thus, a poorly soluble particle is considered to be one whose rate of clearance by dissolution is insignificant compared to its rate of clearance as an intact particle. All deposited particles, therefore, are subject to clearance by the same basic mechanisms, with their ultimate fate a function of deposition site, physicochemical properties (including solubility and any toxicity), and sometimes deposited mass or number concentration. Clearance routes from the various regions of the respiratory tract have been discussed previously in detail (U.S. Environmental Protection Agency, 1996a; Schlesinger et al., 1997). They are schematically shown in Figure 6-11 (for extrathoracic and tracheobronchial regions) and in Figure 6-12 (for poorly soluble particle clearance from the alveolar region) and are reviewed only briefly below.

TABLE 6-2. OVERVIEW OF RESPIRATORY TRACT PARTICLE CLEARANCE AND TRANSLOCATION MECHANISMS

Extrathoracic region (ET)
- Mucociliary transport
- Sneezing
- Nose wiping and blowing
- Dissolution and absorption into blood

Tracheobronchial region (TB)
- Mucociliary transport
- Endocytosis by macrophages/epithelial cells
- Coughing
- Dissolution and absorption into blood/lymph

Alveolar region (A)
- Macrophages, epithelial cells
- Dissolution and absorption into blood/lymph

Source: Schlesinger (1995).

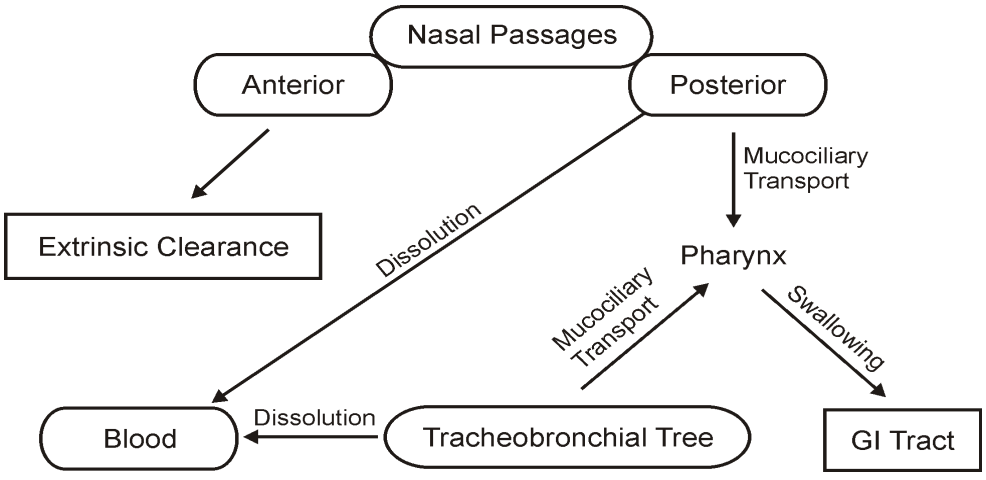

Figure 6-11. Major clearance pathways for particles deposited in the extrathoracic region and tracheobronchial tree.

Source: Adapted from Schlesinger et al. (1997).

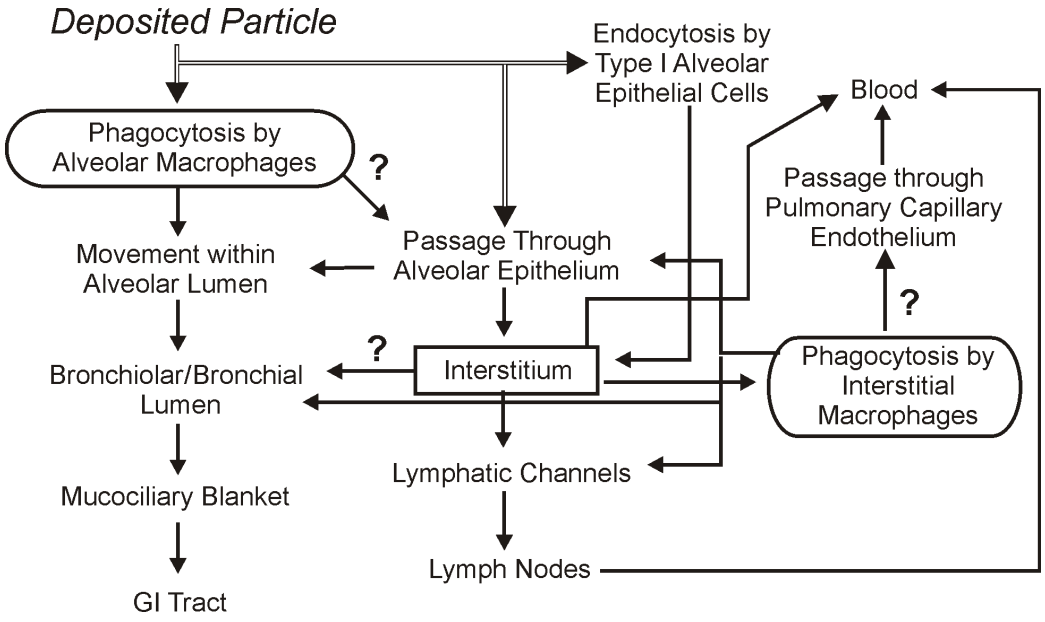

Figure 6-12. Known and suspected (?) clearance pathways for poorly soluble particles depositing in the alveolar region. (The magnitude of various pathways may depend upon size of deposited particle.)

Source: Modified from Schlesinger et al. (1997).

6.3.1.1 Extrathoracic Region

The clearance of poorly soluble particles deposited in the posterior portions of the nasal passages occurs via mucociliary transport, with the general flow of mucus being towards the nasopharynx. Mucus flow in the most anterior portion of the nasal passages is forward, clearing deposited particles to the vestibular region where removal occurs by sneezing, wiping, or blowing. Soluble material deposited on the nasal epithelium is accessible to underlying cells via diffusion through the mucus. Dissolved substances may be translocated subsequently into the bloodstream. The nasal passages have a rich vasculature, and uptake into the blood from this region may occur rapidly.

Clearance of poorly soluble particles deposited in the oral passages is by coughing and expectoration or by swallowing into the gastrointestinal tract. Soluble particles are likely to be rapidly absorbed after deposition, but deposition depends on the rate of dissolution of the particle and the molecular size of the solute.

6.3.1.2 Tracheobronchial Region

Poorly soluble particles deposited within the TB region are cleared by mucociliary transport towards the oropharynx, followed by swallowing. Poorly soluble particles also may traverse the epithelium by endocytotic processes, entering the peribronchial region, where they may be phagocytized by airway macrophages (which can then be cleared via the mucociliary blanket), or enter the airway lumen from the bronchial or bronchiolar mucosa. Soluble particles may be absorbed through the epithelium into the blood. It has been shown that blood flow affects translocation from the TB region in that decreased bronchial blood flow is associated with increased airway retention of soluble particles (Wagner and Foster, 2001). There is, however, evidence that even soluble particles may be cleared by mucociliary transport (Bennett and Ilowite, 1989; Matsui et al., 1998; Wagner and Foster, 2001).

6.3.1.3 Alveolar Region

Clearance from the A region occurs via a number of mechanisms and pathways. Particle removal by macrophages is the main nonabsorptive clearance process in this region. Alveolar macrophages, which reside on the epithelium, phagocytize and transport deposited material that they contact by random motion or via directed migration under the influence of chemotactic factors.

Although alveolar macrophages normally account for up to about 3 to 19% of the total alveolar cells in healthy, nonsmoking humans and other mammals (Crapo et al., 1982), the actual cell count may be altered by particle loading. The magnitude of any increase in cell number is related to the number of deposited particles rather than to total deposition by weight. Thus, equivalent masses of an identically deposited substance would not produce the same response if particle sizes differed; and the deposition of smaller particles would tend to result in a greater elevation in macrophage number than would deposition of larger particles.

Particle-laden macrophages may be cleared from the A region via a number of pathways. As noted in Figure 6-11, this includes transport toward the pharynx via the mucociliary system after the cells reach the distal terminus of the mucus blanket; movement within the interstitium to a lymphatic channel; or possibly traversing of the alveolar-capillary endothelium and directly entering the bloodstream. Note that the latter pathway of particle-laden macrophages entering the bloodstream is speculative and not yet demonstrated. Particles within the lymphatic system

may be translocated to TB lymph nodes, which can become reservoirs of retained material. Particles subsequently reaching the postnodal lymphatic circulation will enter the blood. Once in the systemic circulation, these particles can travel to extrapulmonary organs. Deposited particles (especially those < 0.5 to 1.0 μm) that are not ingested by alveolar macrophages may enter the interstitium and be phagocytized by resident interstitial macrophages, and may travel to perivenous, peribronchiolar or subpleural sites where they become trapped, increasing particle burden. The migration and grouping of particles and macrophages within the lungs can lead to the redistribution of initially diffuse deposits into focal aggregates. Some particles or components can bind to epithelial cell membranes, to macromolecules, or to other cell components, delaying their clearance from the lungs.

Churg and Brauer (1997) examined lung autopsy tissue from 10 people who had never smoked from Vancouver, Canada. They noted that the geometric mean particle diameter (GMPD) in lung parenchymal tissue was 0.38 μm (σ_g = 2.4). Ultrafine particles accounted for less than 5% of the total retained particulate mass. Metal particles had a GMPD of 0.17 μm and silicates, 0.49 μm. Ninety-six percent of retained PM had a GMPD less than 2.5 μm.
A subsequent study considered retention of ambient particles in the lungs. Brauer et al. (2001) showed that small particles could undergo significant steady-state retention within the lungs. Using lungs obtained at autopsy from long-term, nonsmoking residents of an area having high levels of ambient PM (Mexico City, Mexico) and those from an area with relatively low PM levels (Vancouver, Canada), the investigators measured the particle concentration per gram of lung within the parenchyma. They found that living in the high PM region resulted in significantly greater retention of both fine and ultrafine particles within the lungs: levels in the lungs from residents of Mexico City contained over 7.4 times the concentration of these particles as did lungs from residents of Vancouver. These results indicate a clear relationship between ambient exposure concentration and retention in the A region.

Clearance by the absorptive mechanism involves dissolution in the alveolar surface fluid followed by transport through the epithelium and into the interstitium, and then diffusion into the lymph or blood. Solubility is influenced by the particle's surface to volume ratio and other properties, such as hydrophilicity and lipophilicity (Mercer, 1967; Morrow, 1973; Patton, 1996).

6.3.2 Clearance Kinetics

The kinetics of clearance have been reviewed in U.S. Environmental Protection Agency (1996a) and in a number of monographs (e.g., Schlesinger et al., 1997) and are discussed only briefly here. The actual time frame over which clearance occurs affects the cumulative dose delivered to the respiratory tract, as well as the dose delivered to extrapulmonary organs.

6.3.2.1 Extrathoracic Region

Mucus flow rates in the posterior nasal passages are highly nonuniform, but the median rate in a healthy adult human is about 5 mm/min, resulting in a mean anterior to posterior transport time of about 10 to 20 min for poorly soluble particles (Rutland and Cole, 1981; Stanley et al., 1985). Particles deposited in the anterior portion of the nasal passages are cleared more slowly by mucus transport and are usually more effectively removed by sneezing, wiping, or nose blowing (Fry and Black, 1973; Morrow, 1977).

6.3.2.2 Tracheobronchial Region

Mucus transport in the TB tree occurs at different rates in different local regions: the velocity of movement is fastest in the trachea, and it becomes progressively slower in more distal airways. In healthy nonsmoking humans, using noninvasive procedures and no anesthesia, average tracheal mucus transport rates have been measured at 4.3 to 5.7 mm/min (Yeates et al., 1975, 1981; Foster et al., 1980; Leikauf et al., 1981, 1984), whereas that in the main bronchi has been measured at ≈2.4 mm/min (Foster et al., 1980). Estimates for human medium bronchi range between 0.2 to 1.3 mm/min, while those in the most distal ciliated airways range down to 0.001 mm/min (Morrow et al., 1967; Cuddihy and Yeh, 1988; Yeates and Aspin, 1978).

The total duration of bronchial clearance or some other time parameter is often used as an index of mucociliary kinetics. Although clearance from the TB region is generally rapid, experimental evidence, discussed in U.S. Environmental Protection Agency (1996a), was shown that a fraction of material deposited in the TB region is retained much longer than the 24 h commonly considered the outer range of clearance time for particles within this region (Stahlhofen et al., 1986a,b; Scheuch and Stahlhofen, 1988; Smaldone et al., 1988). A study by Asgharian et al. (2001) showed that it is not necessary to have a slow- and fast-phase TB clearance for particles to be retained longer than 24 h. Based upon asymmetric stochastic

human-lung modeling-data, inter-subject variability in path length and the number of generations to the alveoli, may result in some material reaching the alveoli even with shallow breathing, this can explain experimental observations while still describing TB clearance as a single compartment model. Other studies described below, however, do support the concept that TB regional clearance consists of both a fast and a slow component.

Falk et al. (1997) studied clearance in healthy adults using monodisperse polytetraflouethylene (PTFE; Teflon) particles (6.2 μm) inhaled at two flow rates. Each subject inhaled twice at two flow rates (0.45 and 0.045 L/s). Theoretical calculations indicated that the particles inhaled at 0.45 L/s should deposit mainly in large bronchi and in the alveolar region; whereas the particles inhaled at 0.045 L/s should deposit mainly in small ciliated airways. At twenty-four hours after inhalation about half of the particles inhaled by both modes of inhalation had cleared. Clearance beyond twenty-four hours was biphasic. For the inhalation rate of 0.45 L/s, 15% cleared with a half-time of 3.4 days and 85% with a half-time of 190 days. For the inhalation rate of 0.045 L/s, 20% cleared with a half-time of 2.0 days and 80% with a half-time of 50 days. The results indicate that a considerable fraction of particles deposited in small ciliated airways had not cleared within 24 h, and that these particles cleared differently from particles deposited in the alveolar region. The authors observed that the experimental data agreed well with the theoretical predictions. Camner et al. (1997) also noted that clearance from the TB region was incomplete by 24 h postexposure and suggested that this may be caused by incomplete clearance from bronchioles. Healthy adults inhaled teflon particles (6, 8, and 10 μm) under low flow rates to maximize deposition in the small ciliated airways. The investigators noted a decrease in 24-h retention with increasing particle size, indicating a shift toward either a smaller retained fraction, deposition more proximally in the respiratory tract, or both. They calculated that a large fraction, perhaps as high as 75% of particles depositing in generations 12 through 16, was still retained at 24 h postexposure.

In a study to examine retention kinetics in the TB tree (Falk et al., 1999), nonsmoking healthy adults inhaled radioactively tagged 6.1-μm particles at both a normal flow rate and a slow flow rate designed to deposit particles preferentially in small ciliated airways. Lung retention was measured from 24 h to 6 mo after exposure. Following normal flow rate inhalation, 14% of the particles retained at 24 h cleared with a half-time of 3.7 days and 86% with a half-time of 217 days. Following slow flow rate inhalation, 35% of the particles retained

at 24 h cleared with a half-time of 3.6 days and 65% with a half-time of 170 days. Estimates using a number of mathematical models indicated higher deposition in the bronchiolar region (generations 9 through 15) with the slow rate inhalation compared to the normal rate. The experimental data and predictions of the deposition modeling indicated that 40% of the particles deposited in the conducting airways during the slow inhalation were retained after 24 h. The particles that cleared with the shorter half-time were mainly deposited in the bronchiolar region, but only about 25% of the particles deposited in this region cleared in this phase. This study provided additional support for a phase of slow clearance from the bronchial tree.

The underlying sites and mechanisms of long-term TB retention in the smaller airways are not known. Some proposals were presented in the 1996 PM AQCD (U.S. Environmental Protection Agency, 1996a). This slow clearing TB compartment likely is associated with bronchioles < 1 mm in diameter (Lay et al., 1995; Kreyling et al., 1999; Falk et al., 1999). In a study in which an adrenergic agonist was used to stimulate mucus flow to examine the role of mucociliary transport in the bronchioles, clearance from the smaller airways was not influenced by the drug, suggesting to the investigators that mucociliary transport was not as an effective clearance mechanism from this region as it is in larger airways (Svartengren et al., 1998, 1999). Although slower or less effective mucus transport may result in longer retention times in small airways, other factors may account for long-term TB retention. One possibility is that particles are displaced into the gel phase by the surface tension forces of the liquid lining the small airways (Gehr et al., 1990, 1991). The issue of long-term particle retention in the TB tree certainly is not resolved.

Long-term TB retention patterns are not uniform. An enhancement at bifurcation regions (Radford and Martell, 1977; Henshaw and Fews, 1984; Cohen et al., 1988), is likely the result of both greater deposition and less effective mucus clearance within these areas. Thus, doses calculated based on uniform surface retention density may be misleading, especially if the material is toxicologically slow acting.

6.3.2.3 Alveolar Region

Particles deposited in the A region generally are retained longer than are those deposited in airways cleared by mucociliary transport. There are limited data on alveolar clearance rates in humans. Within any species, reported clearance rates vary widely because, in part, of different

properties of the particles used in the various studies. Furthermore, some chronic experimental studies have employed high concentrations of poorly soluble particles that may have interfered with normal clearance mechanisms, resulting in clearance rates different from those that would typically occur at lower exposure levels. Prolonged exposure to high particle concentrations is associated with what is termed particle "overload." This is discussed in greater detail in Section 6.4.

There are numerous pathways of A-region clearance, and the utilization of these may depend on the nature of the particles being cleared. Little is known concerning relative rates along specific pathways. Thus, generalizations about clearance kinetics are difficult to make. Nevertheless, A-region clearance is usually described as a multiphasic process, with each phase representing removal by a different mechanism or pathway and often characterized by increased retention half-times following toxicant exposure.

The initial uptake of deposited particles by alveolar macrophages is very rapid and generally occurs within 24 h of deposition (Lehnert and Morrow, 1985; Naumann and Schlesinger, 1986; Lay et al., 1998). The time for clearance of particle-laden alveolar macrophages via the mucociliary system depends on the site of uptake relative to the distal terminus of the mucus blanket at the bronchiolar level. Furthermore, clearance pathways and subsequent kinetics may depend to some extent on particle size. For example, some smaller ultrafine particles (< 0.02 μm) may be less effectively phagocytosed than larger ones (Oberdörster, 1993).

Nonphagocytized particles may penetrate into the interstitium within a few hours following deposition. This transepithelial passage seems to increase as particle loading increases, especially to that level above which macrophage numbers increase (Ferin, 1977; Ferin et al., 1992; Adamson and Bowden, 1981). It also may be particle-size dependent because insoluble ultrafine particles (< 0.1 μm diameter) of low intrinsic toxicity show increased access to the interstitum and greater lymphatic uptake than do larger particles of the same material (Oberdörster et al., 1992; Ferin et al., 1992). However, ultrafine particles of different materials may not enter the interstitium to the same extent. Similarly, a depression of phagocytic activity, a reduction in macrophage ability to migrate to sites of deposition (Madl et al., 1998), or the deposition of large numbers of ultrafine particles may increase the number of free particles in the alveoli, perhaps enhancing removal by other routes. In any case, free particles may reach the

lymph nodes perhaps within a few days after deposition (Lehnert et al., 1988; Harmsen et al., 1985) although this route is not definitive and may be species dependent.

Kreyling et al. (2002) studied the translocation of insoluble ultrafine ^{192}Ir radiolabeled particles (15 and 80 nm CMD) inhaled by healthy, young adult, male rats ventilated for 1 h via an endotracheal tube. At time points ranging from 6 h to 7 d, rats were sacrificed; and a complete balance of ^{192}Ir activity retained in the body and cleared by excretion was determined. Thoracic deposition fractions of inhaled 15 and 80 nm particles were 0.49 and 0.28, respectively. One week after inhalation, particles were predominantly cleared from the lungs into the gastrointestinal tract and eliminated in feces. Minute particle translocation of < 1% of the deposited particles into secondary organs such as liver, spleen, heart, and brain was measured after systemic uptake from the lungs. The translocated fraction of the 80-nm particles was about an order of magnitude less than that of 15-nm particles. In further investigations, the biokinetics of ultrafine particles and soluble ^{192}Ir was studied after administration by either gavage or intratracheal instillation or intravenous injection. These studies confirmed the low solubility of the ^{192}Ir particles and showed that (1) particles were neither dissolved nor absorbed from the gut, (2) systemically circulating particles were rapidly and quantitatively accumulated and retained in the liver and spleen, and (3) soluble ^{192}Ir instilled in the lungs was rapidly excreted via urine with little retention in the lungs and other organs. This study indicates that only a rather small fraction of ultrafine ^{192}Ir particles are translocated from peripheral lungs to systemic circulation and extrapulmonary organs following short-term exposures.

Oberdörster et al. (2002) exposed Fisher rats for 6 h to ^{13}C-labeled ultrafine carbon particles (CMDs = 20 to 29 nm) at concentrations of 80 or 180 μg/m^3 in compartmentalized whole-body inhalation exposure chambers. Animals were sacrificed at 0.5, 18, and 24 h postexposure; and ^{13}C levels were determined in lung, liver, heart, kidney, olfactory bulb, and brain. Interestingly, the ^{13}C retained in lung at 0.5 h postexposure was ~70% lower than predicted for ultrafine particles in the rat lung by the MPPD model described below (Section 6.6). Also of much interest, significant increases over control levels of ^{13}C in lung and liver (but not the other organs) were observed at all postexposure time points following exposures to 180 μg/m^3 but only after 18- and 24-h for the 80 μg/m^3 exposures. This implies translocation of the insoluble ^{13}C ultrafine particles to liver in < 18-24 h postexposure at the lower 80 μg/m^3 exposure and, possibly, even more rapid translocation to liver (by 0.5 h) at

sufficiently higher concentrations. The relative increase due to translocation from lung to liver is difficult to estimate, given potential contributions to liver ^{13}C levels of carbon particles translocated from the GI tract as derived from ingestion of particles by the rats while grooming during and after the whole-body exposures.

The extent of lymphatic uptake of particles may depend on the effectiveness of other clearance pathways in that lymphatic translocation likely increases when the phagocytic activity of alveolar macrophages decreases. This may be a factor in lung overload. However, it seems that the deposited mass or number of particles must exceed some threshold below which increases in loading do not affect translocation rate to the lymph nodes (Ferin and Feldstein, 1978; LaBelle and Brieger, 1961). In addition, the rate of translocation to the lymphatic system may be somewhat particle-size dependent. Although no human data are available, translocation of latex particles to the lymph nodes of rats was greater for 0.5- to 2-μm particles than for 5- and 9-μm particles (Takahashi et al., 1992). Translocation of 3 μm particles has also been reported (Snipes and Clem, 1981). On the other hand, translocation to the lymph nodes was similar for both 0.4-μm barium sulfate or 0.02-μm gold colloid particles (Takahashi et al., 1987). It seems that particles $\leq$ 2 μm clear to the lymphatic system at a rate independent of size; and it is particles of this size, rather than those $\geq$ 5 μm, that would have significant deposition within the A region following inhalation. In any case, the normal rate of translocation to the lymphatic system is quite slow; and elimination from the lymph nodes is even slower, with half-times estimated in tens of years (Roy, 1989).

Soluble particles depositing in the A region may be cleared rapidly via absorption through the epithelial surface into the blood. Actual rates depend on the size of the particle (i.e., solute size), with smaller molecular weight solutes clearing faster than larger ones. Absorption may be considered as a two-stage process: first, deposited particles are dissolved; second, this dissolved material moves into the blood circulation. Each of these stages may be time dependent. The rate of dissolution depends on a number of factors, including particle surface area and chemical structure. A portion of the dissolved material may be absorbed more slowly because of binding to respiratory tract components. Accordingly, there is a very wide range for absorption rates, depending on the physicochemical properties of the material deposited.

As indicated in both the toxicology and epidemiology chapters (Chapters 7 and 8) of this document, concern exists about how ambient PM affects the cardiovascular system. Thus, an

important dosimetric issue involves the pathways by which inhaled and deposited particles in the lungs could affect extrapulmonary systems. Several studies (Huchon et al., 1987; Peterson et al., 1989; Morrison et al., 1998) had earlier investigated lung clearance of labeled macromolecule solutes with widely varying molecular weight and labeled albumin as well as albumin ultrafine aggregates. Clearance rates found by these studies were much slower than for some more recent studies described below which suggests the possibility of a fast clearing pathway for solid ultrafine particles. Several newer studies have also evaluated possible pathways by which PM, constituents of PM, or cytokines released by the respiratory tract in response to PM could affect systems distal to the respiratory tract.

For example, Takenaka et al. (2001) exposed rats by inhalation to 0.015 μm particles of elemental silver (Ag) and found elevated Ag levels in various extrapulmonary organs up to 7 days postexposure. They found that the amount of Ag in the lungs decreased rapidly with time; by day 7, only about 4% of the initial lung burden remained. On the exposure day, Ag was already found in the blood. By 1 day postexposure, Ag had been distributed to the liver, kidney, heart, and brain. The Ag concentration was highest in the kidney, followed by the liver, and then the heart. A similar clearance pattern was found after intratracheal instillation of $AgNO_3$ solution. Therefore, the investigators hypothesized that the rapid clearance of ultrafine silver particles was due to rapid dissolution into the lung fluid and subsequent diffusion into the bloodstream, although a possibility of direct translocation of solid particles into the bloodstream was not excluded. The investigators also instilled an aqueous suspension of elemental Ag particles (100+ nm) into some animals. In this case, there was more retention in the lungs, which was ascribed to phagocytic accumulation of agglomerated particles in alveolar macrophages and slow dissolution of particles in cells. Thus, this study also suggested that particle size and the tendency of particles to aggregate can affect the translocation pathway from the lungs.

In another study, Nemmar et al. (2001) evaluated the movement of radiolabeled (^{99m}Tc) ultrafine particles out of the lungs of hamsters receiving a single IT instillation of albumin colloid particles ($\leq$80 nm) and killed after 5, 15, 30, and 60 min. Blood radioactivity, at 5, 15, 30, and 60 min, respectively, expressed as percentage of total body radioactivity per gram blood, was 2.88 ± 0.80%, 1.30 ± 0.17%, 1.52 ± 0.46%, and 0.21 ± 0.06%. Liver radioactivity, at 5, 15, 30, and 60 min, respectively, expressed as a percentage of total radioactivity per organ, was

0.10 ± 0.07%, 0.23 ± 0.06%, 1.24 ± 0.27%, and 0.06 ± 0.02%. Lower values were observed in the heart, spleen, kidneys, and brain. Dose dependence was assessed at 30 min after instillation of 10 μg and 1 μg ^{99m}Tc-albumin per animal (n = 3 at each dose), and values of the same relative magnitudes as after instillation of 100 μg were obtained. The authors concluded that a significant fraction of ultrafine ^{99m}Tc-albumin diffuses rapidly from the lungs into the systemic circulation.

Nemmar et al. (2002) investigated the extent to which inhaled particles entered into the systemic circulation in 5 healthy volunteers who inhaled "Technegas," an aerosol consisting mainly of ultrafine ^{99m}Tc -labeled carbon particles (< 100 nm). Radioactivity detected in blood at 1 minute, reached a maximum between 10 and 20 minutes, and remained at this level for up to 60 minutes. Thin layer chromatography of blood showed that in addition to a species corresponding to oxidized ^{99m}Tc (i.e., pertechnetate) there was also a species corresponding to particle-bound ^{99m}Tc. Gamma camera images showed substantial radioactivity over the liver and other areas of the body. These workers concluded that inhaled ^{99m}Tc-labeled ultrafine carbon particles pass rapidly into the systemic circulation. This appears to suggest that ultrafine particles can rapidly diffuse from the lungs into the systemic circulation, thus providing a pathway by which ambient PM may rapidly affect the heart and other extrapulmonary organs. However, the stability of the ^{99m}Tc label of ultrafine particles could pose a serious problem in the interpretation of the study. If the ^{99m}Tc label is leached from the particles, it can quickly spread to other organs.

Results in marked contrast to Nemmar et al. (2001, 2002) have been reported by Brown et al. (2002). The deposition and clearance of a ^{99m}Tc-labeled ultrafine aerosol (CMD, 33 ± 2 nm; AMD, 61 ± 4nm) were studied by Brown et al. (2002) in 9 healthy human adult volunteers (aged 40 to 67 yrs) and 10 COPD patients (45 to 70 yrs) with moderate to severe airway obstruction. No differences in clearance rates were detected between healthy and COPD patients; nor was any rapid accumulation of radiolabeled particles found in the liver, based on analyses at 10-min increments up to two hours postexposure. Brown et al. (2002) noted that during Technegas generation by the method employed by Nemmar et al. (2002), the presence of minimal oxygen (0.1 to 0.2%) can cause the formation of Pertechnegas. Unlike Technegas, which is generally stable in the lung, Pertechnegas is rapidly ionized into pertechnetate and, with Pertechnegas, the radiolabel quickly dissociates from the ultrafine particles following deposition

in the lung. Highly soluble in normal saline, pertechnetate clears rapidly from the lung with a half-time of ~10 minutes and accumulates most notably in the bladder, stomach, thyroid, and salivary glands. Brown et al. (2002) contend that the findings reported by Nemmar et al. (2002) are consistent with pertechnetate clearance, but not insoluble ultrafine particles. Burch (2002) also suggested that the Nemmar et al. (2002) findings were due to a Pertechnegas-like aerosol and not Technegas (which shows < 3% lung clearance by 24-h post inhalation). Thus, the dosimetric pathways by which inhaled particles may rapidly exert acute cardiovascular or other systemic effects remain to be delineated.

6.3.3 Interspecies Patterns of Clearance

The inability to study the retention of certain materials in humans for direct risk assessment requires use of laboratory animals. Because dosimetry depends on clearance rates and routes, adequate toxicological assessment necessitates that clearance kinetics in such animals be related to those in humans. The basic mechanisms and overall patterns of clearance from the respiratory tract are similar in humans and most other mammals. However, regional clearance rates can show substantial variation between species, even for similar particles deposited under comparable exposure conditions, as extensively reviewed elsewhere (U.S. Environmental Protection Agency, 1996a; Schlesinger et al., 1997; Snipes et al., 1989).

In general, there are species-dependent rate constants for various clearance pathways. Differences in regional and total clearance rates between some species are a reflection of differences in mechanical clearance processes. For example, the relative proportion of particles cleared from the A region in the short- and longer-term phases differs between laboratory rodents and larger mammals, with a greater percentage cleared in the faster phase in rodents. A recent study (Oberdörster et al., 1997) showed inter-strain differences in mice and rats in the handling of particles by alveolar macrophages. Macrophages of B6C3F1 mice could not phagocytize 10-µm particles, but those of C57 black/6J mice could. In addition, the nonphagocytized 10-µm particles were efficiently eliminated from the alveolar region; whereas previous work in rats found that these large particles were retained persistently after uptake by macrophages (Snipes and Clem, 1981; Oberdörster et al., 1992). The ultimate implication of interspecies differences in clearance that need to be considered in assessing particle dosimetry is

that the retention of deposited particles can differ between species and may result in differences in response to similar PM exposure atmospheres.

Hsieh and Yu (1998) summarized the existing data on pulmonary clearance of inhaled, poorly soluble particles in the rat, mouse, guinea pig, dog, monkey, and human. Clearance at different initial lung burdens, ranging from 0.001 to 10 mg particles/g lung, was analyzed using a two-phase exponential decay function. Two clearance phases in the alveolar region, namely fast and slow, were associated with mechanical clearance along two pathways, the former with the mucociliary system and the latter with the lymph nodes. Rats and mice were fast clearers in comparison to the other species. Increasing the initial lung burden resulted in an increasing mass fraction of particles cleared by the slower phase. As lung burden increased beyond 1 mg particles/g lung, the fraction cleared by the slow phase increased to almost 100% for all species. However, the rate for the fast phase was similar in all species and did not change with increasing lung burden of particles; whereas the rate for the slow phase decreased with increasing lung burden. At elevated burdens, the effect on clearance rate was greater in rats than in humans, an observation consistent with previous findings (Snipes, 1989).

6.3.4 Factors Modulating Clearance

A number of factors have previously been assessed in terms of modulation of normal clearance patterns, including age, gender, workload, disease, and irritant inhalation. Such factors have been discussed in detail previously (U.S. Environmental Protection Agency, 1996a).

6.3.4.1 Age

Studies described in the 1996 PM AQCD (U.S. Environmental Protection Agency, 1996a) indicated that there appeared to be no clear evidence for any age-related differences in clearance from the lung or total respiratory tract, either from child to adult, or young adult to elderly. Studies of mucociliary function have shown either no changes or some slowing in mucus clearance function with age after maturity, but at a rate that would be unlikely to significantly affect overall clearance kinetics.

6.3.4.2 Gender

Previously reviewed studies (U.S. Environmental Protection Agency, 1996a) indicated no gender-related differences in nasal mucociliary clearance rates in children (Passali and Bianchini Ciampoli, 1985) nor in tracheal transport rates in adults (Yeates et al., 1975).

6.3.4.3 Physical Activity

The effect of increased physical activity on mucociliary clearance is unresolved: previously discussed studies (U.S. Environmental Protection Agency, 1996a) indicate either no effect or an increased clearance rate with exercise. There are only limited data concerning changes in A region clearance with increased activity levels (Sweeney et al., 1990). Breathing with an increased tidal volume was noted to increase the rate of particle clearance from the A region, and this was suggested to result from distension-related evacuation of surfactant into proximal airways leading to a facilitated movement of particle-laden macrophages or uningested particles because of the accelerated motion of the alveolar fluid film (John et al., 1994).

6.3.4.4 Respiratory Tract Disease

Various respiratory tract diseases are associated with clearance alterations. Evaluation of clearance in individuals with lung disease requires careful interpretation of results because differences in deposition of particles used to assess clearance function may occur between normal individuals and those with disease; this would directly affect the measured clearance rates, especially in the tracheobronchial tree. Studies reported in the 1996 PM AQCD (U.S. Environmental Protection Agency, 1996a) noted findings of (a) slower nasal mucociliary clearance in humans with chronic sinusitis, bronchiectasis, rhinitis, or cystic fibrosis and (b) slowed bronchial mucus transport associated with bronchial carcinoma, chronic bronchitis, asthma, and various acute respiratory infections. However, a study by Svartengren et al. (1996a) concluded, based on deposition and clearance patterns, that particles cleared equally effectively from the small ciliated airways of healthy humans and those with mild to moderate asthma; but, this similarity was attributed to effective asthma therapy.

In another study, Svartengren et al. (1996b) examined clearance from the TB region in adults with chronic bronchitis who inhaled 6-μm Teflon particles. Based on calculations, particle deposition was assumed to be in small ciliated airways at low flow and in larger airways

at higher flow. The results were compared to those obtained in healthy subjects from other studies. At low flow, a larger fraction of particles was retained over 72 h in people with chronic bronchitis compared to healthy subjects, indicating that clearance resulting from spontaneous cough could not fully compensate for impaired mucociliary transport in small airways. For larger airways, patients with chronic bronchitis cleared a larger fraction of the deposited particles over 72 h than did healthy subjects, but this was reportedly because of differences in deposition resulting from airway obstruction.

Cough is an important mechanism of clearance from the TB region, under some circumstances. Although cough can be a reaction to an inhaled stimulus, in most individuals with respiratory infections and disease, spontaneous coughing also serves to clear the upper bronchial airways by dislodging mucus from the airway surface. Recent studies confirm that this mechanism likely plays a significant role in clearance for people with mucus hypersecretion, at least for the upper bronchial tree, and for a wide range of deposited particle sizes (0.5 to 5 μm) (Toms et al., 1997; Groth et al., 1997). There appears to be a general trend towards an association between the extent (i.e., number) of spontaneous coughs and the rate of particle clearance; faster clearance is associated with a greater number of coughs (Groth et al., 1997). Thus, recent evidence continues to support cough as an adjunct to mucociliary movement in the removal of particles from the lungs of individuals with COPD. However, some recent evidence suggests that, like mucociliary function, cough-induced clearance may become depressed with worsening airway disease. Noone et al. (1999) found that the efficacy of clearance via cough in patients with primary ciliary dyskinesia (who rely on coughing for clearance because of immotile cilia) correlated with lung function in that decreased cough clearance was associated with decreased percentage of predicted FEV_1.

Earlier studies (U.S. Environmental Protection Agency, 1996a) indicated that rates of A region particle clearance were reduced in humans with COPD and in laboratory animals with viral infections, whereas the viability and functional activity of macrophages were impaired in human asthmatics and in animals with viral-induced lung infections. However, any modification of the functional properties of macrophages appears to be injury-specific in that they reflect the nature and anatomic pattern of disease.

One factor that may affect clearance of particles is the integrity of the epithelial surface lining of the lungs. Damage or injury to the epithelium may result from disease or from the

inhalation of chemical irritants or cigarette smoke. Earlier studies performed with particle instillation showed that alveolar epithelial damage in mice at the time of deposition resulted in increased translocation of inert carbon to pulmonary interstitial macrophages (Adamson and Hedgecock, 1995). A similar response was observed in a more recent assessment (Adamson and Prieditis, 1998), in which silica (< 0.3 μm) was instilled into a lung having alveolar epithelial damage (as evidenced by increased permeability) and particles were noted to reach the interstitium and lymph nodes.

6.3.4.5 Inhaled Irritants

Inhaled irritants of various kinds can affect clearance functions in both humans and laboratory animals (Wolff, 1986; Schlesinger, 1990). As previously reviewed in the 1996 PM AQCD, single exposures to certain materials may increase or decrease the overall rate of TB clearance, often depending on the irritant exposure concentration, with alterations in clearance rates generally being transient (i.e., lasting < 24 hrs). Repeated exposures, however, may result in increased intra-individual variability in clearance rates and persistently slowed clearance. Alveolar region clearance can also be altered by acute and chronic exposures to inhaled irritants, as noted in the 1996 PM AQCD, including acceleration or slowing of clearance depending on the specific irritant inhaled and/or exposure duration. Of particular interest are studies noted in the 1996 PM AQCD which (a) show increased numbers of macrophages recovered by bronchoalveolar lavage in smoke-exposed humans and animals and (b) retardation of particle clearance from alveolar regions of the lung in cigarette smokers, in part, due to impaired alveolar macrophage-mediated clearance.

6.4 PARTICLE OVERLOAD

Experimental studies using some laboratory rodents have employed high exposure concentrations of relatively nontoxic, poorly soluble particles. These particle loads interfered with normal clearance mechanisms and produced clearance rates different from those that would occur at lower exposure levels. Prolonged exposure to high particle concentrations is associated with a phenomenon that has been termed particle "overload," defined as the overwhelming of macrophage-mediated clearance by the deposition of particles at a rate that exceeds the capacity

of that clearance pathway. It has been suggested that volumetric overloading will begin when particle retention approaches 1 mg particles/g lung tissue (Morrow, 1988) and that, in the rat, overload is more dependent upon total particle surface area (Tran et al., 2000). The importance of surface area to inflammation and the tumorogenic response is detailed in an analysis performed by Driscoll (1995). He observed a positive tumor response associated with pulmonary inflammation and epithelial cell proliferation in the rat. Moreover, there was a significant relationship between lung particle dose, expressed as particle surface area/lung, and the lung tumor response. There was a positive correlation between the surface area characteristics of various chemically distinct particulate materials and tumorogenic activity. Overload is a nonspecific effect noted in experimental studies using many different kinds of poorly soluble particles and results in A region clearance slowing or stasis, with an associated chronic inflammation and aggregation of macrophages in the lungs and increased translocation of particles into the interstitium.

The relevance of lung overload to humans exposed to poorly soluble, nonfibrous particles remains unclear. Although it is likely to be of little relevance for most "real world" ambient exposures, it may be of concern in interpreting some long-term experimental exposure data and, perhaps, also for occupational exposures. For example, it has been suggested that a condition called progressive massive fibrosis, which is unique to humans, has features indicating that dust overload is a factor in its pathogenesis (Green, 2000). This condition is associated with cumulative dust exposure and impaired clearance and can occur following high exposure concentrations associated with occupational situations. In addition, any relevance to humans is clouded by the suggestion that macrophage-mediated clearance is normally slower, and perhaps of less relative importance in overall clearance, in humans than in rats (Morrow, 1994) and that there can be significant differences in macrophage loading between species. On the other hand, overload may be a factor in individuals with compromised lungs even under normal exposure conditions. Thus, it has been hypothesized (Miller et al., 1995) that localized overload of particle clearance mechanisms in people with compromised lung status may occur whereby clearance is overwhelmed and results in morbidity or mortality from particle exposure.

6.5 COMPARISON OF DEPOSITION AND CLEARANCE PATTERNS OF PARTICLES ADMINISTERED BY INHALATION AND INTRATRACHEAL INSTILLATION

The most relevant exposure route by which to evaluate the toxicity of particulate matter is inhalation. However, many toxicological studies deliver particles by intratracheal instillation. This latter technique has been used because it is easy to perform; requires significantly less effort, cost, and amount of test material than does inhalation; and can deliver a known, exact dose of a toxicant to the lungs. It is also an extremely useful technique for mechanistic studies. Because particle disposition is a determinant of dose, it is important to compare deposition and clearance of particles delivered by these two routes in order to evaluate the relevance of studies using instillation. However, in most instillation studies, the effect of this route of administration on particle deposition and clearance per se was not examined. Although these parameters were evaluated in some studies, it has been very difficult to compare particle deposition/clearance between different inhalation and instillation studies because of differences in experimental procedures and in the manner by which particle deposition/clearance was quantitated. Thus, while instillation studies are valuable in providing mechanistic insights, inhalation studies are more appropriate for risk assessment. A recent paper provides a detailed evaluation of the role of instillation in respiratory tract dosimetry and toxicology studies (Driscoll et al., 2000). A short summary derived from this paper is provided below in this section.

The pattern of initial regional deposition is strongly influenced by the exposure technique used. Furthermore, the patterns within specific respiratory tract regions also are influenced in this regard. Depending on particle size, inhalation results in varying degrees of deposition within the ET airways, a region that is completely bypassed by instillation. Thus, differences in amount of particles deposited in the lower airways will occur between the two procedures, especially for those particles in the coarse mode. This is important if inhaled particles in ambient air affect the upper respiratory tract and such responses are then involved in the evaluation of health outcomes.

Exposure technique also influences the intrapulmonary distribution of particles, which potentially would affect routes and rates of ultimate clearance from the lungs and dose delivered to specific sites within the respiratory tract or to extrapulmonary organs. Intratracheal instillation tends to disperse particles fairly evenly within the TB region but can result in heterogeneous distribution in the A region, whereas inhalation tends to produce a more

homogeneous distribution throughout the major conducting airways as well as the A region for the same particles. Thus, inhalation results in a randomized distribution of particles within the lungs; whereas intratracheal instillation produces an heterogeneous distribution, in that the periphery of the lung receives little particle load and most of the instilled particles are found in regions that have a short path length from the major airways. Furthermore, inhalation results in greater deposition in apical areas of the lungs and less in basal areas; whereas intratracheal instillation results in less apical than basal deposition. Thus, toxicological effects from instilled materials may not represent those which would occur following inhalation, due to differences in sites of initial deposition following exposure. In addition, instillation studies generally deliver high doses to the lungs, much higher than those which would occur with realistic inhalation exposure. This would also clearly affect the initial dose delivered to target tissue and its relevance to ambient exposure.

Comparison of the kinetics of clearance of particles administered by instillation or inhalation have shown similarities, as well as differences, in rates for different clearance phases depending on the exposure technique used (Oberdörster et al., 1997). However, some of the differences in kinetics can be explained by differences in the initial sites of deposition. One of the major pathways of clearance involves particle uptake and removal via pulmonary macrophages. Dorries and Valberg (1992) noted that inhalation resulted in a lower percentage of particles recovered in lavaged cells and a more even distribution of particles among macrophages. More individual cells received measurable amounts of particles via inhalation than via intratracheal instillation; whereas with the latter, many cells received little or no particles and others received very high burdens. Furthermore, with intratracheal instillation, macrophages at the lung periphery contained few, if any, particles; whereas cells in the regions of highest deposition were overloaded, reflecting the heterogeneity of particle distribution when particles are administered via instillation. Additionally, both the relative number of particles phagocytized by macrophages as well as the percentage of these cells involved in phagocytosis is affected by the burden of administered particles, which is clearly different in instillation and inhalation (Suarez et al., 2001). Thus, when guinea pigs were administered latex microspheres (1.52 to 3.97 μm MMAD) by inhalation or instillation, the percentage of cells involved in phagocytosis, as well as the amount of particles per cell, were both significantly higher with the

latter route. The route of exposure, therefore, influences particle distribution in the macrophage population and could, by assumption, influence clearance pathways and clearance kinetics.

In summary, inhalation may result in deposition within the ET region, and the extent of deposition depends on the size of the particles used. Of course, intratracheal instillation bypasses this portion of the respiratory tract and delivers particles directly to the tracheobronchial tree. Although some studies indicate that short (0 to 2 days) and long (100 to 300 days) postexposure phases of clearance of insoluble particles delivered either by inhalation or intratracheal instillation are similar, other studies indicate that the percentage retention of particles delivered by instillation is greater than that for inhalation at least up to 30 days postexposure. Thus, there is some inconsistency in this regard.

Perhaps the most consistent conclusion regarding differences between inhalation and intratracheal instillation is related to the intrapulmonary distribution of particles. Inhalation generally results in a fairly homogeneous distribution of particles throughout the lungs. On the other hand, instillation results in a heterogeneous distribution, especially within the alveolar region, and focally high concentrations of particles. The bulk of instilled material penetrates beyond the major tracheobronchial airways, but the lung periphery is often virtually devoid of particles. This difference is reflected in particle burdens within macrophages, with those from animals inhaling particles having more homogeneous burdens and those from animals with instilled particles showing groups of cells with no particles and others with heavy burdens. This difference affects clearance pathways, dose to cells and tissues, and systemic absorption. Exposure method, thus, clearly influences dose distribution.

Dosimetric Considerations in Comparing Dosages for Inhalation, Instillation, and Exposure of Cultured Cells

There are three common experimental approaches for studying the biological effects of particulate material: inhalation, instillation, and in vitro. Inhalation studies are the more realistic physiologically, and thus the most applicable to risk assessment. However, because they are expensive, time consuming, and require specialized equipment and personnel, they must be supplemented by other techniques. In vitro studies using live cells are cost-effective, provide for precise dose delivery, and permit investigators who do not have access to inhalation techniques to perform mechanistic and comparative toxicity studies of particulate material.

Commonly, the initial information on likely mechanisms of action of particles is obtained through in vitro techniques.

Instillation studies, in which particles suspended in a carrier such as physiological saline are applied to the airways, have certain advantages over in vitro studies. The exposed cells have normal attachments to basement membranes and adjacent cells; circulatory support; surrounding cells; and normal endocrine, exocrine and neuronal relationships. Thus, instillation experiments can bridge between in vitro and inhalation studies as well as produce useful mechanistic and comparative toxicity information (Benson et al., 1986; Dorries and Valberg, 1992; Henderson et al., 1995; Kodavanti et al., 2002; Leong et al., 1998; Oberdörster et al., 1997; Osier and Oberdörster, 1997; Pritchard et al., 1985; Sabaitis et al., 1999; Suarez et al., 2001; Warheit et al., 1991). Although the tracheobronchial region is most heavily dosed, alveolar regions can also be exposed via instillation techniques (Kodavanti et al., 2002; Leong et al., 1998; Oberdörster et al., 1997; Pritchard et al., 1985; Suarez et al., 2001; Warheit et al., 1991).

Selection of the doses of particles used in instillation studies is important because it is easy to overwhelm normal defense mechanisms; but it is far from an exact process. If the goal is to expose tracheobronchial tree cell populations to particle concentrations (on a number of particles per unit surface area basis) that are similar to those occurring with ambient environmental exposures of humans (or to a known multiple of such exposures), dosimetric calculations must be performed. Such calculations require selecting characteristics associated with the particles, the exposed subject, and the environmental exposure scenario. Hence, each study can present a unique dosimetric analysis. In most cases, it will be useful to know the relationship between the surface doses in instillation studies and realistic local surface doses that could occur in vivo among those human subpopulations receiving maximum potential doses derived from "real-world" ambient air exposures. Although these subpopulations have not been completely defined (NRC, 2001), some characteristics of individuals do serve to enhance the local PM surface doses to respiratory tract cells. These characteristics include: exercise and mouth breathing (ICRP, 1994; NCRP, 1997); nonuniform inhaled air distribution such as occurs in COPD and chronic bronchitis (Smaldone et al., 1993; Subramaniam et al., 2003; Sweeney et al., 1995; Segal et al., 2002; Brown et al., 2002; Kim and Kang, 1997); impaired particle clearance as occurs in some disease states (Pavia, 1987; Pavia et al., 1980; Smaldone, 1993) and location near pollutant sources (Adgate et al., 2002; Zhu et al., 2002). In addition, even normal subjects

exposed by inhalation are expected to have numerous sites of high local particle deposition (specifically at bifurcations) within the tracheobronchial tree (Balásházy et al., 1999; Oldham et al., 2000; Kaye et al., 2000).

It is difficult to provide precise estimates of dose. However, by considering the several factors discussed above that enhance local surface doses, order of magnitude estimates can be made. As an example, consider the scenario of a physically active nose breather with chronic lung disease that lives near a PM source. The increase in minute ventilation during exercise, due to an increase in breaths per minute and in tidal volume, results in an increase in the number of particles inhaled per unit time. Even light exertion can double the minute ventilation, and heavy exertion can produce a six-fold increase (Phalen et al., 1985). Exercise can also cause a shift from nasal to oral breathing which bypasses the filtering efficiency of the nose (ICRP, 1994; NCRP, 1997), leading to increased exposure of the TB and A regions in a particle size-dependent fashion. As particle aerodynamic diameter increases from 1 to 10 μm, nasal region deposition at rest increases from 17 to 71% (NCRP, 1997). It is reasonable to assume that oral breathing can lead to a doubling of TB and A deposition of thoracic coarse particles ($PM_{10-2.5}$) in many individuals (see Figure 6-13). In disease states that produce uneven distribution of inhaled air, available measurements and models indicate that an enhancement factor of 2 to 5 is realistic for surface doses (Bennett et al., 1997b; Brown et al., 2002; Kim and Kang, 1997; Miller et al., 1995; Segal et al., 2002).

The airflow patterns at airway bifurcations lead to high surface deposition doses of inhaled particles in the TB region. An enhanced deposition of particles (for all sizes that have been examined) is seen at bifurcations in the TB tree (Bell and Friedlander, 1973; Schlesinger et al., 1982; Kim and Iglesias, 1989; Kim et al., 1994; Kim and Fisher, 1999; Balásházy et al., 1999; Kaye et al., 2000; Oldham et al., 2000). The dose enhancement factor is dependent on both inhaled particle diameter and size of the deposition region. In experimental studies using a bifurcating airway structure, a majority of deposition (~90% of total) was found within a short distance (one airway diameter) from the carina and the local deposition pattern was further intensified when a local obstruction was imposed on the airway structure (Kim et al., 1994). Using the computational fluid dynamic modeling in a physiologically realistic (human TB tree) three-dimensional group of bifurcations, Balásházy et al. (1999) provided numerical enhancement (over average airway surface deposition doses) factors. For the smallest region

considered, which would comprise less than a few hundred epithelial cells, the enhancement factors ranged from 52-fold for 0.01 μm diameter particles up to 113-fold for 10 μm diameter particles. An enhancement factor of 81-fold was calculated for 1 μm diameter particles. The local deposition enhancement factor could reach higher if factors such as increased ventilation, oral vs. nasal breathing, and lung disease were considered. However, one must be cautious in applying the enhancement factor, in that such a high enhancement factor is based on a very small spot (i.e., a surface area of ~1 mm^2). Thus, for the purposes of simulating the exposure of the heavily dosed TB bifurcation cells to PM_{10} and/or $PM_{2.5}$, an enhancement factor of as much as 80-fold could be reasonable. Taken together, the combined dose enhancing effects of increased ventilation (2-fold), oral breathing (2-fold), lung disease (2-fold) and bifurcation effects (80-fold), one could expect populations of epithelial cells to experience enhanced deposition (over average surface deposition) of as much as 640-fold. Under these conditions, the average deposition also increases. Considering that clearance impairment may also be a factor in subpopulations with some disease states, the buildup of particles at such TB bifurcations could further increase the maximum dose in relation to healthy individuals.

As a final consideration in this susceptibility scenario, the proximity of exposure to sources of PM may be important. Although data are sparse in this regard, Zhu et al. (2002) have measured time-averaged concentrations of black carbon and particle number at various distances downwind from freeways in Los Angeles. In comparison to upwind concentrations, concentrations at 30 m downwind were about 4-fold higher for black carbon, and about 3-fold higher for particle number. A factor of 3 for increased dose over the average might be expected for this subpopulation. By taking all of the above factors into account, it is reasonable to expect that highly localized PM doses to groups of cells in potentially susceptible subpopulations could be 3,000 to 4,000 times greater than the average TB surface exposures for the general population. Other scenarios could be evaluated that lead to greater, or to lesser, local dose estimates.

In conclusion, well-conducted instillation studies are valuable for examining the relative toxicity of particulate materials and for providing mechanistic information that is useful for interpreting in vitro and inhalation studies. However, because mechanisms of injury may vary with the delivered dose, published instillation studies designed to provide information relevant to

human risk assessment should report dosimetric calculations, taking into account the types of dosimetric considerations just discussed.

6.6 MODELING THE DEPOSITION AND DISPOSITION OF PARTICLES IN THE RESPIRATORY TRACT

6.6.1 Modeling Deposition, Clearance, and Retention

Over the years, mathematical models for predicting deposition, clearance and, ultimately, retention of particles in the respiratory tract have been developed. Such models help interpret experimental data and can be used to make dosimetry predictions for cases where data are not available. In fact, model predictions described below are estimates based on the best available models at the time of publication and, except where noted, have not been verified by experimental data.

A review of various mathematical deposition models was given by Morrow and Yu (1993) and in U.S. Environmental Protection Agency (1996a). There are three major elements involved in mathematical modeling. First, a structural model of the airways must be specified in mathematical terms. Second, deposition efficiency in each airway must be derived for each of the various deposition mechanisms. Finally, a computational procedure must be developed to account for the transport and deposition of the particles in the airways. As noted earlier, most models are deterministic in that particle deposition probabilities are calculated using anatomical and airflow information on an airway generation by airway generation basis. Other models are stochastic, whereby modeling is performed using individual particle trajectories and finite element simulations of airflow.

Recent reports involve modeling the deposition of ultrafine particles and deposition at airway bifurcations. Zhang and Martonen (1997) used a mathematical model to simulate diffusion deposition of ultrafine particles in the human upper tracheobronchial tree and compared the results to those in a hollow cast obtained by Cohen et al. (1990). The model results were in good agreement with experimental data. Zhang et al. (1997) studied the inertial deposition of particles in symmetric three-dimensional models of airway bifurcations, mathematically examining effects of geometry and flow. They developed equations for use in predicting deposition based on Stokes numbers, Reynolds numbers (a dimensionless number that

describes the tendency for a flowing fluid to change from laminar flow to turbulent flow), and bifurcation angles for specific inflows.

Models for deposition, clearance, and dosimetry of the respiratory tract of humans have been available for the past four decades. For example, the International Commission on Radiological Protection (ICRP) has recommended three different mathematical models during this time period (International Commission on Radiological Protection, 1960, 1979, 1994). These models make it possible to calculate the mass deposition and retention in different parts of the respiratory tract and provide, if needed, mathematical descriptions of the translocation of portions of the deposited material to other organs and tissues beyond the respiratory tract. A somewhat simplified variation of the 1994 ICRP dosimetry model was used by Snipes et al. (1997) to predict average particle deposition in the ET, T, and A regions and retention patterns in the A region under a repeated exposure situation for two characterized environmental aerosols obtained from Philadelphia, PA and Phoenix, AZ. Both of these aerosols contained both fine and coarse particles. They found similar retention for the fine particles in both aerosols, but significantly different retention for the coarse-mode particles. Because the latter type dominated the aerosol in the Phoenix sample, this type of evaluation can be used to improve the understanding of the relationship between exposures to ambient PM and retention patterns that affect health endpoints in residents of areas where the particle distributions and particle chemistry may differ.

A morphological model based on laboratory data from planar gamma camera and single-photon emission tomography images has been developed (Martonen et al., 2000). This model defines the parenchymal wall in mathematical terms, divides the lung into distinct left and right components, derives a set of branching angles from experimental measurements, and confines the branching network within the left and right components (so there is no overlapping of airways). The authors conclude that this more physiologically realistic model can be used to calculate PM deposition patterns for risk assessment.

Musante and Martonen (2000c) developed an age-dependent theoretical model to predict dosimetry in the lungs of children. The model includes the dimensions of individual airways and the geometry of branching airway networks within developing lungs and breathing parameters as a function of age. The model suggests that particle size, age, and activity level markedly affect deposition patterns of inhaled particles. Simulations thus far predict a lung deposition fraction of

38% in an adult and 73% (nearly twice as high) in a 7-mo-old for 2-μm particles inhaled during heavy breathing. The authors conclude that this model will be useful for estimating dose delivered to sensitive subpopulations such as children.

Martonen et al. (2001a) developed a three-dimensional (3D) physiologically realistic computer model of the human upper-respiratory tract (URT). The URT morphological model consists of the extrathoracic region (nasal, oral, pharyngeal, and laryngeal passages) and upper airways (trachea and main bronchi) of the lung. The computer representation evolved from a silicone rubber impression of a medical school teaching model of the human head and throat. The final unified 3D computer model may have significant applications in inhalation toxicology for evaluating lung injuries from PM inhalation.

Segal et al. (2000a) developed a computer model for airflow and particle motion in the lungs of children to study how airway disease, specifically cancer, affects inhaled PM deposition. The model considers how tumor characteristics (size and location) and ventilatory parameters (breathing rates and tidal volumes) influence particle trajectories and deposition patterns. The findings indicate that PM may be deposited on the upstream surfaces of tumors because of enhanced efficiency of inertial impaction. Additionally, submicron particles and larger particles may be deposited on the downstream surfaces of tumors because of enhanced efficiency of diffusion and sedimentation, respectively. The mechanisms of diffusion and sedimentation are functions of the particle residence times in airways. Eddies downstream of tumors would trap particles and allow more time for deposition to occur by diffusion and sedimentation. The authors conclude that particle deposition is complicated by the presence of airway disease and that the effects are systematic and predictable.

Segal et al. (2000b) have used a traditional mathematical model based on Weibel's lung morphology and calculated total lung deposition fraction of 1- to 5-μm diameter particles in healthy adults. Airway dimensions were scaled by individual lung volume. Deposition predictions were made with both plug flow and parabolic flow profiles in the airways. The individualized airway dimensions improved the accuracy of the predicted values when compared with experimental data. There were significant differences, however, between the model predictions and experimental data depending on the flow profiles used, indicating that use of more realistic parameters is essential to improving the accuracy of model predictions.

Broday and Georgopoulos (2001) presented a model that solves a variant of the general dynamic equation for size evolution of respirable particles within human tracheobronchial airways. The model considers polydisperse aerosols of variable thermodynamic states and chemical compositions. The aerosols have an initial bimodal lognormal size distribution that evolves with time in response to condensation-evaporation and deposition processes. Simulations reveal that submicron size particles grow rapidly and cause increased number and mass fractions of the particle population to be found in the intermediate size range. Because deposition by diffusion decreases with increasing size, hygroscopic ultrafine particles may persist longer in the inspired air than nonhygroscopic particles of comparable initial size distribution. In contrast, the enhanced deposition probability of hygroscopic particles initially from the intermediate size range increases their fraction deposited in the airways. The model demonstrates that the combined effect of growth and deposition tends to decrease the nonuniformity of the persistent aerosol, forming an aerosol which is characterized by a size distribution of smaller variance. These factors also alter the deposition profile along airways.

Lazaridis et al. (2001) developed a deposition model for humans that was designed to better describe the dynamics of respirable particles within the airways. The model took into account alterations in aerosol particle size and mass distribution that may result from processes such as nucleation, condensation, coagulation, and gas-phase chemical reactions. The airway geometry used was the regular dichotomous model of Weibel, and it incorporated the influences of airway boundary layers on particle dynamics although simplified velocity profiles were used so as to maintain a fairly uncomplicated description of respiratory physiology. Thus, this model was considered to be an improvement over previous models which did not consider either the effects of boundary layers on both the airborne and deposited particles or the effects of gas-phase transport processes because it can account for the polydispersity, multimodality, and heterogeneous composition of common ambient aerosols. The authors indicate that the model predictions were both qualitatively and quantitatively consistent with experimental data for particle deposition within the TB and A regions.

Another respiratory tract dosimetry model was developed concurrently with the ICRP model by the National Council on Radiation Protection and Measurements (NCRP, 1997). As with the ICRP model, the NCRP model addresses inhalability of particles, revised subregions of the respiratory tract, dissolution-absorption as an important aspect of the model, body size,

and age. The NCRP model defines the respiratory tract in terms of a naso-oro-pharyngo-laryngeal (NOPL) region, which is equivalent to the ICRP (1994) model's ET region, a tracheobronchial (TB) region, a pulmonary (P) region (equivalent to the ICRP model AI region), and lung-associated lymph nodes (LN). Deposition and clearance are calculated separately for each of these regions. As with the 1994 ICRP model, inhalability of aerosol particles was considered, and deposition in the various regions of the respiratory tract was modeled using methods that relate to mechanisms of inertial impaction, sedimentation, and diffusion.

Fractional deposition in the NOPL region was developed from empirical relationships between particle diameter and air flow rate. Deposition in the TB and P regions were based on geometric or aerodynamic particle diameter (where appropriate) and physical deposition mechanisms such as impaction, sedimentation, diffusion, and interception. Deposition in the TB and P regions used the lung model of Yeh and Schum (1980) with a method of calculation similar to that of Findeisen (1935) and Landahl (1950). This method was modified to accomodate an adjustment of lung volume and substitution of realistic deposition equations. These calculations were based on air flow information and idealized morphometry and used a typical pathway model. Comparison of regional deposition fraction predictions between the NCRP and ICRP models was provided in U.S. Environmental Protection Agency (1996a). The definition of inhalability was that of the American Conference of Governmental Industrial Hygenists (1985). Breathing frequency, tidal volume, and functional residual capacity were the ventilatory factors used to model deposition. These were related to body weight and to three levels of physical activity (low activity, light exertion, and heavy exertion).

Clearance from all regions of the respiratory tract was considered to result from competitive mechanical and absorptive mechanisms. Mechanical clearance in the NOPL and TB regions was considered to result from mucociliary transport. This was represented in the model as a series of escalators moving towards the glottis and where each airway had an effective clearance velocity. Clearance from the P region was represented by fractional daily clearance rates to the TB region, the pulmonary LN region, and the blood. A fundamental assumption in the model was that the rates for absorption into blood were the same in all regions of the respiratory tract. The rates of dissolution-absorption of particles and their constituents were derived from clearance data primarily from laboratory animals. The effect of body growth on

particle deposition also was considered in the model, but particle clearance rates were assumed to be independent of age. Some consideration for compromised individuals was incorporated into the model by altering normal rates for the NOPL and TB regions.

Mathematical deposition models for a number of nonhuman species have been developed; these were discussed in the 1996 PM AQCD (U.S. Environmental Protection Agency, 1996a). Despite difficulties, modeling studies in laboratory animals remain a useful step in extrapolating exposure-dose-response relationships from laboratory animals to humans.

Respiratory tract clearance begins immediately upon deposition of inhaled particles. Given sufficient time, the deposited particles may be removed completely by these clearance processes. However, single inhalation exposures may be the exception rather than the rule. It generally is accepted that repeated or chronic exposures are common for environmental aerosols. As a result of such exposures, accumulation of particles may occur. Chronic exposures produce respiratory tract burdens of inhaled particles that continue to increase with time until the rate of deposition is balanced by the rate of clearance. This is defined as the "equilibrium respiratory tract burden."

It is important to evaluate these accumulation patterns, especially when assessing ambient chronic exposures, because they dictate what the equilibrium respiratory tract burdens of inhaled particles will be for a specified exposure atmosphere. Equivalent concentrations can be defined as "species-dependent concentrations of airborne particles which, when chronically inhaled, produce equal lung deposits of inhaled particles per gram of lung during a specified exposure period" (Schlesinger et al., 1997). Other metrics are also possible, i.e., mass of PM, surface area of particles, or number of particles deposited per cm^2 of airway surface or per alveolus. Available data and approaches with which to evaluate exposure atmospheres that produce similar respiratory tract burdens in laboratory animals and humans were discussed in detail in the 1996 PM AQCD. Some examples are given in 6.6.4.

Several laboratory animal models have been developed to help interpret results from specific studies that involved chronic inhalation exposures to nonradioactive particles (Wolff et al., 1987; Strom et al., 1988; Stöber et al., 1994). These models were adapted to data from studies involving high level chronic inhalation exposures in which massive lung burdens of low toxicity, poorly soluble particles were accumulated. Koch and Stöber (2001) further adapted clearance models for more relevant particle deposition in the pulmonary region. They published a pulmonary retention model that accounts for dissolution and macrophage-mediated removal of

deposited polydisperse aerosol particles. The model provides a mathematical solution for the size distribution of particles in the surfactant layer of the alveolar surface and in the cell plasma of alveolar macrophages and accounts for the different kinetics and biological effects in the two compartments. It does not, however, account for particle penetration to the lung interstitium and particle clearance by the lymph system.

Estimating regional particle deposition patterns is important for establishing the comparability of animal models, for understanding interspecies differences in the expression of chemical toxicities, and, ultimately, for the human risk assessment process. Different species exposed to the same particle atmosphere may not receive identical initial doses in comparable respiratory tract regions, and the selection of a certain species for toxicological evaluation of inhaled particles may, thus, influence the estimated human lung or systemic dose, as well as its relationship to potential adverse health effects. Asgharian et al. (1995) described a strategy for summarizing published data on regional deposition of particles of different diameters and calculating a deposited fraction for a specific particle size distribution. The authors constructed nomograms for three species, namely the human, monkey, and rat, to allow estimation of alveolar deposition fractions. They then developed a regression model to permit the calculation of more exact deposition fractions. While this paper describes the procedure for one region of the lungs, the authors maintain that the technique can be applied to other regions of the respiratory tract or to the total system for which deposition data are available. The model is somewhat constrained at present due to the limitations of the underlying deposition database.

Tran et al. (1999) used a mathematical model of clearance and retention in the A region of rats lungs to determine the extent to which a sequence of clearance mechanisms and pathways could explain experimental data obtained from inhalation studies using relatively insoluble particles. These pathways were phagocytosis by macrophages with subsequent clearance, transfer of particles into the interstitium and to lymph nodes, and overloading of defense mechanisms. The model contained a description of the complete defense system in this region using both clearance and transfer processes as represented by sets of equations. The authors suggested that the model could be used to examine the consistency of various hypotheses concerning the fate of inhaled particles and could be used for species other than the rat with appropriate scaling.

Hofmann et al. (2000) used three different morphometric models of the rat lung to compute particle deposition in the acinar (alveolar) airways: the multipath lung (MPL) model with a fixed airway geometry; the stochastic lung (SL) model with a randomly selected branching structure; and a hybrid of the MPL and SL models. They calculated total and regional deposition for a range of particle sizes during quiet and heavy breathing. Although the total bronchial and acinar deposition fractions were similar for the three models, the SL and the hybrid models predicted a substantial variation in particle deposition among different acini. Acinar deposition variances in the MPL model were consistently smaller than in the SL and the hybrid lung models. The authors conclude that the similarity of acinar deposition variations in the latter two models and their independence of the breathing pattern suggest that the heterogeneity of the acinar airway structure is primarily responsible for the heterogeneity of acinar particle deposition.

The combination of MPL and SL models developed for the human lung takes into consideration both intra- and inter-human variability in airway structure. The models also have been developed to approximately the same level of complexity for laboratory animals and, therefore, can be readily used for interspecies extrapolation (Asgharian et al., 1999). A variation of these models will soon be developed for inclusion of the airway geometry of children. By incorporating particle clearance in the TB region (Asgharian et al., 2001) and in the alveolar region (Koch and Stöber, 2001), this suite of models should prove to be very useful in better predicting PM dosimetry in humans.

6.6.2 Models To Estimate Retained Dose

Models have been used routinely to express retained dose in terms of temporal patterns for A region retention of acutely inhaled materials. Available information for a variety of mammalian species, including humans, can be used to predict deposition patterns in the respiratory tract for inhalable aerosols with reasonable degrees of accuracy. Additionally, alveolar clearance data for non-human mammalian species commonly used in inhalation studies are available from numerous experiments that involved inhaled radioactive particles.

An important factor in using models to predict retention patterns in laboratory animals or humans is the dissolution-absorption rate of the inhaled material. Factors that affect the dissolution of materials or the leaching of their constituents in physiological fluids and the

subsequent absorption of these constituents are not fully understood. Solubility is known to be influenced by the surface-to-volume ratio and other surface properties of particles (Mercer, 1967; Morrow, 1973). The rates at which dissolution and absorption processes occur are influenced by factors that include the chemical composition of the material. Temperature history of materials is also an important consideration for some metal oxides. For example, in controlled laboratory environments, the solubility of oxides usually decreases when the oxides are produced at high temperatures, which generally results in compact particles having small surface-to-volume ratios. It is sometimes possible to accurately predict dissolution-absorption characteristics of materials based on physical/chemical considerations, but predictions for in vivo dissolution-absorption rates for most materials, especially if they contain multivalent cations or anions, should be confirmed experimentally.

Phagocytic cells, primarily macrophages, clearly play a role in dissolution-absorption of particles retained in the respiratory tract (Kreyling, 1992). Some particles dissolve within the phagosomes because of the acidic milieu in those organelles (Lundborg et al., 1984, 1985), but the dissolved material may remain associated with the phagosomes or other organelles in the macrophage rather than diffuse out of the macrophage to be absorbed and transported elsewhere (Cuddihy, 1984). This same phenomenon has been reported for organic materials. For example, covalent binding of benzo[*a*]pyrene or metabolites to cellular macromolecules resulted in an increased alveolar retention time for that compound after inhalation exposures of rats (Medinsky and Kampcik, 1985). Understanding these phenomena and recognizing species similarities and differences are important for evaluating alveolar retention and clearance processes and for interpreting the results of inhalation studies.

Dissolution-absorption of materials in the respiratory tract is clearly dependent on the chemical and physical attributes of the material. Although it is possible to predict rates of dissolution-absorption, it is prudent to determine this important clearance parameter experimentally. It is important to understand the effect of this clearance process for the lungs, TB lymph nodes, and other body organs that might receive particles or their constituents that enter the circulatory system from the lung.

Additional research must be done to provide the information needed to evaluate properly retention of particles in conducting airways. However, a number of earlier studies, discussed in the 1996 PM AQCD (U.S. Environmental Protection Agency, 1996a) and in Section 6.3.2.2

herein, noted that some particles were retained for relatively long times in the tracheobronchial regions, effectively contradicting the general conclusion that almost all inhaled particles that deposit in the TB region clear within hours or days. These studies have demonstrated that variable portions of the particles that deposit in, or are cleared through, the TB region are retained with half-times on the order of weeks or months. Long-term retention and clearance patterns for particles that deposit in the ET and TB regions must continue to be thoroughly evaluated because of the implications of this information for respiratory tract dosimetry and risk assessment.

Model projections are possible for the A region using the cumulative information in the scientific literature relevant to deposition, retention, and clearance of inhaled particles. Clearance parameters for six laboratory animal species were summarized by the U.S. Environmental Protection Agency (1996a). Nikula et al. (1997) evaluated results in rats and monkeys exposed to high levels of either diesel soot or coal dust. Although the total amount of retained material was similar in both species, the rats retained a greater portion in the lumens of the alveolar ducts and alveoli than did monkeys; whereas the monkeys retained a greater portion of the material in the interstitium. The investigators concluded that intrapulmonary retention patterns in one species may not be predictive of those in another species at high levels of exposure, but this may not be the case at lower levels of exposure.

The influence of exposure concentration on the pattern of particle retention in rats (exposed to diesel soot) and humans (exposed to coal dust) was examined by Nikula et al. (2000) using histological lung sections obtained from both species. The exposure concentrations for diesel soot were 0.35, 3.5, or 7.0 $\mu g/m^3$; and exposure duration was 7 h/day, 5 days/week for 24 mo. The human lung sections were obtained from nonsmoking nonminers, nonsmoking coal miners exposed to levels $\leq$ 2 mg dust/m^3 for 3 to 20 years, or nonsmoking miners exposed to 2 to 10 mg/m^3 for 33 to 50 years. In both species, the amount of retained material (using morphometric techniques based on the volume density of deposition) increased with increasing dose (which is related to exposure duration and concentration). In rats, the diesel exhaust particles were found to be primarily in the lumens of the alveolar duct and alveoli; whereas in humans, retained dust was found primarily in the interstitial tissue within the respiratory acini.

Dosimetric models may be used to adjust for differences in the exposure-dose relationship in different species, thus allowing for comparison of lung responses at different doses. In a

series of papers (Kuempel 2000, 2001a; Kuempel 2001b), Kuempel presents a biologically-based human dosimetric lung model to describe the fate of respirable particles in the lungs of humans. The model uses data from coal miners and assumptions about the overloading of alveolar clearance from studies in rats. The form of the model that provides the best fit to the lung-dust burden data in the coal miners includes a first-order interstitialization process and either a no-dose-dependent decline in alveolar clearance or a much lower decline than expected from the rodent studies. These findings were consistent with particle retention patterns observed previously in the lungs of primates.

6.6.3 Fluid Dynamics Models for Deposition Calculations

The available models developed to simulate PM deposition in the lung are based on simplifying assumptions about the morphometry of the lung and the fluid dynamics of inspired air through a branching airway system. As new models are developed, they will better predict particle deposition patterns in a more realistic airway geometry under realistic flow conditions that can result in local nonuniformity of particle deposition and the formation of hot spots. One example is the model of ventilation distribution in the human lung developed by Chang and Yu (1999). This model was designed as an improvement over those that assumed uniform ventilation in the lungs because it better simulated the effect of airway dynamics on the distribution of ventilation under different conditions which may occur in the various lobes of the lungs and under various inspiratory flow rates. The authors indicated that the results of the model compared favorably with experimental data and that the model will be incorporated into a particle deposition model which will allow for the evaluation of the nonuniformity of deposition within the lungs resulting from the physiological situation of nonuniform distribution of ventilation. Computational fluid dynamics (CFD) modeling adds another step to better model development by providing increased ability to predict local airflow and particle deposition patterns and provides a better representation of ET deposition in the human respiratory tract. The CFD models developed to date, however, are limited in scope because they are unable to simulate flow in the more complex gas exchange regions. Due to a lack of more realistic simulations for the lower airways, they impose another "idealized" boundary condition at the distal end of the human respiratory tract.

Airflow patterns within the lung are determined by the interplay of structural and ventilatory conditions. These flow patterns govern the deposition kinetics of entrained particles in the inspired air. A number of CFD software programs are available to simulate airflow patterns in the lung by numerically solving the Navier-Stokes equations (White, 1974). The CFD modeling requires a computer reconstruction of the appropriate lung region and the application of boundary conditions. The flow field resulting from the CFD modeling is represented by velocity vectors in the grid points of a two- or three-dimensional mesh. Numerical models of particle deposition patterns are computed by simulating the trajectories of particles introduced into these flow streams after solving for the particles' equation of motion. Such CFD models have been developed for different regions of the respiratory tract, including the nasal cavity (Yu et al., 1998; Sarangapani and Wexler, 2000); larynx (Martonen et al. 1993; Katz et al., 1997; Katz, 2001); major airway bifurcations (Gradoń and Orlicki, 1990; Balásházy and Hofmann, 1993a,b, 1995, 2001; Heistracher and Hofmann, 1995; Lee et al., 1996; Zhang et al., 1997, 2000, 2001, 2002; Comer et al., 2000, 2001a,b); and alveoli (Tsuda et al., 1994a,b; Darquenne, 2001).

Kimbell (2001) has recently reviewed the literature on CFD models of the upper respiratory tract (URT). Most of these models have focused on characterizing the airflow patterns in the URT and have not included simulation of particulate dosimetry. Keyhani et al. (1995) were the first to use computer-aided tomography (CAT) scans of the human nasal cavity to construct an anatomically accurate three-dimensional airflow model of the human nose. Subramaniam et al. (1998) used data from magnetic resonance imaging to extend these CFD studies to include the nasopharynx. However, neither of these studies investigated particle deposition in the upper respiratory tract.

Yu et al. (1998) developed a three-dimensional CFD model of the entire human URT, including the nasal airway, oral airway, laryngeal airway, and the first two generations of the TB airways. They have used this CFD model to investigate the effect of breathing pattern, i.e., nasal breathing, oral breathing, and simultaneous nasal and oral breathing, on airflow and ultrafine particle deposition. They concluded that the ultrafine particle deposition simulated using the CFD model was in reasonable agreement with the corresponding experimental measurements. In a study led by Sarangapani and Wexler (2000), an upper respiratory tract CFD model that included the nasal cavity, nasopharynx, pharynx, and larynx was developed to study the

deposition efficiency of hygroscopic and non-hygroscopic particles in this region. They used the CFD model to simulate the temperature and water vapor conditions in the upper airways and predicted high relative humidity conditions in this region. They also simulated particle trajectories for 0.5 μm, 1 μm, and 5 μm particles under physiologically realistic flow rates. The predictions of the CFD model indicated that high relative humidity conditions contribute to rapid growth of hygroscopic particles and would dramatically alter the deposition characteristics of ambient hygroscopic aerosols.

Stapleton et al. (2000) investigated deposition of a polydisperse aerosol (MMD = 4.8 μm and GSD = 1.65) in a replica of a human mouth and throat using both experimental results and three-dimensional CFD simulation. They found that CFD results were comparable with experimental results for a laminar flow case, but were more than 200% greater for a turbulent flow case. The results suggest that accurate predictions of particle deposition in a complex airway geometry require a careful evaluation of geometric and fluid dynamic factors in developing CFD models.

Due to the complex structural features and physiological conditions of the human laryngeal region, only a limited number of modeling studies have been conducted to evaluate laryngeal fluid dynamics and particle deposition. A high degree of inter-subject variability, a compliant wall that presents challenges in setting appropriate boundary conditions, and a complex turbulent flow field are some of the difficulties encountered in developing CFD models of the laryngeal airways. Martonen et al. (1993) investigated laryngeal airflow using a two-dimensional CFD model and concluded that laryngeal morphology exerts a pronounced influence on regional flow, as well as fluid motion in the trachea and the main bronchi. In this study, the glottal aperture (defined by the geometry of the vocal folds) was allowed to change in a prescribed manner with the volume of inspiratory flow (Martonen and Lowe, 1983), and three flow rates corresponding to different human activity were examined.

In a subsequent CFD analysis, a three-dimensional model of the larynx based on measurements of human replica laryngeal casts (Martonen and Lowe, 1983; Katz and Martonen, 1996; Katz et al., 1997) simulated the flow field in the larynx and trachea under steady inspiratory flow conditions at three flow rates. They observed that the complex geometry produces jets, recirculation zones, and circumferential flow that may directly influence particle deposition at select sites within the larynx and tracheobronchial airways. The primary

characteristics of the simulated flow field were a central jet penetrating into the trachea created by the ventricular and vocal folds, a recirculating zone downstream of the vocal folds, and a circumferential secondary flow. Recently, a computational model for fluid dynamics and particle motion for inspiratory flow through the human larynx and trachea has been described (Katz, 2001). This model calculates the trajectory of single particles introduced at the entrance to the larynx using a stochastic model for turbulent fluctuations incorporated into the particles' equation of motion and time-averaged flow fields in the larynx and trachea. The effects of flow rate and initial particle location on overall deposition were presented in the form of probability density histograms of final particle deposition sites. At present, however, there are no experimental data to validate results of such modeling.

A number of CFD models have been developed to study fluid flow and particle deposition patterns in airway bifurcations. The bifurcation geometries that have been modeled include two-dimensional (Li and Ahmadi, 1995); idealized three-dimensional using circular airways (Kinsara et al., 1993) or square channels (Asgharian and Anjilvel, 1994); symmetric bifurcations (Balásházy and Hofmann, 1993a,b); or physiologically realistic asymmetric single (Balásházy and Hofmann, 1995; Heistracher and Hofmann, 1995) and multiple bifurcation models (Lee et al., 1996; Heistracher and Hofmann, 1997; Comer et al., 2000, 2001a,b; Zhang et al., 2000, 2001, 2002) with anatomical irregularities such as cartilaginous rings (Martonen et al., 1994a) and carinal ridge (Martonen et al., 1994b; Comer et al., 2001a) shapes incorporated. The CFD flow simulations in the bifurcating geometry models show distinct asymmetry in the axial (primary) and radial (secondary) velocity profile in the daughter and parent airway during inspiration and expiration, respectively. In a systematic investigation of flow patterns in airway bifurcations, numerical simulations were performed to study primary flow (Martonen et al., 2001b), secondary currents (Martonen et al., 2001c), and localized flow conditions (Martonen et al., 2001d) for different initial flow rates. The effects of inlet conditions, Reynolds numbers, ratio of airway diameters, and branching angles with respect to intensity of primary flow, vortex patterns of the secondary currents, and reverse flow in the parent-daughter transition region were investigated. These simulated flow patterns match experimentally observed flow profiles in airway bifurcations (Schroter and Sudlow, 1969).

Gradoń and Orlicki (1990) computed the local deposition flux of submicron size particles in a three-dimensional bifurcation model for both inhalation and exhalation, and they found

enhanced deposition in the carinal ridge region during inspiration and in the central zone of the parent airway during expiration. Numerical models of particle deposition in symmetric three-dimensional bifurcations were developed by Balásházy and Hofmann (1993a,b), and these were subsequently extended to incorporate effects of asymmetry in airway branching (Balásházy and Hofmann, 1995) and physiologically realistic shapes of the bifurcation transition zone and the carinal ridge (Heistracher and Hofmann, 1995; Balásházy and Hofmann, 2001). In these numerical models, three-dimensional airflow patterns were computed by finite difference or finite volume methods; and the trajectories of particles entrained in the airstream were simulated using Monte Carlo techniques considering the simultaneous effects of gravitational settling, inertial impaction, diffusion, and interception. The spatial deposition pattern of inhaled particles was examined for a range of particle sizes (0.01 to 10 μm) and flow rates (16 to 32 L/min) by determining the intersection of particle trajectories with the surrounding surfaces. The overall deposition rates derived using the CFD models correspond reasonably well with experimental data (Kim and Iglesias, 1989). These simulations predict deposition hot spots at the inner side of the daughter airway downstream of the carinal ridge during inspiration, corresponding to the secondary fluid motion of the inhaled air stream. During exhalation, the CFD models predict enhanced deposition at the top and bottom parts of the parent airway, consistent with secondary motion in the exhaled air stream. These studies indicate that secondary flow patterns within the bifurcating geometry play a dominant role in determining highly nonuniform local particle deposition patterns.

Zhang et al. (1997) numerically simulated particle deposition in three-dimensional bifurcating airways (having varying bifurcation angles) due to inertial impaction during inspiration for a wide range of Reynolds numbers (100 to 1000). Inlet velocity profile, flow Reynolds number, and bifurcation angle had substantial effects on particle deposition efficiency. Based on the simulated results, equations were derived for particle deposition efficiency as a function of nondimensional parameters (such as Stokes number and Reynolds number) and bifurcation angle and were shown to compare favorably with available experimental results. More recently, Comer et al. (2000) have estimated the deposition efficiency of 3-, 5-, and 7-μm particles in a three-dimensional double bifurcating airway model for both in-plane and out-of-plane configurations for a wide range of Reynolds numbers (500-2000). They demonstrated

deposition in the first bifurcation to be higher than in the second bifurcation, with deposition mostly concentrated near the carinal region. The nonuniform flow generated by the first bifurcation had a dramatic effect on the deposition pattern in the second bifurcation. Based on these results, they concluded that use of single bifurcation models is inadequate to capture the complex fluid-particle interactions that occur in multigeneration airway systems.

Comer et al. (2001a) further investigated detailed characteristics of the axial and secondary flow in a double bifurcation airway model using 3-D CFD simulation. Effects of carina shape (sharp vs. rounded) and bifurcation plane (planar vs. non-planar) were examined. Particle trajectories and deposition patterns were subsequently investigated in the same airway model (Comer et al., 200lb). There was a highly localized deposition at and near the carina both in the first and second bifurcation, and deposition efficiency was much lower in the second bifurcation than in the first bifurcation as demonstrated in the earlier study (Comer et al., 2000). They found that deposition patterns were not much different between the sharp versus rounded carina shape at Stokes numbers of 0.04 and 0.12. However, deposition patterns were altered significantly for these particles when the bifurcation plane was rotated, suggesting that a careful consideration of realistic airway morphology is important for accurate prediction of particle deposition by CFD modeling.

Zhang et al. (2000, 2001) extended the studies of Comer et al. described above and investigated effects of angled inlet tube as well as asymmetric flow distribution between daughter branches. The flow asymmetry caused uneven deposition between downstream daughter branches. Also noted was that the absolute deposition amount was higher, but deposition efficiency per se was lower in the high flow branch than in the low flow branch. The intriguing relationship between flow asymmetry and deposition was in fact consistent with experimental data of Kim and Fisher (1999), indicating that the CFD model could correctly simulate complicated airflow and particle dynamics that may occur in the respiratory airways.

Most CFD models use constant inspiratory or expiratory flows for simplicity and practical reasons. However, the respiratory airflow is cyclic, and such flow characteristics cannot be fully described by constant flows. Recent studies of Zhang et al. (2002) investigated particle deposition in a triple bifurcation airway model under cyclic flow conditions mimicking resting and light activity breathing. Deposition dose was obtained for every mm^2 area. They found that deposition patterns were similar to those obtained with constant flows. However, deposition

efficiencies were greater with the cyclic flows than constant flows, and the difference could be as high as 50% for mean Stokes numbers between 0.02 and 0.12 during normal breathing. The CFD results are qualitatively comparable to experimental data (Kim and Garcia, 1991) that showed about 25% increase in deposition with cyclic flows. With further improvement of airway morphology and computational scheme, CFD modeling could be a valuable tool for exploring the microdosimetry in the airway structure.

Current CFD models of the acinar region are limited due to the complex and dynamic nature of the gas exchange region. Flow simulation in a linearly increasing volume of a spherical truncated two-dimensional alveolus model show distinct velocity maxima in the alveolar ducts close to the entrance and exit points of the alveolus and a radial velocity profile in the interior space of the alveolus (Tsuda et al., 1996). This is in contrast to simulations based on a rigid alveolus (Tsuda, 1994a,b) and suggests that a realistic simulation of the flow pattern in the acinar region should involve application of time-dependent methods with moving boundary conditions. Nonuniform deposition patterns of micron size particles, with higher deposition near the alveolar entrance ring, have been predicted using numerical models (Tsuda, 1994a,b, 1996).

Studies by Darquenne (2001) examined aerosol transport and deposition in 6-generation alveolated ducts using two-dimensional computer simulation. Particle trajectories and deposition patterns were obtained for one complete breathing cycle (2 s inspiration and 2 s expiration). There were large nonuniformities in deposition between generations, between ducts of a given generation, and within each alveolated duct, suggesting that local deposition dose can be much greater than the mean acinar dose.

6.6.4 Modeling Results Obtained with Models Available to the Public

Two relatively user-friendly computer models for calculating fractional deposition in various compartments of the respiratory tract as a function of particle size are publicly available. Several model runs have been done to demonstrate the outputs of the models. Published results from one model are also presented. Model simulations were performed for particles of density of 1 g/cm^3 so aerodynamic, Stokes, and thermodynamic diameters are the same.

6.6.4.1 International Commission on Radiological Protection (ICRP)

The LUDEP (Lung Dose Evaluation Program; National Radiologic Protection Board, 1994) model was developed concurrently with the ICRP (International Commission on Radiological Protection, 1994) respiratory tract model mainly to help the ICRP Task Group examine the model in detail by testing the predictions of deposition, clearance, and retention of inhaled radionuclides against experimental data and by determining the model's implications for doses to the respiratory tract (ICRP, 1994; NRPB, 1994). This model was designed to predict the deposition of inhaled particles in the respiratory tract, the subsequent biokinetic behavior of inhaled radionuclides, and the doses delivered to the respiratory tract. Although created for calculating the internal dose of radionuclides, the model is useful for determining the deposition of nonradioactive materials. In particular, the model has wide applicability for calculating the regional deposition of particles in the respiratory tract based on particle size, body size (age), breathing rate, activity patterns, and exposure environment. The overall dosimetric model for the respiratory tract consists of several critical elements important for deposition and clearance calculations including detailed descriptions of morphometry and respiratory physiology. The morphometric element of the model describes the structure of the respiratory tract and its dimensions. A description of respiratory physiology provides the rates and volumes of inhaled and exhaled air which affects the amount of material deposited in the respiratory tract. The ICRP model covers the particle size range from 0.001 to 100 μm. However, deposition in the size region between 0.001 and 0.01 μm may not be correct due to neglect of axial diffusion of particles and deposition of particles > 25 μm may be uncertain so only the 0.01 to 25 μm range will be shown.

The ICRP model (see Figure 6-1) calculates deposition in five compartments:

- ET1 - the extrathoracic region comprising the anterior nose;
- ET2 - the extrathoracic region comprising the posterior nasal passages, larynx, pharynx and mouth;
- BB - the bronchial region;
- bb - the bronchiolar region consisting of bronchioles and terminal bronchioles; and
- Al - the alveolar-interstitial region consisting of the respiratory bronchioles, the alveolar ducts with their alveoli and the interstitial connective tissue.

Two simulations were run to demonstrate some aspects of deposition as predicted by the ICRP model. Respiratory parameters for a worker with a moderately high activity level (ICRP default) and a young adult with a lower activity level are given in Table 6-3. Each simulation was run for nasal breathing and mouth breathing. In the presentation of model results, ET1 and ET2 are combined to give an ET (extrathoracic) region, BP and bb are combined to give a TB (tracheobronchial) region, and Al gives the A (alveolar) region. Results are shown in Figures 6-13 to 6-15. Figure 6-13 shows the total and regional deposition as a function of particle size for the worker: nasal breathing (13a), mouth breathing (13b), and a comparison of nasal and mouth breathing for the TB and A regions (13c). Figure 6-14 gives similar results for the young adult. For both simulations, the deposition is a minimum between 0.1 and 1 μm diameter (the accumulation mode size range) and increases for larger (coarse mode) and smaller (ultrafine particle) size ranges. For ultrafine particles, A deposition peaks between 0.01 and 0.1 μm and TB deposition increases as particle size decreases below 0.1 μm.

TABLE 6-3. RESPIRATORY PARAMETERS USED IN LUDEP MODEL

			Activity Related Physiological Parameters	
Activity	Percent	Ventilation Rate (m^3/hr)	Frequency (breaths/min)	Tidal Volume (mL)
Adult Male (ICRP default values)				
Sleep	0	0.45	12	625
Sitting	50	0.54	12	750
Light Exercise	38	1.5	20	1250
Heavy Exercise	12	3	26	1923
Young Adult				
Sitting	100	0.45	15	500

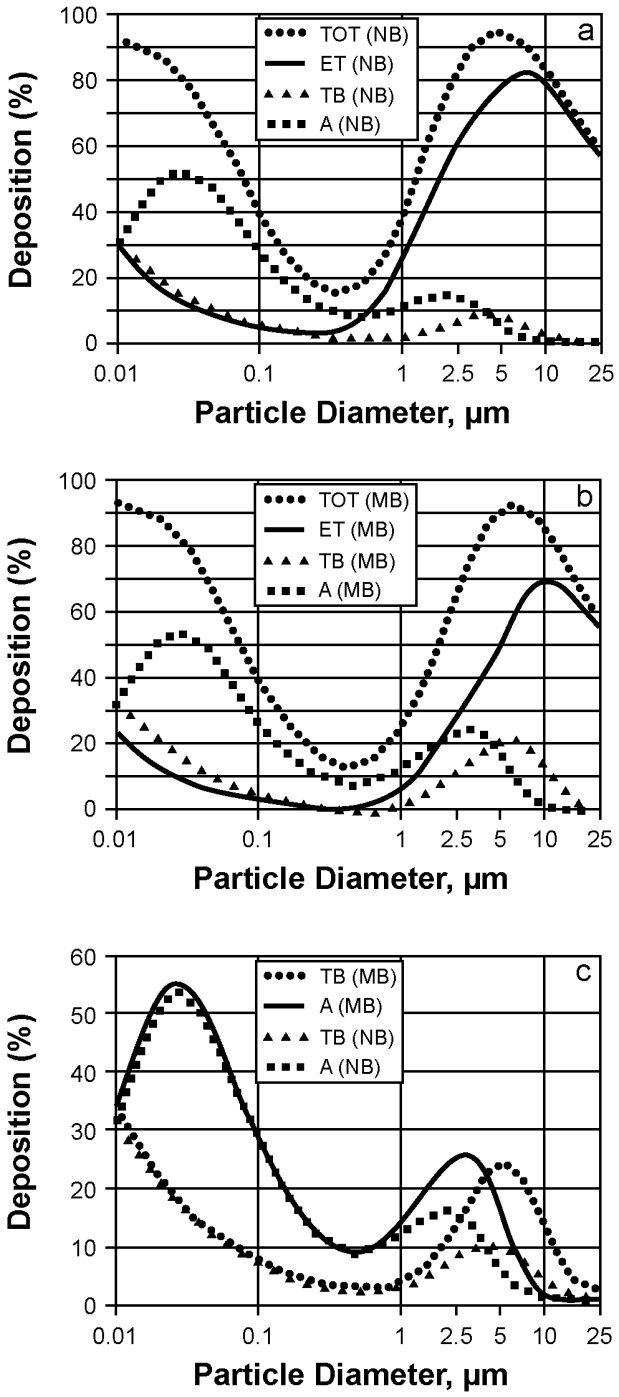

Figure 6-13. Deposition fraction for total results of LUDEP model for an adult male worker (ICRP default breathing parameters as shown in Table 6-3) showing total percent deposition in the respiratory tract (TOT) and in the ET, TB, and A regions: (a) nasal breathing (NB), (b) mouth breathing (MB), (c) comparison of nasal and mouth breathing for TB and A regions.

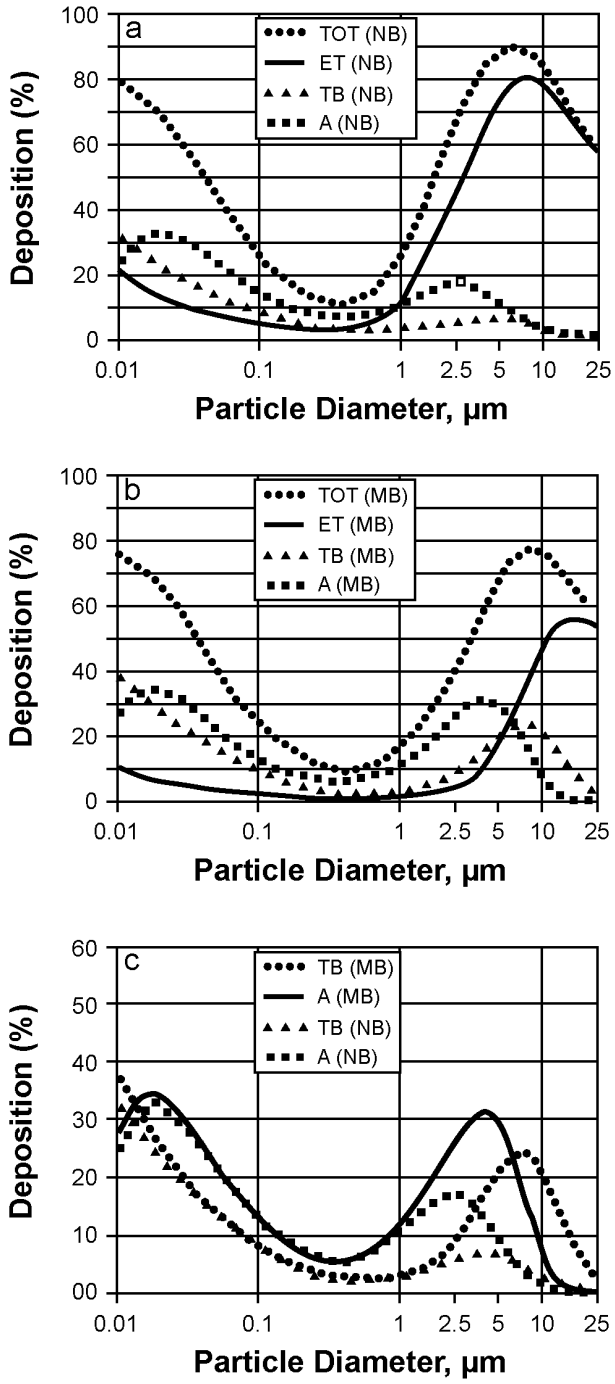

Figure 6-14. Deposition fraction for total results of LUDEP model for a young adult showing total percent deposition in the respiratory tract (TOT) and in the ET, TB, and A regions: (a) nasal breathing (NB), (b) mouth breathing (MB), (c) comparison of nasal and mouth breathing for TB and A regions. Respiratory parameters given in Table 6-3.

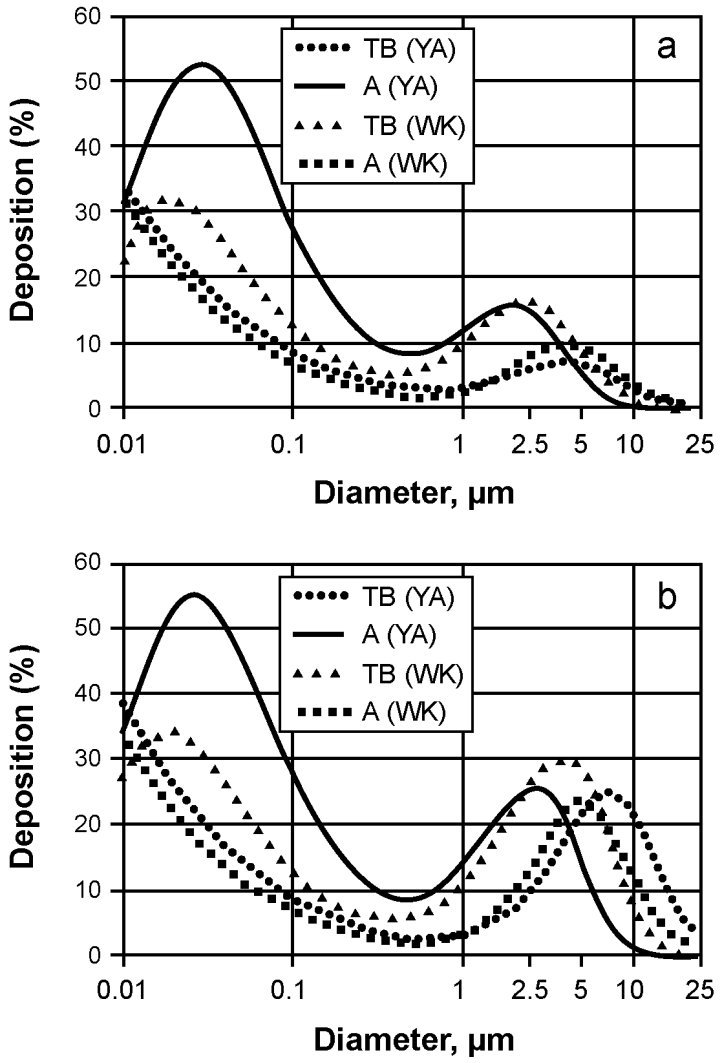

Figure 6-15. Comparison of deposition fraction in the TB and A regions for a worker (WK; light exercise, ICRP default) and a young adult (YA; resting): (a) nasal breathing and (b) mouth breathing.

The comparisons of nasal and mouth breathing in Figures 6-13c and 6-14c show almost no difference in deposition for particles between 0.01 and 1 µm. Below 0.1 µm, more particles are removed by diffusion in the extrathoracic (ET) region while above 1.0 more particles are removed by impaction in the ET region. Due to increased deposition of particles in the head during nasal breathing, switching to breathing through the mouth leads to greater TB and A deposition of coarse mode particles (AED > 1 µm) and of the smaller ultrafine particles

(d_p < 0.01 μm). The A deposition approaches zero as particle size increases to 10 μm. However, TB deposition continues for larger particle sizes.

The TB and A deposition patterns of the worker under moderate activity and the young adult under low activity are compared in Figure 6-15a and b. Increased activity in the worker compared to the resting young adult results in lower A deposition of coarse particles for nasal breathing (Figure 6-15a) and lower A and TB deposition of coarse particles for mouth breathing (Figure 6-15b). It also shifts the maximum deposition for coarse particles to smaller sizes. Increased activity increases A deposition of ultrafine particles and shifts the maximum deposition to larger sizes. Increased activity also increases the A deposition of accumulation-mode particles.

6.6.4.2 Multiple Path Particle Dosimetry Model (MPPD)

The MPPD model, developed by the CIIT Centers for Health Research (formerly the Chemical Industry Institute of Toxicology, USA) with support from the Dutch National Institute of Public Health and the Environment, is described in a RIVM report (Winter-Sorkina and Cassee, 2002). The MPPD model allows calculation of PM deposition and retention for humans and rats. The model includes age-specific human lung models, but some parameters are expected to be modified in a newer version of the model; so, age-specific results will not be discussed here. The MPPD model covers the particle size range from 0.01 to 20 μm. With the MPPD model, parameters such as the particle size distribution, inhalability, particle density, and respiratory pause can be modeled and dose per airway surface area can be calculated. The model may be used to improve understanding of the exposure-dose-response relationships observed in environmental epidemiological studies and for extrapolation of studies in experimental animals to humans. Factors resulting in increased susceptibility can also be studied.

The RIVM report (Winter-Sorkina and Cassee, 2002) describes the results of monodisperse aerosol deposition calculations with the MPPD model and its sensitivity to various parameters. The deposition fraction of inhaled PM depends primarily on physical characteristics of the particles, lung morphometry, and breathing parameters, and is difficult to measure for the many possible variations in parameters. Therefore, computer models such as the MPPD model have proven to be important tools to analyze PM dosimetry. Dosimetric models, such as those discussed above, use an explicit set of equations which describe real-life processes, based on

theory or empirical data, and may be used to analyze effects of scenarios such as particulate exposure control strategies. The age of the subject, the functional capacity of the lungs, and breathing parameters, as well as the individual lung morphometry, are factors that significantly affect particle deposition and can explain variations in susceptibility of subpopulations due to differences in dose per unit exposure. First, the predictions of the MPPD model will be compared to those of the LUDEP model. Next, results from the MPPD model depicting deposition as a function of minute ventilation (a surrogate for exertion or exercise level) for various respiratory tract regions will be shown.

6.6.4.2.1 Comparisons of LUDEP and MPPD models

Predicted regional deposition patterns, calculated using the ICRP (LUDEP) model and the MPPD (Yeh-Schum 5-lobe) model, for two breathing patterns (Table 6-4) are shown in Figures 6-16 and 6-17. The total deposition patterns are similar: low for the accumulation mode size range (0.1 to 1.0 μm), with increasing deposition at smaller and larger sizes. However, the MPPD model shows somewhat greater total deposition in the accumulation size range. The ET deposition is also similar except for slightly higher depositions in the ultrafine (UF) region for the MPPD model. In the A region, the UF deposition predicted by the MPPD model is lower for particle sizes below about 0.05 μm for resting and 0.03 μm for exercising. In the coarse particle size range, the A deposition peaks predicted by the MPPD model are shifted to larger particle sizes. While the absolute values of the deposition fraction are low in the accumulation mode size range for both models, the relative deposition is much higher for the MPPD model in this size region where most of the fine particle mass is found. The TB differences become more pronounced for higher exertion. The MPPD model predicts that TB deposition will decrease during exercise relative to rest whereas the LUDEP model predicts a large increase in TB deposition.

Both models are for nonhygroscopic particles. Hygroscopic particles, mostly found in the fine particle size range (although sea salt may be present as larger size particles), will grow in the high relative humidity of the respiratory system. As shown in Figures 6-16 and 6-17, deposition fractions decrease with increasing particle size above about 0.01 to 0.02 μm until around 0.3 to 0.5 μm. This suggests that as hygroscopic particles in these size ranges grow their deposition fraction will decrease. Particles in the accumulation mode, however, will grow into a

TABLE 6-4. BREATHING PATTERNS FOR COMPARISON OF ICRP AND MPPD MODELS

	Breathing Parameters		
Activity	Minute Ventilation L/m	Breathing Frequency min^{-1}	Tidal Volume mL
Resting	7.5	12	625
Light Exercise	25	20	1250

size range with a larger deposition fraction. The amount of growth will depend on the specific hygroscopic components and the fraction of the particle that is hygroscopic. The effects of hygroscopicity on dosimetry, therefore, will depend on the size distribution and composition of the particles and will be difficult to model. However, studies of the effects of hygroscopicity on dosimetry have been reported. (Martonen, 1982; Martonen et al., 1985; Martonen et al., 1989; Schroeter et al., 2001; Broday and Georgopoulos, 2001). The implications of hygroscopic growth on deposition have been reviewed extensively by Morrow (1986) and Hiller (1991), whereas the difficulties of studying lung deposition of hygroscopic aerosols have been reviewed by Kim (2000). See Chapter 2 for a detailed description of particle hygroscopicity.

Figures 6-16 and 6-17 compare deposition fractions as a function of particle size for monodisperse particles. In practice, most exposures are to polydisperse size distributions. The comparison might be somewhat different for size distributions with a given MMD as compared to monodisperse particles. Several examples are shown in Table 6-5 based on the three modes in the urban average size distribution reported by Whitby (1978) and a distribution with MMD = 2 μm and $\sigma_g = 2$ as representative of resuspended particles used in laboratory studies. The fractional deposition values are given for the specified size distributions and for monodisperse particles with the same MMD as well as for the ratio of the two model predictions. As can be seen, the differences between the two models are reduced in some cases and increased in others.

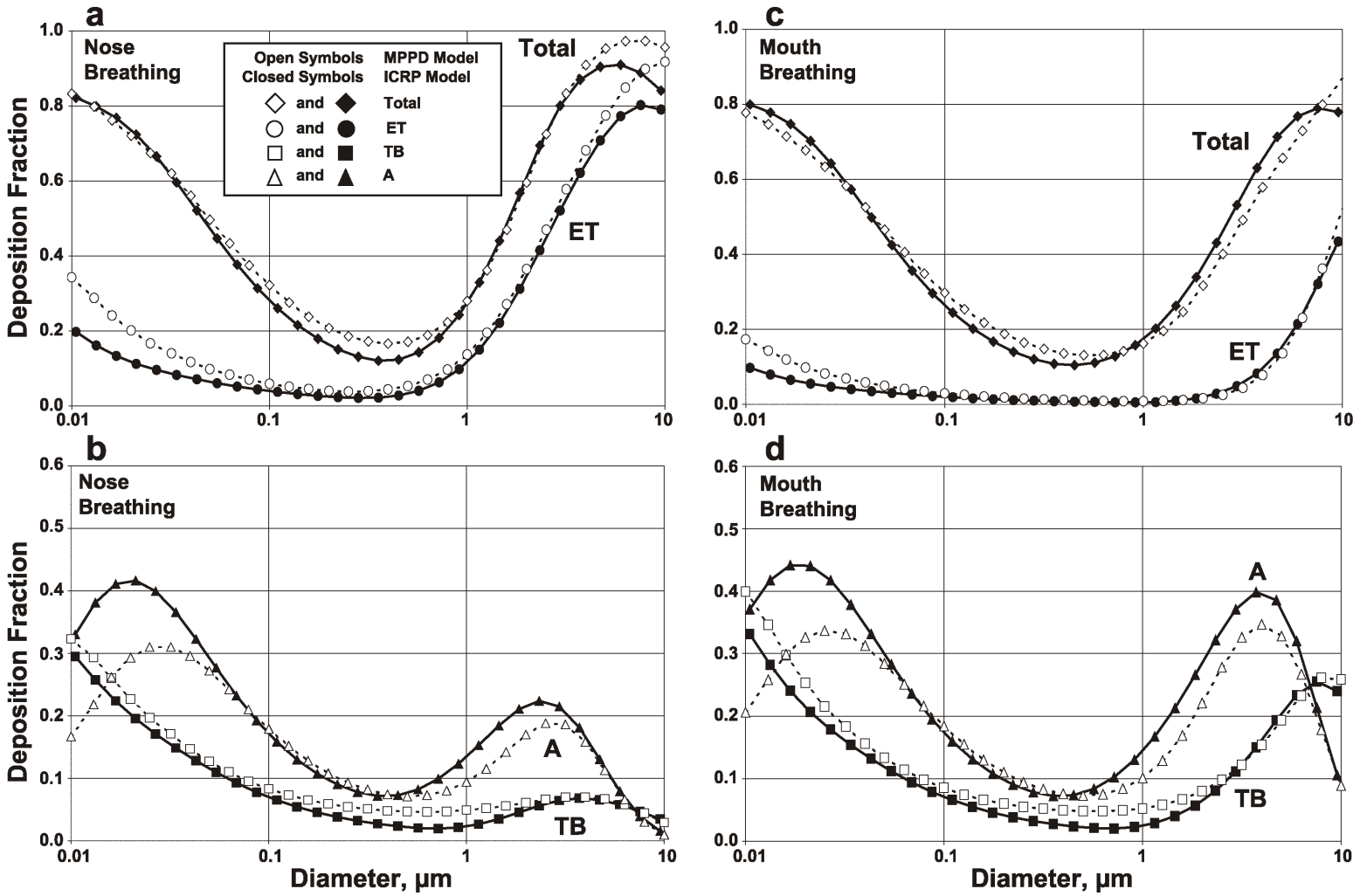

Figure 6-16. Comparison of regional deposition results from the ICRP (LUDEP) and the MPPD models for a resting breathing pattern: (a) and (b), nose breathing; (c) and (d), mouth breathing.

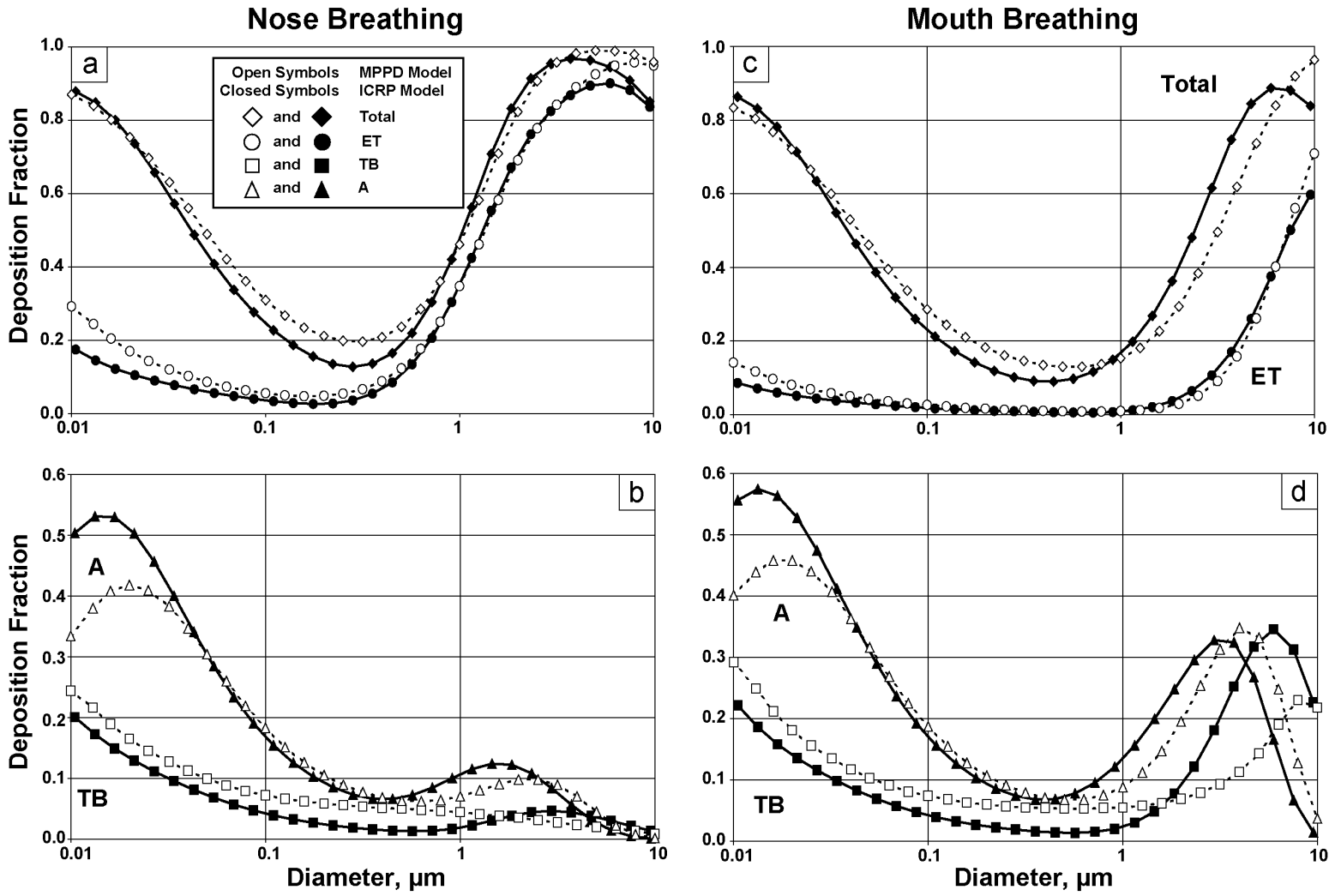

Figure 6-17. Comparison of regional deposition results from the ICRP (LUDEP) and the MPPD models for a light exercise breathing pattern: (a) and (b), nose breathing; (b) and (c), mouth breathing.

TABLE 6-5. RATIO OF MPPD TO ICRP DEPOSITION FRACTION FOR SEVERAL SIZE DISTRIBUTIONS

	Nose Breathing, Light Exercise						Mouth Breathing, Light Exercise					
	ICRP	MPPD	Ratio (M/I)[a]	Ratio (M/I)[a]	ICRP	MPPD		ICRP	MPPD	Ratio (M/I)[a]	Ratio (M/I)[a]	ICRP	MPPD
MMD 5.7	σ_g = 2.15			σ_g = 1.00			MMD 5.7	σ_g = 2.15			σ_g = 1.00		
Total	0.86	0.905	1.05	1.04	0.95	0.99	Total	0.717	0.719	1	0.9	0.883	0.797
ET	0.796	0.844	1.06	1.04	0.901	0.94	ET	0.349	0.413	1.18	0.96	0.351	0.336
TB	0.027	0.018	0.67	0.57	0.032	0.018	TB	0.208	0.143	0.69	0.49	0.345	0.168
A	0.037	0.044	1.2	1.87	0.017	0.032	A	0.16	0.163	1.02	1.57	0.187	0.293
MMD 2	σ_g = 2.00			σ_g = 1.00			MMD 2	σ_g = 2			σ_g = 1.00		
Total	0.757	0.741	0.98	0.95	0.866	0.825	Total	0.445	0.371	0.83	0.74	0.401	0.297
ET	0.635	0.631	0.99	0.98	0.706	0.692	ET	0.099	0.09	0.88	0.67	0.045	0.03
TB	0.033	0.033	1.01	0.84	0.041	0.034	TB	0.125	0.08	0.67	0.76	0.091	0.069
A	0.089	0.077	0.87	0.84	0.119	0.099	A	0.221	0.2	0.91	0.75	0.265	0.198
MMD 0.31	σ_g = 2.03			σ_g = 1.00			MMD 0.31	σ_g = 2.03			σ_g = 1.00		
Total	0.211	0.264	1.25	1.53	0.129	0.197	Total	0.135	0.176	1.3	1.54	0.096	0.148
ET	0.095	0.112	1.18	1.55	0.042	0.065	ET	0.01	0.01	1.35	1.48	0.008	0.012
TB	0.022	0.055	2.5	3.16	0.017	0.054	TB	0.024	0.06	2.5	3.14	0.018	0.055
A	0.095	0.097	1.03	1.12	0.069	0.078	A	0.101	0.103	1.02	1.15	0.071	0.081
MMD 0.031	σ_g = 1.7			σ_g = 1.00			MMD 0.031	σ_g = 1.7			σ_g = 1.00		
Total	0.598	0.625	1.05	1.05	0.605	0.637	Total	0.577	0.594	1.03	1.04	0.581	0.606
ET	0.087	0.133	1.53	1.49	0.082	0.122	ET	0.043	0.06	1.49	1.46	0.04	0.059
TB	0.106	0.135	1.27	1.26	0.101	0.128	TB	0.111	0.146	1.32	1.3	0.105	0.136
A	0.405	0.357	0.88	0.92	0.422	0.387	A	0.423	0.384	0.91	0.94	0.437	0.411

[a]MPPD model prediction/ICPP model prediction.

6.6.4.2.2 Deposition as a function of physical exertion

Prior studies show that PM deposition depends on the level of physical exertion. Taking into account exertion levels and activity patterns is necessary in order to estimate the actual exposure of a whole population.

Winter-Sorkina and Cassee (2002) used the MPPD with the five-lobe lung model of Yeh and Schum (1980) to calculate aerosol deposition in the human adult at different levels of physical exertion. Results are quoted directly from Winter-Sorkina and Cassee (2002). Note: Table and figure numbers were changed in the quotation that follows in order to fit sequence in this chapter:

> Levels of physical exertion for adults, corresponding representative activities and corresponding minute ventilation (CARB, 1987) used in the calculation are presented in Table 6-6. The breathing frequency and tidal volume for different physical exertion levels (Table 6-6) are calculated from minute ventilation keeping the ratio of breathing frequency and tidal volume nearly constant. For normal augmenters, the switch to oronasal breathing (combined nose and mouth breathing) is considered to occur at a minute ventilation of 35.3 L/min. Partitions of airflow between the nose and mouth as given by Niinimaa et al. (1981) are used for the oronasal breathing. The partitioning flow is assumed to be the same for inhaled and exhaled air. For minute ventilation lower than this value, breathing is only through the nose, therefore, the calculations present a discontinuity at this point. Calculations are performed for monodisperse aerosol particles with 10 different aerodynamic diameters ranging from 0.01 μm to 10 μm and with a particle density of 1 g/cm^3. The deposited mass rates were calculated for an aerosol concentration of 140 $\mu g/m^3$.
>
> Results on aerosol deposition as a function of physical exertion for different particle sizes are shown in Figure 6-18. The head deposition fractions for 1.3 μm, 2.5 μm and 5 μm particles increase from rest to light exercise. They decrease with a factor of respectively 2.3, 1.8, and 1.5 and further stay about constant when breathing is changed from nasal to oronasal at modest and heavy exercise with minute ventilation of 40 L/min and higher. The head deposition fraction of ultrafine particles decreases slightly from rest to light exercise. Tracheobronchial deposition fractions for ultrafine particles of 0.01 μm, 0.02 μm, and 0.04 μm decrease from rest to light exercise, decrease slightly further to heavy exercise for 0.01 μm particles and stay constant for 0.04 μm particles.
>
> Tracheobronchial deposition fraction for coarse particles decreases slightly from rest to light exercise and rises when breathing is changed from nasal to oronasal. It increases from modest to heavy exercise especially for 5 μm particles. Tracheobronchial deposition fraction of ultrafine particles is larger than deposition fraction of coarse particles at rest, light and modest exercise; however, at heavy exercise the deposition fraction of 5 μm particles is larger than that of ultrafine particles. Pulmonary or alveolar deposition fraction of ultrafine particles increases from rest to light exercise, deposition fraction of coarse 2.5 μm and 5 μm particles decreases from rest to light exercise, rises when breathing is changed from nasal to oronasal and decreases slightly from modest to heavy exercise. Thoracic deposition fraction shows a [s]light increase for 0.01 μm and 0.02 μm particles and a decrease for 2.5 μm and 5 μm particles from rest to light exercise. Deposited

TABLE 6-6. LEVELS OF PHYSICAL EXERTION FOR ADULT, CORRESPONDING REPRESENTATIVE ACTIVITIES, AND BREATHING PARAMETERS

Minute Ventilation, L/min	Breathing Frequency, min^{-1}	Tidal Volume, mL	Exertion Level	Representative Activity
5	10	500	Rest	Sleep
7.5	12	625	Rest	Awake
13	16	813	Light	Walk (4 km/h); washing clothes
19	19	1,000	Light	Walk (5 km/h); bowling; scrubbing floors
25	22	1136	Light	Dance; push a l5 kg wheelbarrow; building activities; piling firewood; walk (7 km/h)
30	24	1,250	Modest	Quiet cycling; pushing a 75 kg wheelbarrow; using a sledgehammer
35	26	1,346	Modest	Climb 3 stairs; play tennis; digging soil
40	28	1,429	Modest	Cycle (23 km/h); walk in snow; digging a trench; jogging
59 (55-63)	34	1735	Heavy	Skiing cross-country; mountaineering; climbing stairs with weight
72	37	1,946	Very heavy	Squash and handball; chopping wood
85	40	2,125	Very heavy	Running (18 km/h); cycle racing
100 (> 100)	44	2273	Extremely heavy	Marathon; triathlon; cross-country ski race

Source: California Air Resources Board (1987).

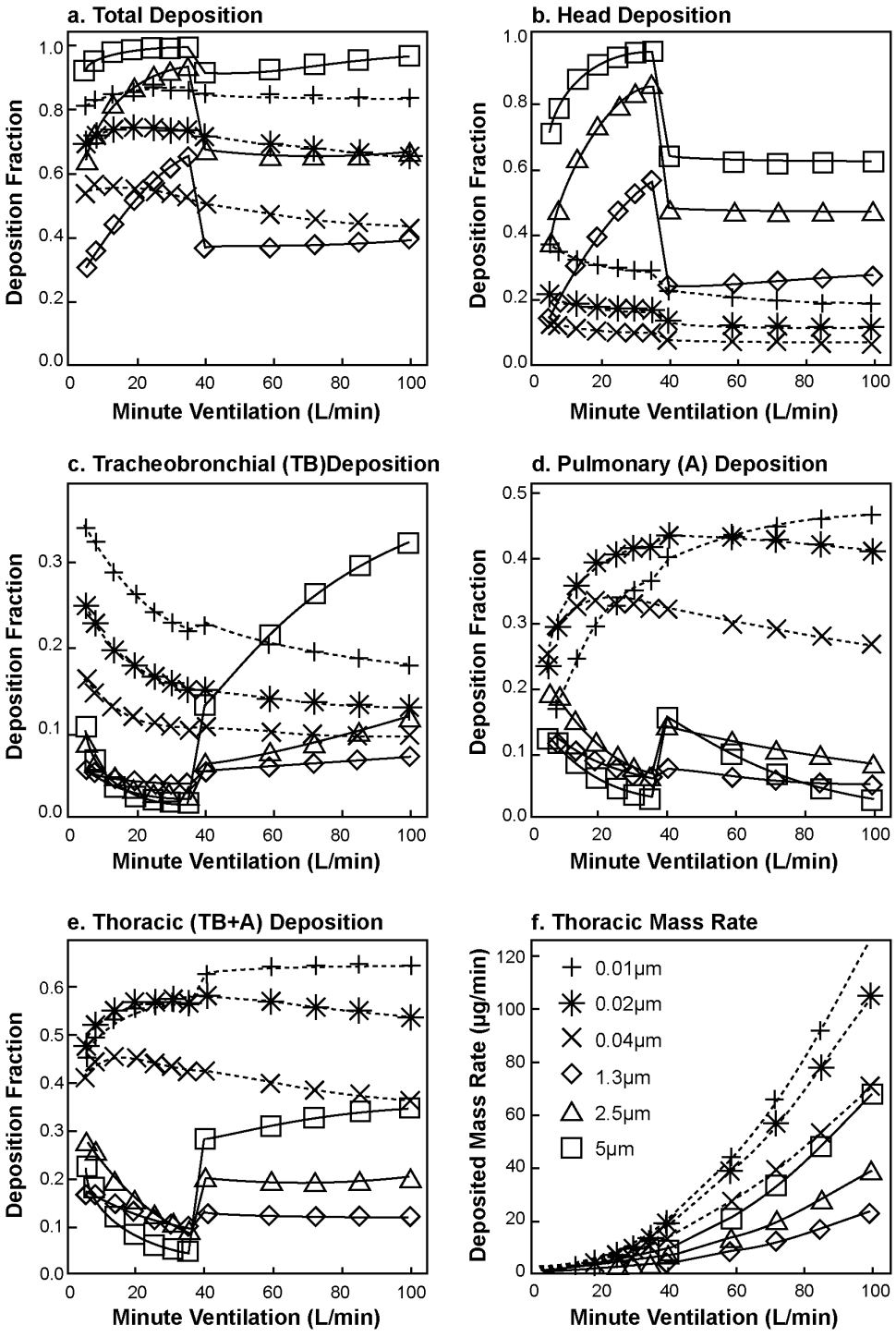

Figure 6-18. Dependency of aerosol deposition in human adults on physical exertion expressed as minute ventilation for different particle sizes. Aerosol concentration used for mass calculation is 140 µg/m^3.

Source: Winter-Sorkina and Cassee (2002).

thoracic mass rate increases with increasing physical exertion, faster for heavy exercise. At light exercise with a minute ventilation of 25 L/min the deposited thoracic mass rate is 13 times larger than at rest awake (7.5 L/min) for 0.01 μm particles and 4 times larger for 5 μm particles. At modest exercise with minute ventilation of 40 L/min the deposited thoracic mass rate is 36 times larger than at rest awake (7.5 L/min) for 0.01 μm particles and 44 times larger for 5 μm particles.

6.6.4.3 Comparisons of Deposition in Humans and Rats

This section presents some results in which the MPPD model was used to compare deposition in humans and rats. The MPPD model uses the multiple-path aerosol deposition model for a rat (Anjilvel and Asgharian, 1995) which incorporates asymmetry in the lung branching structure and calculates deposition at the individual airway level. Deposition calculations for humans used the 5-lobe lung model (Yeh and Schum, 1980). Respiratory parameters used in the model runs are shown in Table 6-7. Resting conditions were used for the rat since rats are usually resting in exposure studies. However, humans are exposed during a variety of conditions from sleep to heavy exercise. Light exercise, as specified in the ICRP model, was chosen for the human. The resulting human to rat ratios would differ for different breathing patterns. The percent deposition for human mouth breathing, human nasal breathing, and rat nasal breathing (rats are obligate nose breathers) are shown in Figure 6-19a, b, and c for ET, TB, and A deposition, respectively. Figure 6-19 also shows the ratios of percent deposition for human to rat for mouth breathing and nasal breathing humans.

TABLE 6-7. RESPIRATORY PARAMETERS FOR HUMANS AND RATS [a]

	Breaths min^{-1}	Tidal Volume mL	FRC [b] mL	URT [b] mL
Rat	102	2.1	4	0.42
Human	20	1250	3300	50

[a] Parameters are for light exercise in humans and at rest in rats.
[b] FRC, functional residual capacity; URT, upper respiratory tract volume.

ET deposition is shown in Figure 6-19a-1. Deposition of coarse mode particles in the ET region increases significantly with particle size because of impaction. However, increased inertia poses a limitation to the ability of particles to enter the ET region. This reduction in the fraction of the aerosol that is actually inhaled is relevant for particle sizes larger than 3 to 4 μm for rats and larger than about 8 μm for humans and is more significant for rats than for humans. The inhalability adjustment (Ménache et al., 1995) used in the MPPD model does not change deposition results for humans significantly; the TB deposition fraction is reduced only 3.5% and thoracic deposition fraction only 2.5% for 10 μm particles. However, in rats, inhalability reduces the nasal deposition fraction by about 80% for 2.5 μm particles, 65% for 5 μm particles, and 44% for 10 μm particles. As a result, TB and pulmonary deposition fractions for large particles are also reduced by about the same fractions. For particle sizes above about 0.15 μm, the ET fractional deposition for nose breathing is greater for humans than rats. This leads to a peak in the human/rat ET deposition ratio for nose breathing at 1 μm (Figure 6-19, Panel a-2). The ET deposition ratio is lower for mouth breathing up to about 8 μm.

The TB deposition fraction (Figure 6-19b-1) is lower for rats than humans in the accumulation mode size range. However, between 1.5 and 5 μm, the fractional deposition for the rat is greater than that for the nasal breathing human. Above about 2.5 μm, the fractional deposition for the mouth breathing human increases rapidly relative to that of the rat.
For A deposition (Figure 6-19c-1), rats and humans have almost the same fractional deposition in the accumulation mode size range. However, the fractional deposition for the nasal breathing human and the rat fall off for particles above about 3 μm, with deposition in the rat decreasing more rapidly than the human. These differences are borne out in the human/rat ratios which become very high for particles above 3 μm.

The relationship between dose per given exposure concentration and time for humans and rats can be understood better if the dose is normalized to a parameter such as lung mass, TB surface area, or A surface area. Values for these parameters are given in Table 6-8. The volume and the surface areas of the lung are not fixed but increase with inhalation and decrease with exhalation. It seems reasonable, therefore, to choose the functional reserve capacity (FRC) at rest as the appropriate lung size to use in normalizing rat and human deposition to lung surface areas. Tracheobronchial and A surface areas were estimated from the human morphology given

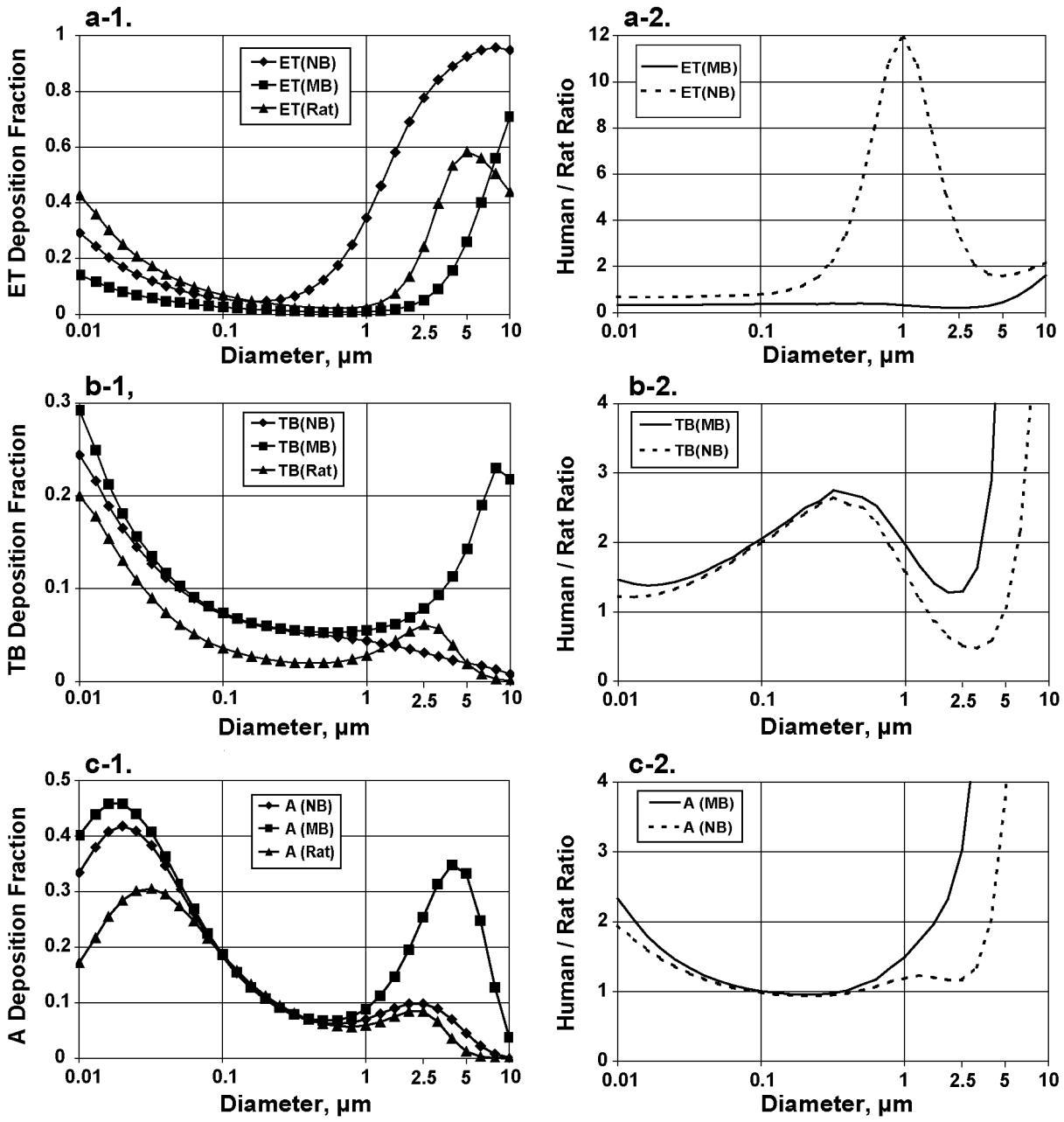

Figure 6-19. Comparison of fractional deposition for rats (nasal breathing, at rest) and humans (nasal and mouth breathing, light exercise) and the ratio of human to rat for nasal and mouth breathing humans for the (a) ET, (b) TB, and (c) A regions of the respiratory tract.

in Yeh and Schum (1980) and the rat morphology given in Yeh et al. (1979) and scaling the lung surface area to the FRC volume.

The fractional deposition values for human and rat, shown in Figure 6-19, can be used with the parameters shown in Table 6-8 to normalize dose for a given exposure to lung mass, TB surface area, or A surface area. Such normalization could be applied to the amount of material deposited or retained in the lung. Retained dose was not considered in these simulations. However, both TB and A clearance are more rapid in rats than in humans and would need to be considered in any estimation of retained dose. While the MPPD model can estimate the clearance of poorly soluble particles, many exposure durations and levels would need to be presented here in order to illustrate the complexity of clearance on retained dose and therefore on human to rat dose ratios.

TABLE 6-8. SURFACE AREA VALUES FOR LUNG MASS AND OF TRACHEOBRONCHIAL AND ALVEOLAR REGIONS FOR HUMANS AND RATS

	Human		*Rat*		*Human/Rat Ratios*	
Lung mass, g	1100		4.34		253	
Surface Areas, m^2						
	TB	A	TB	A	TB	A
Values used in analyses	.442 [a]	57.2 [a]	.00235 [b]	.300 [b]	188	191
Other values	.269 [c]	54 [c]				
		150.3 [d]		.55 [e]		

[a] Based on morphology of Yeh and Schum (1980) scaled to FRC of 3300 cm^3.
[b] Based on morphology of Yeh et al. (1979) scaled to FRC of 4 cm^3.
[c] U.S. EPA (1996a) based on U.S. EPA 1994).
[d] Gehr et al. (1978). (143 m^2 alveolar + 7.3 m^2 respiratory bronchioles).
[e] Mauderly (1979).

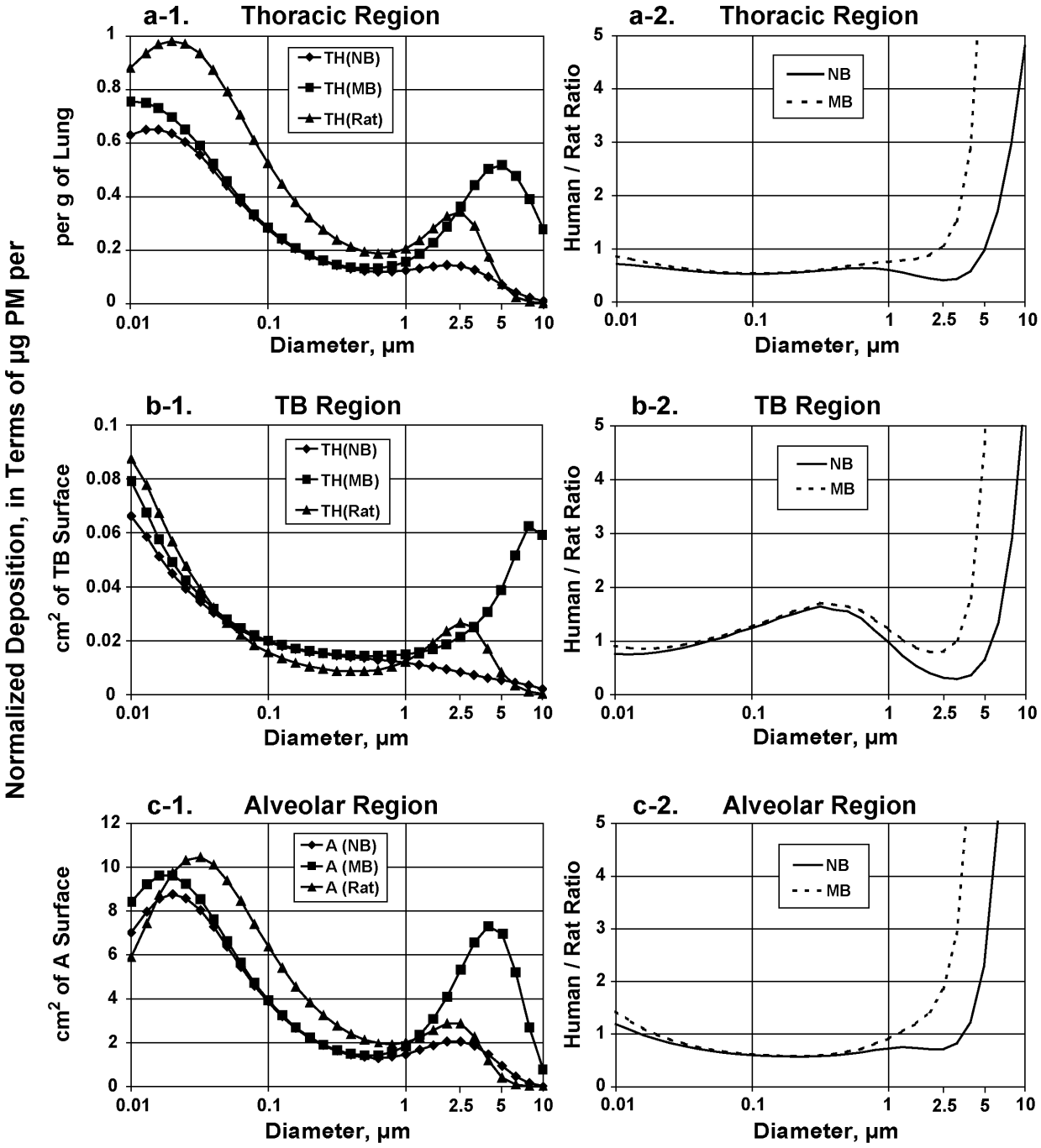

Figure 6-20. Normalized deposition patterns for rats (nasal breathing) and humans (nasal breathing [NB] and mouth breathing [MB]) and the ratio of human to rat. Quantity of PM deposited based on 8-h exposure to 100 µg/m^3.

a. Normalized deposition in the thoracic region (in terms of µg PM per g of lung).

b. Normalized deposition in the TB region C (in terms of µg PM per cm^2 of TB surface).

c. Normalized deposition in the A region (in terms of µg PM per m^2 of A surface).

Figure 6-20a compares deposition of PM by size in humans and rats normalized to lung mass for thoracic (TB + A) deposition. Thoracic deposition, in terms of μg of PM deposited per gram of lung, is smaller for humans than rats for particles below about 2.5 μm for mouth breathing humans and for particles below about 5 μm for nasal breathing humans. As can be seen in 6-20a-2, the ratio of human to rat deposition, especially for mouth breathing, increases to very high values for particles above about 2.5 μm.

Normalized results for surface areas are shown in Figure 6-20b,c. For TB deposition in terms of μg of PM per cm^2 of TB surface, shown in Figure 6-20b, the normalized deposition in the human is greater than that in the rat for accumulation mode particles. However, for particles between about 1 and 2.5 μm, the normalized deposition in the rat is greater than that in the nasal breathing human. Again, the ratios increase rapidly, especially for mouth breathing and for larger particles. The normalized A deposition (Figure 6-20c) for rats is greater than that for humans from about 0.02 to 1 μm. From about 1 to 5 μm, particle deposition is lower in the rat than the mouth breathing human but higher than the nose breathing human. Above about 5 μm, deposition in rats decreases rapidly.

To use the deposited dose ratio plots in Figure 6-20, the following equation applies for exposure (E) levels in humans (H) and rats (R) that yield equivalent doses for a specific particle size and a given dose metric when both species are exposed for the same length of time:

$$E_H = E_R/X \text{ or } E_R = XE_H$$

where X is the human to rat dose ratio for a specific particle size and given dose metric (Miller, 2000a,b). From the above comparison of rats and humans, it would appear that for inhalation studies with accumulation mode aerosols, as might be done using concentrated air particles, equivalent thoracic deposition in rats could be obtained with about 75% of the concentrations for humans (for particles < 2.5 μm). However, for coarse particles the deposition ratios are very sensitive to particle size. Thus, for coarse particles resuspended from bulk material particle size distribution measurements would be needed and very high concentration ratio might be needed for equivalent deposition on a per gram of lung basis.

The ratio would be changed if different tidal volumes or breathing rates were used. For example, the ratio would be higher if a breathing pattern for more rigorous exercise were

used for the humans. The ratio would be lower if a breathing pattern for a human at rest or sleeping or a rat exercising was used. However, for the breathing patterns used, the human/rat comparisons, whether normalized by lung mass or surface areas, indicate that for particles < 2.5 μm normalized human and rat depositions differ by only a factor of about 2. However, for particles between 2.5 and 5 μm, much higher exposures may be required for rats to obtain equivalent normalized doses. As shown in Figure 20, panels a-2, b-2, and c-2, for particles > 5 μm, the inhalation exposure level required to obtain a dose in a rat equivalent to the dose in a human at a given inhalation concentration becomes almost boundless. Given the poor inhalability of particles > 5 μm in rats, few inhaled coarse particles will reach the thorax no matter how high the concentration. Therefore, in order to study the effects of coarse mode particles, either larger animals (e.g., dog, pig, monkey) should be used or rats should be used with an endotracheal inhalation system that allows 100% thoracic penetration.

6.7 SUMMARY AND CONCLUSIONS

6.7.1 Particle Dosimetry

Understanding the mechanisms of action and ultimate biological effects of inhaled particulate matter (PM) requires knowledge of the dosimetry of such material. This is because the proximal cause of the biological response is due to the dose of particles delivered to and retained at the target site, rather than the exposure concentration. Deposition, clearance, and retention comprise the essential elements of dosimetry. Properly characterizing the dosimetry of inhaled particles is essential for extrapolating effects found in controlled exposure studies of laboratory animals to those observed in human exposure studies and for relating effects in healthy individuals to those in potentially susceptible persons.

The understanding of total and regional deposition as a function of particle size has improved since publication of the 1996 PM AQCD. The extrathoracic (ET) region, especially the nasal passages, is an efficient filter for small ultrafine (< 0.01 μm) and larger coarse particles, but filtration is less efficient for larger ultrafine and fine particles. Accordingly, particles removed in the ET region are not available for deposition in the tracheobronchial (TB) and alveolar (A) regions of the respiratory tract. Within the thoracic region, the deposition distribution of ultrafine particles (0.01 to 0.1 μm) is highly skewed towards the proximal airway

regions and resembles that of coarse particles. Thus, the deposition patterns for ultrafine particles are similar to those of coarse-mode particles, with significant fractional deposition in all three regions. Particles in the accumulation mode size range (0.1 to 1.0 μm) have lower fractional deposition in all three regions.

The dose information expressed by fractional deposition may be applied only to acute exposure conditions. Retained dose at any given time is determined by the balance between deposition and clearance. In this regard, a long-term retained dose can be much greater than an acute exposure dose in individuals with impaired clearance mechanisms.

6.7.2 Host Factors

Certain host factors have a marked effect on particle dosimetry and can affect the fraction of inhaled particles that are deposited and/or retained.

Gender

There are small but statistically significant gender differences in the homogeneity of deposition as well as the deposition rate of particles. These differences arise from differences between males and females in body size, conducting airway size, and ventilatory parameters. At a fixed breathing pattern (i.e., tidal volume and breathing frequency), females have a greater deposition of coarse mode particles in the ET and TB regions, and lower deposition in the A region. This gender effect appears to be particle-size dependent, showing a greater fractional deposition in females for very small ultrafine and large coarse particles. Specifically, total fractional lung deposition for 0.04 and 0.06 μm particles is slightly greater in females than males but only negligibly so for particles in the 0.8 to 1.0 μm size range. As the particle size increases (3 to 5 μm), total fractional deposition increases more rapidly in females than in males. While deposition is greater in certain particle size ranges and more localized in females than males at a fixed breathing condition, the gender difference may not be evident unless breathing patterns are controlled. In fact, the deposition rate can be greater in males during spontaneous breathing because of a greater ventilation rate in males compared to women.

Exercise

Exercise may also increase the potential health risks of inhaled particles because exercise increases the rate of oxygen consumption and changes ventilatory parameters (airflow rate and breathing patterns). The switch from nose breathing to mouth breathing, which occurs as exercise intensity increases, leads to an increase in fractional deposition of coarse particles in the TB and A regions. The higher breathing rate and larger tidal volume lead to a greater amount of deposition. Total lung deposition rate may be 3 to 4 times greater during exercise. The more rapid breathing of children also leads to a greater amount of deposition.

Age

Airway structure and physiological function vary with age and health status of the respiratory tract. Such variations may alter the deposition patterns for inhaled particles. Significant age differences have been predicted by mathematical models and observed in experimental studies. Although reported data are insufficient for making a firm conclusion, these studies generally indicate that ET and TB deposition is greater in children and that children receive greater doses of particles per lung surface area than adults. Unfortunately, deposition studies in another susceptible population, the elderly, are still limited.

Lung Disease

A number of studies have examined particle deposition in chronic lung disease. These studies indicate that total lung deposition is generally increased with airways obstruction. Airflow distribution is uneven in obstructive diseases, and deposition can be enhanced locally in areas of active ventilation.

6.7.3 Laboratory Animal Studies

It is difficult to systematically compare deposition patterns in laboratory animals used in dosimetric studies. Deposition patterns are generally similar between laboratory animals and humans, but there are absolute differences in deposition fractions. In most laboratory animal species, deposition in the ET region is near 100% for particles greater than 5 μm, indicating greater nasal deposition efficiency than that seen in humans. Clearance processes are similar in

animals and humans, but the clearance rate for particles is typically faster in small laboratory animals.

Once particles are deposited on the surface of the airways, they are subsequently cleared from the respiratory tract or translocated to other sites within the body by distinct regional processes. Ultrafine particles can be rapidly cleared from the lungs into the systemic circulation where they can be transported to extrapulmonary regions. Such transport could provide a mechanism whereby particles could affect cardiovascular function as reported in the epidemiology studies (Chapter 8). However, there is a need for better laboratory animal models of susceptible human populations.

6.7.4 Mathematical Models

There has been significant improvement in the mathematical and computational fluid dynamic modeling of particle dosimetry in the respiratory tract. Although the models have become more sophisticated and adaptable, models inevitably use simplistic lung morphology and idealistic airflow patterns. Models use a number of assumptions in deposition processes and employ different computational schemes. As such, model predictions can vary substantially depending on approaches used. Validation of the models by experimental data is critical as new experimental data become available.

6.7.5 Key Points

- Dosimetry establishes the relationship between PM exposure and the dose of PM delivered to and retained at the target site. Deposition, clearance, translocation, and retention comprise the essential elements of dosimetry.
- Dosimetric information is critical for extrapolating effects found in controlled exposure studies of laboratory animals to those observed in human exposure studies and for relating effects in normal healthy persons to those in potentially susceptible persons.
- Based on anatomical features, the respiratory tract may be divided into three regions: extrathoracic (ET), tracheobronchial (TB), and alveolar (A). Particle deposition and clearance differ for these regions.
- Particles in the middle of accumulation mode size range (0.3 to 1.0 μm) have the lowest deposition fraction in the ET and TB regions.

- The fractional deposition of ultrafine particles in the A region peaks between 0.02 and 0.03 μm and is greater than predicted for both accumulation and coarse mode particles. For coarse particles, fractional deposition peaks between 4 and 6 μm for the TB region and between 2.5 and 5 μm for the A region.

- A significant fraction of ultrafine and coarse particles, but not particles in the accumulation-mode size range, are deposited in the ET region.

- Once particles are deposited on the surface of the airways, they are subsequently cleared from the respiratory tract or translocated to other sites within the system by distinct regional processes.

- Fractional deposition depends on particle size, lung size, tidal volume, and breathing rate. Exercising subjects receive higher thoracic doses of particles per cm^2 of lung surface than subjects at rest. This occurs mainly due to an increase in tidal volume and minute ventilation during exercise. Shifting from nasal to oronasal breathing is another factor for increased thoracic deposition.

- Airway structure and physiological function vary with age. Such variations may alter the deposition patterns for inhaled particles. Airflow distribution can be very uneven in obstructed lungs, and deposition can be enhanced locally in areas of active ventilation. Total lung deposition is generally increased by obstructed airways, so that particle deposition is enhanced in people with chronic lung disease. Unfortunately, deposition studies in another susceptible population, the elderly, are still limited.

- Computational models allow calculation of fractional deposition and dose per cm^2 of lung surface as a function of particle size and respiratory parameters for humans and some animals (e.g., the laboratory rat). Such calculations can be used to predict the exposures needed to produce comparable doses for animal to human extrapolation.

- Computational models have been improved in recent years, but experimental validation of model predictions is still required.

REFERENCES

Adamson, I. Y. R.; Bowden, D. H. (1981) Dose response of the pulmonary macrophagic system to various particulates and its relationship to transepithelial passage of free particles. Exp. Lung Res. 2: 165-175.

Adamson, I. Y. R.; Hedgecock, C. (1995) Patterns of particle deposition and retention after instillation to mouse lung during acute injury and fibrotic repair. Exp. Lung Res. 21: 695-709.

Adamson, I. Y. R.; Prieditis, H. (1998) Silica deposition in the lung during epithelial injury potentiates fibrosis and increases particle translocation to lymph nodes. Exp. Lung Res. 24: 293-306.

Adgate, J. L.; Ramachandran, G.; Pratt, G. C.; Waller, L. A.; Sexton, K. (2002) Spatial and temporal variability in outdoor, indoor, and personal $PM_{2.5}$ exposure. Atmos. Environ. 36: 3255-3265.

American Conference of Governmental Industrial Hygienists (ACGIH). (1985) Particle size-selective sampling in the workplace: report of the ACGIH technical committee on air sampling procedures. Cincinnati, OH: American Conference of Governmental Industrial Hygienists.

Anjilvel, S.; Asgharian, B. (1995) A multiple-path model of particle deposition in the rat lung. Fundam. Appl. Toxicol. 28: 41-50.

Asgharian, B.; Anjilvel, S. (1994) Inertial and gravitational deposition of particles in a square cross section bifurcating airway. Aerosol Sci. Technol. 20: 177-193.

Asgharian, B.; Wood, R.; Schlesinger, R. B. (1995) Empirical modeling of particle deposition in the alveolar region of the lungs: a basis for interspecies extrapolation. Fundam. Appl. Toxicol. 27: 232-238.

Asgharian, B.; Miller, F. J.; Subramaniam, R. P. (1999) Dosimetry software to predict particle deposition in humans and rats. CIIT Activities 19(3). Available: http://libpc.ciit.org/Activities/1999/V19N3.pdf [30 September, 2004].

Asgharian, B.; Hofmann, W.; Miller, F. J. (2001) Mucociliary clearance of insoluble particles from the tracheobronchial airways of the human lung. Aerosol Sci. 32: 817-832.

Balásházy, I.; Hofmann, W. (1993a) Particle deposition in airway bifurcations–I: inspiratory flow. J. Aerosol Sci. 24: 745-772.

Balásházy, I.; Hofmann, W. (1993b) Particle deposition in airway bifurcations–II: expiratory flow. J. Aerosol Sci. 24: 773-786.

Balásházy, I.; Hofmann, W. (1995) Deposition of aerosols in asymmetric airway bifurcations. J. Aerosol Sci. 26: 273-292.

Balásházy, I.; Hofmann, W. (2001) Fluid dynamics and related particle deposition patterns in human airway bifurcations. In: Martonen, T. B., ed., Medical Applications of Computer Modeling: The Respiratory System. WIT Press, Southampton, Boston. p. 84-108.

Balásházy, I.; Hofmann, W.; Heistracher, T. (1999) Computation of local enhancement factors for the quantification of particle deposition patterns in airway bifurcations. J. Aerosol Sci. 30: 185-203.

Becquemin, M. H.; Swift, D.L.; Bouchikhi, A.; Roy, M.; Teillac, A. (1991) Particle deposition and resistance in the noses of adults and children. Eur. Resp. J. 4: 694-702.

Bell, K. A.; Friedlander, S. K. (1973) Aerosol deposition in models of a human lung bifurcation. Staub Reinhalt. Luft 33: 178-182.

Bennett, W. D.; Ilowite, J. S. (1989) Dual pathway clearance of ^{99m}Tc-DTPA from the bronchial mucosa. Am. Rev. Respir. Dis. 139: 1132-1138.

Bennett, W. D.; Zeman, K. L. (1998) Deposition of fine particles in children spontaneously breathing at rest. Inhalation Toxicol. 10: 831-842.

Bennett, W. D.; Zeman, K. L.; Kim, C. (1996) Variability of fine particle deposition in healthy adults: effect of age and gender. Am. J. Respir. Crit. Care Med. 153: 1641-1647.

Bennett, W. D.; Zeman, K. L.; Kang, C. W.; Schechter, M. S. (1997a) Extrathoracic deposition of inhaled, coarse particles (4.5 μm) in children vs. adults. In: Cherry, N.; Ogden, T., eds. Inhaled particles VIII: proceedings of an international symposium on inhaled particles organized by the British Occupational Hygiene Society; August 1996; Cambridge, UK. Ann. Occup. Hyg. 41(suppl. 1): 497-502.

Bennett, W. D.; Zeman, K. L.; Kim, C.; Mascarella, J. (1997b) Enhanced deposition of fine particles in COPD patients spontaneously breathing at rest. Inhalation Toxicol. 9: 1-14.

Bennett, W. D.; Scheuch, G.; Zeman, K. L.; Brown, J. S.; Kim, C.; Heyder, J.; Stahlhofen, W. (1998) Bronchial airway deposition and retention of particles in inhaled boluses: effect of anatomic dead space. J. Appl. Physiol. 85: 685-694.

Bennett, W. D.; Scheuch, G.; Zeman, K. L.; Brown, J. S.; Kim, C.; Heyder, J.; Stahlhofen, W. (1999) Regional deposition and retention of particles in shallow, inhaled boluses: effect of lung volume. J. Appl. Physiol. 86: 168-173.

Benson, J. M.; Henderson, R. F.; McClellan, R. O.; Hanson, R. L.; Rebar, A. H. (1986) Comparative acute toxicity of four nickel compounds to F344 rat lung. Fundam. Appl. Toxicol. 7: 340-347.

Brauer, M.; Avila-Casado, C.; Fortoul, T. I.; Vedal, S.; Stevens, B.; Churg, A. (2001) Air pollution and retained particles in the lung. Environ. Health Perspect. 109: 1039-1043.

Broday, D. M.; Georgopoulos, P. G. (2001) Growth and deposition of hygroscopic particulate matter in the human lungs. Aerosol Sci. Technol. 34: 144-159.

Brown, J. S.; Kirby, Z. L.; Bennett, W. D. (2001) Regional deposition of coarse particles and ventilation distribution in healthy subjects and patients with cystic fibrosis. J. Aerosol Med. 14: 443-454.

Brown, J. S.; Zeman, K. L.; Bennett, W. D. (2002) Ultrafine particle deposition and clearance in the healthy and obstructed lung. Am. J. Respir. Crit. Care Med. 166: 1240-1247.

Burch, W. M. (2002) Comment on "Passage of inhaled particles into the blood circulation in humans". Circulation 106: e141-e142.

California Air Resources Board. (1987) Ambient air quality standard for ozone: health and welfare effects. Sacramento, CA: California Air Resources Board.

Camner, P.; Anderson, M.; Philipson, K.; Bailey, A.; Hashish, A.; Jarvis, N.; Bailey, M.; Svartengren, M. (1997) Human bronchiolar deposition and retention of 6-, 8-, and 10-μ particles. Exp. Lung Res. 23: 517-535.

Chang, Y. H.; Yu, C. P. (1999) A model of ventilation distribution in the human lung. Aerosol Sci. Technol. 30: 309-319.

Cheng, Y.-S.; Smith, S. M.; Yeh, H.-C.; Kim, D.-B.; Cheng, K.-H.; Swift, D. L. (1995) Deposition of ultrafine aerosols and thoron progeny in replicas of nasal airways of young children. Aerosol. Sci. Technol. 23: 541-552.

Cheng, K.-H.; Cheng, Y.-S.; Yeh, H.-C.; Guilmette, R. A.; Simpson, S. Q.; Yang, Y.-H.; Swift, D. L. (1996) *In vivo* measurements of nasal airway dimensions and ultrafine aerosol deposition in the human nasal and oral airways. J. Aerosol Sci. 27: 785-801.

Cheng, K.-H.; Cheng, Y.-S.; Yeh, H.-C.; Swift, D. L. (1997) An experimental method for measuring aerosol deposition efficiency in the human oral airway. Am. Ind. Hyg. Assoc. J. 58: 207-213.

Churg, A.; Brauer, M. (1997) Human lung parenchyma retains $PM_{2.5}$. Am. J. Respir. Crit. Care Med. 155: 2109-2111.

Churg, A.; Vedal, S. (1996) Carinal and tubular airway particle concentrations in the large airways of non-smokers in the general population: evidence for high particle concentration at airway carinas. Occup. Environ. Med. 53: 553-558.

Cohen, B. S.; Harley, N. H.; Schlesinger, R. B.; Lippmann, M. (1988) Nonuniform particle deposition on tracheobronchial airways: implications for lung dosimetry. In: Dodgson, J.; McCallum, R. I.; Bailey, M. R.; Fisher, D. R., eds. Inhaled particles VI: proceedings of an international symposium and workshop on lung dosimetry; September 1985; Cambridge, United Kingdom. Ann. Occup. Hyg. 32 (suppl. 1): 1045-1053.

Cohen, B. S.; Sussman, R. G.; Lippmann, M. (1990) Ultrafine particle deposition in a human tracheobronchial cast. Aerosol Sci. Technol. 12: 1082-1091.

Cohen, B. S.; Xiong, J. Q.; Fang, C.-P.; Li, W. (1998) Deposition of charged particles on lung airways. Health Phys. 74: 554-560.

Comer, J. K.; Kleinstreuer, C.; Hyun, S.; Kim, C. S. (2000) Aerosol transport and deposition in sequentially bifurcating airways. J. Biomech. Eng. 122: 152-158.

Comer, J. K.; Kleinstreuer, C.; Zhang, Z. (2001a) Flow structures and particle deposition patterns in double bifurcation airway models. Part 1. Air flow fields. J. Fluid Mech. 435: 24-54.

Comer, J. K.; Kleinstreuer, C.; Kim, C. S. (2001b) Flow structures and particle deposition patterns in double bifurcation airway models. Part 2. Aerosol transport and deposition. J. Fluid Mech. 435: 55-80.

Crapo, J. D.; Barry, B. E.; Gehr, P.; Bachofen, M.; Weibel, E. R. (1982) Cell characteristics of the normal human lung. Am. Rev. Respir. Dis. 125: 740-745.

Crystal, R. G., West, J. B.; Barnes, P. J.; Weibel, E. R., eds. (1997) The lung: scientific foundations. Volume 1. Section III: major components. 2nd ed. Philadelphia, PA: Lippincott-Raven; chapters 30-67, pp. 445-991.

Cuddihy, R. G. (1984) Mathematical models for predicting clearance of inhaled radioactive materials. In: Smith, H.; Gerber, G., eds. Lung modelling for inhalation of radioactive materials: proceedings of a meeting jointly organized by the Commission of the European Communities and the National Radiological Protection Board; March; Oxford, United Kingdom. Luxembourg: Commission of the European Communities; pp. 167-179; report no. EUR 9384 EN.

Cuddihy, R. G.; Yeh, H. C. (1988) Respiratory tract clearance of particles and substances dissociated from particles. In: Mohr, U.; Dungworth, D.; Kimmerle, G.; Lewkowski, J.; McClellan, R.; Stöber, W., eds. Inhalation toxicology: the design and interpretation of inhalation studies and their use in risk assessment. New York, NY: Springer-Verlag; pp. 169-193.

Darquenne, C. (2001) A realistic two-dimensional model of aerosol transport and deposition in the alveolar zone of the human lung. J. Aerosol Sci. 32: 1161-1174.

Dorries, A. M.; Valberg, P. A. (1992) Heterogeneity of phagocytosis for inhaled versus instilled material. Am. Rev. Respir. Dis. 146: 831-837.

Driscoll, K. E. (1995) The toxicology of crystalline silica studied *in vitro*. Appl. Occup. Environ. Hyg. 10: 1118-1125.

Driscoll, K. E.; Costa, D. L.; Hatch, G.; Henderson, R.; Oberdörster, G.; Salem, H.; Schlesinger, R. B. (2000) Intratracheal instillation as an exposure technique for the evaluation of respiratory tract toxicity: uses and limitations. Toxicol. Sci. 55: 24-35.

Falk, R.; Philipson, K.; Svartengren, M.; Jarvis, N.; Bailey, M.; Camner, P. (1997) Clearance of particles from small ciliated airways. Exp. Lung Res. 23: 495-515.

Falk, R.; Philipson, K.; Svartengren, M.; Bergmann, R.; Hofmann, W.; Jarvis, N.; Bailey, M.; Camner, P. (1999) Assessment of long-term bronchiolar clearance of particles from measurements of lung retention and theoretical estimates of regional deposition. Exp. Lung Res. 25: 495-516.

Ferin, J. (1977) Effect of particle content of lung on clearance pathways. In: Sanders, C. L.; Schneider, R. P.; Dagle, G. E.; Ragan, H. A., eds. Pulmonary macrophages and epithelial cells: proceedings of the sixteenth annual Hanford biology symposium; September 1976; Richland, WA. Oak Ridge, TN: Energy Research and Development Administration; pp. 414-423. Available from: NTIS, Springfield, VA; CONF-760927. (ERDA symposium series 43).

Ferin, J.; Feldstein, M. L. (1978) Pulmonary clearance and hilar lymph node content in rats after particle exposure. Environ. Res. 16: 342-352.

Ferin, J.; Oberdörster, G.; Penney, D. P. (1992) Pulmonary retention of ultrafine and fine particles in rats. Am. J. Respir. Cell Mol. Biol. 6: 535-542.

Findeisen, W. (1935) Über das Absetzen kleiner, in der Luft suspendierter Teilchen in der menschlichen Lunge bei der Atmung [The deposition of small airborne particles in the human lung during respiration]. Pfluegers Arch. Gesamte Physiol. Menschen Tiere 236: 367-379.

Foster, W. M.; Langenback, E.; Bergofsky, E. H. (1980) Measurement of tracheal and bronchial mucus velocities in man: relation to lung clearance. J. Appl. Physiol.: Respir. Environ. Exercise Physiol. 48: 965-971.

Frampton, M. W.; Chalupa, D.; Morrow, P. E.; Gibb, F. R.; Oberdörster, G.; Speers, D. M.; Zareba, W.; Utell, M. J. (2000) Deposition and effects of inhaled ultrafine carbon particles in healthy subjects at rest. Presented at: PM2000: particulate matter and health—the scientific basis for regulatory decision-making, specialty conference & exhibition; January; Charleston, SC. Pittsburgh, PA: Air & Waste Management Association.

Fry, F. A.; Black, A. (1973) Regional deposition and clearance of particles in the human nose. J. Aerosol Sci. 4: 113-124.

Gehr, P.; Bachofen, M.; Weibel, E. R. (1978) The normal human lung: ultrastructure and morphometric estimation of diffusion capacity. Respir. Physiol. 32: 121-140.

Gehr, P.; Schürch, S.; Berthaiume, Y.; Im Hof, V.; Geiser, M. (1990) Particle retention in airways by surfactant. J. Aerosol Med. 3: 27-43.

Gehr, P.; Im Hof, V.; Geiser, M.; Schürch, S. (1991) The fate of particles deposited in the intrapulmonary conducting airways. J. Aerosol Med. 4: 349-362.

Gradoń, L.; Orlicki, D. (1990) Deposition and inhaled aerosol particles in a generation of the tracheobronchial tree. J. Aerosol Sci. 21: 3-19.

Green, F. H. Y. (2000) Pulmonary responses to inhaled poorly soluble particulate in the human. In: Gardner, D. E., ed. ILSI Risk Science Institute Workshop: The Relevance of the Rat Lung Response to Particle Overload for Human Risk Assessment; March, 1998. Inhalation Toxicol. 12: 59-95.

Groth, M. L.; Macri, K.; Foster, W. M. (1997) Cough and mucociliary transport of airway particulate in chronic obstructive lung disease. In: Cherry, N.; Ogden, T., eds. Inhaled Particles VIII: proceedings of an international symposium on inhaled particles organised by the British Occupational Hygiene Society; August 1996; Cambridge, UK. Ann. Occup. Hyg. 41(suppl.): 515-521.

Guilmette, R. A.; Cheng, Y. S.; Griffith, W. C. (1997) Characterising the variability in adult human nasal airway dimensions. In: Cherry, N.; Ogden, T., eds. Inhaled Particles VIII: proceedings of an international symposium on inhaled particles organised by the British Occupational Hygiene Society; August 1996; Cambridge, UK. Ann. Occup. Hyg. 41(suppl. 1): 491-496.

Harmsen, A. G.; Muggenburg, B. A.; Snipes, M. B.; Bice, D. E. (1985) The role of macrophages in particle translocation from lungs to lymph nodes. Science (Washington, DC) 230: 1277-1280.
Heistracher, T.; Hofmann, W. (1995) Physiologically realistic models of bronchial airway bifurcation. J. Aerosol Sci. 26: 497-509.
Heistracher, T.; Hofmann, W. (1997) Flow and deposition patterns in successive airway bifurcations. In: Cherry, N.; Ogden, T., eds. Inhaled Particles VIII: proceedings of an international symposium on inhaled particles organised by the British Occupational Hygiene Society; August 1996; Cambridge, UK. Ann. Occup. Hyg. 41(suppl.): 537-542.
Henderson, R. F.; Driscoll, K. E.; Harkema, J. R.; Lindenschmidt, R. C.; Chang, I.-Y.; Maples, K. R.; Barr, E. B. (1995) A comparison of the inflammatory response of the lung to inhaled versus instilled particles in F344 rats. Fundam. Appl. Toxicol. 24: 183-197.
Henshaw, D. L.; Fews, A. P. (1984) The microdistribution of alpha emitting particles in the human lung. In: Smith, H.; Gerber, G., eds. Lung modelling for inhalation of radioactive materials: proceedings of a meeting jointly organized by the Commission of the European Communities and the National Radiological Protection Board; March; Oxford, United Kingdom. Luxembourg: Commission of the European Communities; pp. 199-218; report no. EUR 9384 EN.
Heyder, J.; Rudolf, G. (1977) Deposition of aerosol particles in the human nose. In: Walton, W. H.; McGovern, B., eds. Inhaled particles IV: proceedings of an international symposium, part 1; September 1975; Edinburgh, United Kingdom. Oxford, United Kingdom: Pergamon Press, Ltd.; pp. 107-126.
Hiller, F. C. (1991) Health implications of hygroscopic particle growth in the human respiratory tract. J. Aerosol Med. 4: 1-23.
Hinds, W. C. (1999) Aerosol technology: properties, behavior, and measurement of airborne particles. 2nd ed. New York, NY: John Wiley & Sons.
Hofmann, W.; Bergmann, R. (1998) Predictions of particle deposition patterns in human and rat airways. Inhalation Toxicol. 10: 557-583.
Hofmann, W.; Martonen, T. B.; Graham, R. C. (1989a) Predicted deposition of nonhygroscopic aerosols in the human lung as a function of subject age. J. Aerosol Med. 2: 49-68.
Hofmann, W.; Koblinger, L.; Martonen, T. B. (1989b) Structural differences between human and rat lungs: implications for Monte Carlo modeling of aerosol deposition. In: Mahaffey, J. A., ed. 26th Hanford life sciences symposium, modeling for scaling to man: biology, dosimetry, and response. Health Phys. 57(suppl. 1): 41-47.
Hofmann, W.; Balásházy, I.; Heistracher, T.; Koblinger, L. (1996) The significance of particle deposition patterns in bronchial airway bifurcations for extrapolation modeling. Aerosol Sci. Technol. 25: 305-327.
Hofmann, W.; Bergmann, R.; Koblinger, L. (1999) Characterization of local particle deposition patterns in human and rat lungs by different morphometric parameters. J. Aerosol Sci. 30: 651-667.
Hofmann, W.; Asgharian, B.; Bergmann, R.; Anjilvel, S.; Miller, F. J. (2000) The effect of heterogeneity of lung structure on particle deposition in the rat lung. Toxicol. Sci. 53: 430-437.
Hsieh, T. H.; Yu, C. P. (1998) Two-phase pulmonary clearance of insoluble particles in mammalian species. Inhalation Toxicol. 10: 121-130.
Huchon, G. J.; Montgomery, A. B.; Lipavsky, A.; Hoeffel, J. M.; Murray, J. F. (1987) Respiratory clearance of aerosolized radioactive solutes of varying molecular weight. J. Nucl. Med. 28: 894-902.
International Commission on Radiological Protection. (1960) Report of Committee II on permissible dose for internal radiation (1959). Health Phys. 3.
International Commission on Radiological Protection. (1979) Limits for intakes of radionuclides by workers. Oxford, United Kingdom: Pergamon Press; ICRP publication 30, part 1.
International Commission on Radiological Protection. (1994) Human respiratory tract model for radiological protection: a report of a task group of the International Commission on Radiological Protection. Oxford, United Kingdom: Elsevier Science Ltd. (ICRP publication 66; Annals of the ICRP: v. 24, pp. 1-482).
Jaques, P. A.; Kim, C. S. (2000) Measurement of total lung deposition of inhaled ultrafine particles in healthy men and women. Inhalation Toxicol. 12: 715-731.
John, J.; Wollmer, P.; Dahlbäck, M.; Luts, A.; Jonson, B. (1994) Tidal volume and alveolar clearance of insoluble particles. J. Appl. Physiol. 76: 584-588.
Katz, I. M. (2001) Computer modeling of fluid dynamics and particle motion in the larynx and trachea. In: Martonen, T. B., ed. Medical Applications of Computer Modeling: The Respiratory System. Boston, MA: WIT Press, pp. 47-63.
Katz, I. M.; Martonen, T. B. (1996) Three-dimensional fluid particle trajectories in the human larynx and trachea. J. Aerosol Med. 9: 513-520.

Katz, I. M., Martonen, T. B., and Flaa, W. (1997) Three-dimensional computational study of inspiratory aerosol flow through the larynx: the effect of glottal aperture modulation. J. Aerosol Sci. 28: 1073-83.
Katz, I. M.; Davis, B. M.; Martonen, T. B. (1999) A numerical study of particle motion within the human larynx and trachea. J. Aerosol Sci. 30: 173-183.
Kaye, S. R.; Phillips, C. G.; Winlove, C. P. (2000) Measurement of non-uniform aerosol deposition patterns in the conducting airways of the porcine lung. J. Aerosol Sci. 31: 849-866.
Kesavanathan, J.; Swift, D. L. (1998) Human nasal passage particle deposition: the effect of particle size, flow rate, and anatomical factors. Aerosol Sci. Technol. 28: 457-463.
Keyhani, K.; Scherer, P. W.; Mozell, M. M. (1995) Numerical simulation of airflow in the human nasal cavity. J. Biomech. Eng. 117: 429-41.
Kim, C. S. (2000) Methods of calculating lung delivery and deposition of aerosol particles. Respir. Care 45: 695-711.
Kim, C. S.; Fisher, D. M. (1999) Deposition characteristics of aerosol particles in sequentially bifurcating airway models. Aerosol Sci. Technol. 31:198-220.
Kim, C. S.; Garcia, L. (1991) Particle deposition in cyclic bifurcating tube flow. Aerosol Sci. Technol. 14: 302-315.
Kim, C. S.; Hu, S. C. (1998) Regional deposition of inhaled particles in human lungs: comparison between men and women. J. Appl. Physiol. 84: 1834-1844.
Kim, C. S.; Iglesias, A. J. (1989) Deposition of inhaled particles in bifurcating airway models: I. inspiratory deposition. J. Aerosol Med. 2: 1-14.
Kim, C. S.; Jaques, P. A. (2000) Respiratory dose of inhaled ultrafine particles in healthy adults. Phil. Trans. Roy. Soc. London A 358: 2693-2705.
Kim, C. S.; Kang, T. C. (1997) Comparative measurement of lung deposition of inhaled fine particles in normal subjects and patients with obstructive airway disease. Am. J. Respir. Crit. Care Med. 155: 899-905.
Kim, C. S.; Fisher, D. M.; Lutz, D. J.; Gerrity, T. R. (1994) Particle deposition in bifurcating airway models with varying airway geometry. J. Aerosol Sci. 25: 567-581.
Kim, C. S.; Hu, S. C.; DeWitt, P.; Gerrity, T. R. (1996) Assessment of regional deposition of inhaled particles in human lungs by serial bolus delivery method. J. Appl. Physiol. 81: 2203-2213.
Kimbell, J. S. (2001) Computational fluid dynamics of the extrathoracic airways. In: Martonen, T. B., ed. Medical Applications of Computer Modeling: The Respiratory System. Boston, MA: WIT Press; pp. 11-45.
Kinsara, A. A.; Tompson, R. V.; Loyalka, S. K. (1993) Computational flow and aerosol concentration profiles in lung bifurcations. Health Phys. 64: 13-22.
Koblinger, L.; Hofmann, W. (1985) Analysis of human lung morphometric data for stochastic aerosol deposition calculations. Phys. Med. Biol. 30: 541-556.
Koblinger, L.; Hofmann, W. (1988) Stochastic morphological model of the rat lung. Anat. Rec. 221: 533-539.
Koch, W.; Stöber, W. (2001) A simple pulmonary retention model accounting for dissolution and macrophage-mediated removal of deposited polydisperse particles. Inhalation Toxicol. 13: 129-148.
Kodavanti, U. P.; Schladweiler, M. C. J.; Ledbetter, A. D.; Hauser, R.; Christiani, D. C.; Samet, J. M.; McGee, J.; Richards, J. H.; Costa, D. L. (2002) Pulmonary and systemic effects of zinc-contining emission particles in three rat strains: multiple exposure scenarios. Toxicol. Sci. 70: 73-85.
Kohlhäufl, M.; Brand, P.; Scheuch, G.; Meyer, T. S.; Schulz, H.; Häussinger, K.; Heyder, J. (1999) Increased fine particle deposition in women with asymptomatic nonspecific airway hyperresponsiveness. Am. J. Respir. Crit. Care Med. 159: 902-906.
Kreyling, W. G. (1992) Intracellular particle dissolution in alveolar macrophages. Environ. Health Perspect. 97 :121-126.
Kreyling, W. G.; Blanchard, J. D.; Godleski, J. J.; Haeussermann, S.; Heyder, J.; Hutzler, P.; Schulz, H.; Sweeney, T. D.; Takenaka, S.; Ziesenis, A. (1999) Anatomic localization of 24- and 96-h particle retention in canine airways. J. Appl. Physiol. 87: 269-284.
Kreyling, W. G.; Semmler, M.; Erbe, F.; Mayer, P.; Takenaka, S.; Schulz, H.; Oberdörster, G.; Ziesenis, A. (2002) Translocation of ultrafine insoluble iridium particles from lung epithelium to extrapulmonary organs is size dependent but very low. J. Toxicol. Environ. Health Part A 65: 1513-1530.
Kuempel, E. D. (2000) Comparison of human and rodent lung dosimetry models for particle clearance and retention. Drug Chem. Toxicol. 23: 203-222.
Kuempel, E. D.; O'Flaherty, E. J.; Stayner, L. T.; Smith, R. J.; Green, F. H. Y.; Vallyathan, V. (2001a) A biomathematical model of particle clearance and retention in the lungs of coal miners. I. Model development. Regul. Toxicol. Pharmacol. 34: 69-87.

Kuempel, E. D.; Tran, C.-L.; Smith, R. J.; Bailer, A. J. (2001b) A biomathematical model of particle clearance and retention in the lungs of coal miners. II. Evaluation of variability and uncertainty. Regul. Toxicol. Pharmacol. 34: 88-101.

LaBelle, C. W.; Brieger, H. (1961) Patterns and mechanisms in the elimination of dust from the lung. In: Davies, C. N., ed. Inhaled particles and vapours: proceedings of an international symposium; March-April 1960; Oxford, United Kingdom. New York, NY: Pergamon Press; pp. 356-368.

Landahl, H. D. (1950) On the removal of air-borne droplets by the human respiratory tract: I. the lung. Bull. Math. Biophys. 12: 43-56.

Lay, J. C.; Berry, C. R.; Kim, C. S.; Bennett, W. D. (1995) Retention of insoluble particles after local intrabronchial deposition in dogs. J. Appl. Physiol. 79: 1921-1929.

Lay, J. C.; Bennett, W. D.; Kim, C. S.; Devlin, R. B.; Bromberg, P. A. (1998) Retention and intracellular distribution of instilled iron oxide particles in human alveolar macrophages. Am. J. Respir. Cell Mol. Biol. 18: 687-695.

Lazaridis, M.; Broday, D. M.; Hov, Ø.; Georgopoulos, P. G. (2001) Integrated exposure and dose modeling and analysis system. 3. Deposition of inhaled particles in the human respiratory tract. Environ. Sci. Technol. 35: 3727-3734.

Lee, J. W.; Goo, J. H.; Chung, M. K. (1996) Characteristics of inertial deposition in a double bifurcation. J. Aerosol Sci. 27: 119-138.

Lehnert, B. E.; Morrow, P. E. (1985) Association of ^{59}iron oxide with alveolar macrophages during alveolar clearance. Exp. Lung Res. 9: 1-16.

Lehnert, B. E.; Valdez, Y. E.; Bomalaski, S. H. (1988) Analyses of particles in the lung free cell, tracheobronchial lymph nodal, and pleural space compartments following their deposition in the lung as related to lung clearance mechanisms. In: Dodgson, J.; McCallum, R. I.; Bailey, M. R.; Fisher, D. R., eds. Inhaled particles VI: proceedings of an international symposium and workshop on lung dosimetry; September 1985; Cambridge, United Kingdom. Ann. Occup. Hyg. 32(suppl. 1): 125-140.

Leikauf, G.; Yeates, D. B.; Wales, K. A.; Spektor, D.; Albert, R. E.; Lippmann, M. (1981) Effects of sulfuric acid aerosol on respiratory mechanics and mucociliary particle clearance in healthy nonsmoking adults. Am. Ind. Hyg. Assoc. J. 42: 273-282.

Leikauf, G. D.; Spektor, D. M.; Albert, R. E.; Lippmann, M. (1984) Dose-dependent effects of submicrometer sulfuric acid aerosol on particle clearance from ciliated human lung airways. Am. Ind. Hyg. Assoc. J. 45: 285-292.

Lennon, S.; Zhang, Z.; Lessmann, R.; Webster, S. (1998) Experiments on particle deposition in the human upper respiratory system. Aerosol Sci. Technol. 28: 464-474.

Leong, B. K. J.; Coombs, J. K.; Sabaitis, C. P.; Rop, D. A.; Aaron, C. S. (1998) Quantitative morphometric analysis of pulmonary deposition of aerosol particles inhaled via intratracheal nebulization, intratracheal instillation or nose-only inhalation in rats. J. Appl. Toxicol. 18: 149-160.

Li, A.; Ahmadi, G. (1995) Computer simulation of particle deposition in the upper tracheobronchial tree. Aerosol Sci. Tech. 23: 201-223.

Lundborg, M.; Lind, B.; Camner, P. (1984) Ability of rabbit alveolar macrophages to dissolve metals. Exp. Lung Res. 7: 11-22.

Lundborg, M.; Eklund, A.; Lind, B.; Camner, P. (1985) Dissolution of metals by human and rabbit alveolar macrophages. Br. J. Ind. Med. 42: 642-645.

Madl, A. K.; Wilson, D. W.; Segall, H. J.; Pinkerton, K. E. (1998) Alteration in lung particle translocation, macrophage function, and microfilament arrangement in monocrotaline-treated rats. Toxicol. Appl. Pharmacol. 153: 28-38.

Martonen, T. B. (1982) Analytical model of hygroscopic particle behavior in human airways. Bull. Math. Biol. 44: 425-442.

Martonen, T. B.; Lowe, J. (1983) Assessment of aerosol deposition patterns in human respiratory tract casts. In: Marple, V. A.; Liu, B. Y. H., eds. Aerosols in the Mining and Industrial Work Environments Vol. 1 Fundamentals and Status, p. 151-164. Ann Arbor, MI: Ann Arbor Science Publishers.

Martonen, T. B.; Barnett, A. E.; Miller, F. J. (1985) Ambient sulfate aerosol deposition in man: modeling the influence of hygroscopicity. Environ. Health Perspect. 63: 11-24.

Martonen, T. B.; Hofmann, W.; Eisner, A. D.; Ménache, M. G. (1989) The role of particle hygroscopicity in aerosol therapy and inhalation toxicology. In: Crapo, J. D.; Miller, F. J.; Smolko, E. D.; Graham, J. A.; Hayes, A. W., eds. Extrapolation of dosimetric relationships for inhaled particles and gases. San Diego, CA: Academic Press, Inc.; pp. 303-316.

Martonen, T. B.; Zhang, Z.; Lessmann, R. (1993) Fluid dynamics of the human larynx and upper tracheobronchial airways. Aerosol Sci. Technol. 19: 133-156.

Martonen, T. B.; Yang, Y.; Xue, Z. Q. (1994a) Influences of cartilagious rings on tracheobronchial fluid dynamics. Inhalation Toxicol. 6: 185-203.
Martonen, T. B.; Yang, Y.; Xue, Z. Q. (1994b) Effects of carinal ridge shapes on lung airstreams. Aerosol Sci. Technol. 21: 119-136.
Martonen, T. B.; Schroeter, J. D.; Hwang, D.; Fleming, J. S.; Conway, J. H. (2000) Human lung morphology models for particle deposition studies. In: Grant, L. D., ed. PM2000: particulate matter and health. Inhalation Toxicol. 12(suppl. 4): 109-121.
Martonen, T. B.; Zhang, Z; Yu, G.; Musante, C. J. (2001a) Three-dimensional computer modeling of the human upper respiratory tract. Cell Biochem. Biophys. 35: 255-261.
Martonen, T. B.; Guan, X.; Schreck, R. M. (2001b) Fluid dynamics in airway bifurcations: I. Primary flows. Inhalation Toxicol. 13: 261-79.
Martonen, T. B.; Guan, X.; Schreck, R. M. (2001c) Fluid dynamics in airway bifurcations: II. Secondary currents. Inhalation Toxicol. 13: 281-9.
Martonen, T. B.; Guan, X.; Schreck, R. M. (2001d) Fluid dynamics in airway bifurcations: III. Localized flow conditions. Inhalation Toxicol. 13: 291-305.
Matsui, H.; Randell, S. H.; Peretti, S. W.; Davis, C. W.; Boucher, R. C. (1998) Coordinated clearance of periciliary liquid and mucus from airway surfaces. J. Clin. Invest. 102: 1125-1131.
Mauderly, J. L. (1979) Effect of age on pulmonary structure and function of immature and adult animals and man. Fed. Proc. 38: 173-177.
Medinsky, M. A.; Kampcik, S. J. (1985) Pulmonary retention of [^{14}C]benzo*[a]*pyrene in rats as influenced by the amount instilled. Toxicology 35: 327-336.
Ménache, M. G.; Miller, F. J.; Raabe, O. G. (1995) Particle inhalability curves for humans and small laboratory animals. Ann. Occup. Hyg. 39: 317-328.
Mercer, T. T. (1967) On the role of particle size in the dissolution of lung burdens. Health Phys. 13: 1211-1221.
Miller, F. J. (2000a) Dosimetry of particles in laboratory animals and humans in relationship to issues surrounding lung overload and human health risk assessment: a critical review. Inhalation Toxicol. 12: 19-57.
Miller, F. J. (2000b) Errata: F. J. Miller, 2000. Dosimetry of particles in laboratory animals and humans in relationship to issues surrounding lung overload and human health risk assessment: a critical review. Inhal. Toxicol. 12: 19-57. Inhalation Toxicol. 12: 1257-1259.
Miller, F. J.; Anjilvel, S.; Ménache, M. G.; Asgharian, B.; Gerrity, T. R.. (1995) Dosimetric issues relating to particulate toxicity. Inhalation Toxicol. 7: 615-632.
Morrison, D.; Skwarski, D.; Millar, A. M.; Adams, W.; MacNee, W. (1998) A comparison of three methods of measuring ^{99m}Tc-DTPA lung clearance and their repeatability. Eur. Respir. J. 11: 1141-1146.
Morrow, P. E. (1973) Alveolar clearance of aerosols. Arch. Intern. Med. 131: 101-108.
Morrow, P. E. (1977) Clearance kinetics of inhaled particles. In: Brain, J. D.; Proctor, D. F.; Reid, L. M., eds. Respiratory defense mechanisms (in two parts), part II. New York, NY: Marcel Dekker, Inc.; pp. 491-543. (Lenfant, C., ed. Lung biology in health and disease: v. 5).
Morrow, P. E. (1986) Factors determining hygroscopic aerosol deposition in airways. Physiol. Rev. 66: 330-376.
Morrow, P. E. (1988) Possible mechanisms to explain dust overloading of the lungs. Fundam. Appl. Toxicol. 10: 369-384.
Morrow, P. E. (1994) Mechanisms and significance of "particle overload." In: Mohr, U.; Dungworth, D. L.; Mauderly, J. L.; Oberdörster, G., eds. Toxic and carcinogenic effects of solid particles in the respiratory tract: [proceedings of the 4th international inhalation symposium]; March 1993; Hannover, Germany. Washington, DC: International Life Sciences Institute Press; pp. 17-25.
Morrow, P. E.; Yu, C. P. (1993) Models of aerosol behavior in airways and alveoli. In: Morén, F.; Dolovich, M. B.; Newhouse, M. T.; Newman, S. P., eds. Aerosols in medicine: principles, diagnosis and therapy. 2nd rev. ed. Amsterdam, The Netherlands: Elsevier; pp. 157-193.
Morrow, P. E.; Gibb, F. R.; Gazioglu, K. M. (1967) A study of particulate clearance from the human lungs. Am. Rev. Respir. Dis. 96: 1209-1221.
Musante, C. J.; Martonen, T. B. (1999) Predicted deposition patterns of ambient particulate air pollutants in children's lungs under resting conditions. In: Proceedings of the third colloquium on particulate air pollution and human health; June; Durham, NC. Irvine, CA: University of California, Air Pollution Health Effects Laboratory, p. 7-15 - 7-20.
Musante, C. J.; Martonen, T. B. (2000a) Computer simulations of particle deposition in the developing human lung. J. Air Waste Manage. Assoc. 50: 1426-1432.

Musante, C. J.; Martonen, T. B. (2000b) An extrapolation model to aid in toxicological studies of particulate air pollutants. Presented at: PM2000: particulate matter and health—the scientific basis for regulatory decision-making, specialty conference & exhibition; January; Charleston, SC. Pittsburgh, PA: Air & Waste Management Association.

Musante, C. J.; Martonen, T. B. (2000c) Particulate matter deposition in the lungs of children and adults: predictions of an age-dependent computer model. Presented at: PM2000: particulate matter and health—the scientific basis for regulatory decision-making, specialty conference & exhibition; January; Charleston, SC. Pittsburgh, PA: Air & Waste Management Association.

National Council on Radiation Protection and Measurements (NCRP). (1997) Deposition, retention and dosimetry of inhaled radioactive substances. Bethesda, MD: National Council on Radiation Protection and Measurements; report no. 125.

National Radiologic Protection Board (NRPB). (1994) National Radiologic Protection Board Report R287, implementation of the ICRP publication 66 respiratory tract model: LUDEP 2.0 (LUng Dose Evaluation Program). Richland, WA: ACJ & Associates, Inc. Software information available: www.acj-associates.com (13 June 2003).

National Research Council. (2001) Research priorities for airborne particulate matter. III. Early research progress. Washington, DC: National Academy Press. Available: http://www.nap.edu/books/0309073375/html/ (4 June 2003).

Naumann, B. D.; Schlesinger, R. B. (1986) Assessment of early alveolar particle clearance and macrophage function following an acute inhalation of sulfuric acid mist. Exp. Lung Res. 11: 13-33.

Nemmar, A.; Vanbilloen, H.; Hoylaerts, M. F.; Hoet, P. H. M.; Verbruggen, A.; Nemery, B. (2001) Passage of intratracheally instilled ultrafine particles from the lung into the systemic circulation in hamster. Am. J. Respir. Crit. Care Med. 164: 1665-1668.

Nemmar, A.; Hoet, H. M.; Vanquickenborne, B.; Dinsdale, D.; Thomeer, M.; Hoylaerts, M. F.; Vanbilloen, H.; Mortelmans, L.; Nemery, B. (2002) Passage of inhaled particles into the blood circulation in humans. Circulation 105: 411-414.

Niinimaa, V.; Cole, P.; Mintz, S.; Shephard, R. J. (1981) Oronasal distribution of respiratory airflow. Respir. Physiol. 43: 69-75.

Nikula, K. J.; Avila, K. J.; Griffith, W. C.; Mauderly, J. L. (1997) Lung tissue responses and sites of particle retention differ between rats and cynomolgus monkeys exposed chronically to diesel exhaust and coal dust. Fundam. Appl. Toxicol. 37: 37-53.

Nikula, K. J.; Vallyathan, V.; Green, F. H. Y.; Hahn, F. F. (2000) Influence of dose on the distribution of retained particulate material in rat and human lungs. Presented at: PM2000: particulate matter and health–the scientific basis for regulatory decision-making, specialty conference & exhibition; January; Charleston, SC. Pittsburgh, PA: Air & Waste Management Association.

Noone, P. G.; Bennett, W. D.; Regnis, J. A.; Zeman, K. L.; Carson, J. L.; King, M.; Boucher, R. C.; Knowles, M. R. (1999) Effect of aerosolized uridine-5'-triphosphate on airway clearance with cough in patients with primary ciliary dyskinesia. Am. J. Respir. Crit. Care Med.: 160: 144-149.

Oberdörster, G. (1993) Lung dosimetry: pulmonary clearance of inhaled particles. Aerosol Sci. Technol. 18: 279-289.

Oberdörster, G.; Ferin, J.; Gelein, R.; Soderholm, S. C.; Finkelstein, J. (1992) Role of the alveolar macrophage in lung injury: studies with ultrafine particles. Environ. Health Perspect. 97: 193-199.

Oberdörster, G.; Cox, C.; Gelein, R. (1997) Intratracheal instillation versus intratracheal inhalation of tracer particles for measuring lung clearance function. Exp. Lung Res. 23: 17-34.

Oberdörster, G.; Sharp, Z.; Atudorei, V.; Elder, A.; Gelein, R.; Lunts, A.; Kreyling, W.; Cox, C. (2002) Extrapulmonary translocation of ultrafine carbon particles following whole-body inhalation exposure of rats. J. Toxicol. Environ. Health A 65: 1531-1543.

Oldham, M. J.; Mannix, R. C.; Phalen, R. F. (1997) Deposition of monodisperse particles in hollow models representing adult and child-size tracheobronchial airways. Health Phys. 72: 827-834.

Oldham, M. J.; Phalen, R. F.; Heistracher, T. (2000) Computational fluid dynamic predictions and experimental results for particle deposition in an airway model. Aerosol Sci. Technol. 32: 61-71.

Osier, M.; Oberdörster, G. (1997) Intratracheal inhalation vs intratracheal instillation: differences in particle effects. Fundam. Appl. Toxicol. 40: 220-227.

Passàli, D.; Bianchini Ciampoli, M. (1985) Normal values of mucociliary transport time in young subjects. Int. J. Pediatr. Otorhinolaryngol. 9: 151-156.

Patton, J. S. (1996) Mechanisms of macromolecule absorption by the lungs. Adv. Drug Delivery Rev. 19: 3-36.

Pavia, D. (1987) Acute respiratory infections and mucociliary clearance. Eur. J. Respir. Dis. 71: 219-226.

Pavia, D.; Bateman, J. R. M.; Clarke, S. W. (1980) Deposition and clearance of inhaled particles. Bull. Eur. Physiopath. Respir. 16: 335-366.
Peterson, B. T.; Dickerson, K. D.; James, H. L.; Miller, E. J.; McLarty, J. W.; Holiday, D. B. (1989) Comparison of three tracers for detecting lung epithelial injury in anesthetized sheep. J. Appl. Physiol. 66: 2374-2383.
Phalen, R. F.; Oldham, M. J. (2001) Methods for modeling particle deposition as a function of age. Respir. Physiol. 128: 119-130.
Phalen, R. F.; Oldham, M. J.; Beaucage, C. B.; Crocker, T. T.; Mortensen, J. D. (1985) Postnatal enlargement of human tracheobronchial airways and implications for particle deposition. Anat. Rec. 212: 368-380.
Pritchard, J. N.; Holmes, A.; Evans, J. C.; Evans, N.; Evans, R. J.; Morgan, A. (1985) The distribution of dust in the rat lung following administration by inhalation and by single intratracheal instillation. Environ. Res. 36: 268-297.
Pritchard, J. N.; Jefferies, S. J.; Black, A. (1986) Sex differences in the regional deposition of inhaled particles in the 2.5-7.5 μm size range. J. Aerosol Sci. 17: 385-389.
Raabe, O. G.; Al-Bayati, M. A.; Teague, S. V.; Rasolt, A. (1988) Regional deposition of inhaled monodisperse, coarse, and fine aerosol particles in small laboratory animals. In: Dodgson, J.; McCallum, R. I.; Bailey, M. R.; Fischer, D. R., eds. Inhaled particles VI: proceedings of an international symposium and workshop on lung dosimetry; September 1985; Cambridge, United Kingdom. Ann. Occup. Hyg. 32(suppl. 1): 53-63.
Radford, E. P.; Martell, E. A. (1977) Polonium-210: lead-210 ratios as an index of residence time of insoluble particles from cigarette smoke in bronchial epithelium. In: Walton, W. H.; McGovern, B., eds. Inhaled particles IV: proceedings of an international symposium, part 2; September 1975; Edinburgh, United Kingdom. Oxford, United Kingdom: Pergamon Press, Ltd.; pp. 567-581.
Rasmussen, T. R.; Andersen, A.; Pedersen, O. F. (2000) Particle deposition in the nose related to nasal cavity geometry. Rhinology 38: 102-107.
Roy, M. (1989) Lung clearance modeling on the basis of physiological and biological parameters. Health Phys. 57(suppl. 1): 255-262.
Rutland, J.; Cole, P. J. (1981) Nasal mucociliary clearance and ciliary beat frequency in cystic fibrosis compared with sinusitis and bronchiectasis. Thorax 36: 654-658.
Sabaitis, C. P.; Leong, B. K. J.; Rop, D. A.; Aaron, C. S. (1999) Validation of intratracheal instillation as an alternative for aerosol inhalation toxicity testing. J. Appl. Toxicol. 19: 133-140.
Sarangapani, R.; Wexler, A. S. (2000) Modeling particle deposition in extrathoracic airways. Aerosol Sci. Technol. 32: 72-89.
Scheuch, G.; Stahlhofen, W. (1988) Particle deposition of inhaled aerosol boluses in the upper human airways. J. Aerosol Med. 1: 29-36.
Scheuch, G.; Philipson, K.; Falk, R.; Svartengren, M.; Stahlhofen, W.; Camner, P. (1995) Retention of particles inhaled in boli with and without induced bronchoconstriction. Exp. Lung Res. 21: 901-916.
Schlesinger, R. B. (1985) Clearance from the respiratory tract. Fundam. Appl. Toxicol. 5: 435-450.
Schlesinger, R. B. (1988) Biological disposition of airborne particles: basic principles and application to vehicular emissions. In: Watson, A. Y.; Bates, R. R.; Kennedy, D., eds. Air pollution, the automobile, and public health. Washington, DC: National Academy Press; pp. 239-298.
Schlesinger, R. B. (1989) Deposition and clearance of inhaled particles. In: McClellan, R. O.; Henderson, R. F., eds. Concepts in inhalation toxicology. New York, NY: Hemisphere Publishing Corp.; pp. 163-192.
Schlesinger, R. B. (1990) The interaction of inhaled toxicants with respiratory tract clearance mechanisms. Crit. Rev. Toxicol. 20: 257-286.
Schlesinger, R. B. (1995) Deposition and clearance of inhaled particles. In: McClellan, R. O.; Henderson, R. F., eds. Concepts in inhalation toxicology. 2nd ed. Washington, DC: Taylor & Francis; pp. 191-224.
Schlesinger, R. B.; Gurman, J. L.; Lippmann, M. (1982) Particle deposition within bronchial airways: comparisons using constant and cyclic inspiratory flows. Ann. Occup. Hyg. 26: 47-64.
Schlesinger, R. B.; Ben-Jebria, A.; Dahl, A. R.; Snipes, M. B.; Ultman, J. (1997) Disposition of inhaled toxicants. In: Massaro, E. J., ed. Handbook of human toxicology. Boca Raton, FL: CRC Press; pp. 493-550.
Schroeter, J. D.; Musante, C. J.; Hwang, D.; Burton, R.; Guilmette, R.; Martonen, T. B. (2001) Hygroscopic growth and deposition of inhaled secondary cigarette smoke in human nasal pathways. Aerosol Sci. Technol.: 34: 137-143.
Schroter, R. C.; Sudlow, M. F. (1969) Flow patterns in models of the human bronchial airways. Respir. Physiol. 7: 341-55.
Segal, R. A.; Guan, X.; Shearer, M; Martonen, T. B. (2000a) Mathematical model of airflow in the lungs of children I: effects of tumor sizes and locations. J. Theor. Med. 2:199-213.

Segal, R. A.; Martonen, T. B.; Kim, C. S. (2000b) Comparison of computer simulations to total lung deposition to human subject data in healthy test subjects. J. Air Waste Manage. Assoc. 50: 1262-1268.
Segal, R. A.; Martonen, T. B.; Kim, C. S.; Shearer, M. (2002) Computer simulations of particle deposition in the lungs of chronic obstructive pulmonary disease patients. Inhalation Toxicol. 14: 705-720.
Smaldone, G. C.; Perry, R. J.; Bennett, W. D.; Messina, M. S.; Zwang, J.; Ilowite, J. (1988) Interpretation of "24 hour lung retention" in studies of mucociliary clearance. J. Aerosol Med. 1: 11-20.
Smaldone, G. C.; Foster, W. M.; Oriordan, T. G.; Messina, M. S.; Perry, R. J.; Langenback, E. G. (1993) Regional impairment of mucociliary clearance in chronic obstructive pulmonary disease. Chest 103: 1390-1396.
Snipes, M. B. (1989) Long-term retention and clearance of particles inhaled by mammalian species. CRC Crit. Rev. Toxicol. 20: 175-211.
Snipes, M. B.; Clem, M. F. (1981) Retention of microspheres in the rat lung after intratracheal instillation. Environ. Res. 24: 33-41.
Snipes, M. B.; McClellan, R. O.; Mauderly, J. L.; Wolff, R. K. (1989) Retention patterns for inhaled particles in the lung: comparisons between laboratory animals and humans for chronic exposures. Health Phys. 57(suppl. 1): 69-78.
Snipes, M. B.; James, A. C.; Jarabek, A. M. (1997) The 1994 ICRP66 human respiratory tract dosimetry model as a tool for predicting lung burdens from exposures to environmental aerosols. Appl. Occup. Environ. Hyg. 12: 547-554.
Stahlhofen, W.; Gebhart, J.; Rudolf, G.; Scheuch, G.; Philipson, K. (1986a) Clearance from the human airways of particles of different sizes deposited from inhaled aerosol boli. In: Aerosols: formation and reactivity, proceedings of the second international aerosol conference; September; Berlin, Federal Republic of Germany. Oxford, United Kingdom: Pergamon Press; pp. 192-196.
Stahlhofen, W.; Gebhart, J.; Rudolf, G.; Scheuch, G. (1986b) Measurement of lung clearance with pulses of radioactively-labelled aerosols. J. Aerosol Sci. 17: 333-336.
Stanley, P. J.; Wilson, R.; Greenstone, M. A.; Mackay, I. S.; Cole, P. J. (1985) Abnormal nasal mucociliary clearance in patients with rhinitis and its relationship to concomitant chest disease. Br. J. Dis. Chest 79: 77-82.
Stapleton, K. W.; Guentsch, E.; Hoskinson, M. K.; Finlay, W. H. (2000) On the suitability of κ-ε turbulence modeling for aerosol deposition in the mouth and throat: a comparison with experiment. J. Aerosol Sci. 31: 739-749.
Stöber, W.; Morrow, P. E.; Koch, W.; Morawietz, G. (1994) Alveolar clearance and retention of inhaled insoluble particles in rats simulated by a model inferring macrophage particle load distributions. J. Aerosol Sci. 25: 975-1002.
Strom, K. A.; Chan, T. L.; Johnson, J. T. (1988) Pulmonary retention of inhaled submicron particles in rats: diesel exhaust exposures and lung retention model. In: Dodgson, J.; McCallum, R. I.; Bailey, M. R.; Fischer, D. R., eds. Inhaled particles VI: proceedings of an international symposium and workshop on lung dosimetry; September 1985; Cambridge, United Kingdom. Ann. Occup. Hyg. 32(suppl. 1): 645-657.
Suarez, S.; Kazantseva, M.; Bhat, M.; Costa, D.; Hickey, A. J. (2001) The influence of suspension nebulization or instillation on particle uptake by guinez pig alveolar macrophages. Inhalation Toxicol. 13: 773-788.
Subramaniam, R. P.; Richardson, R. B.; Morgan, K. T.; Guilmette, R. A.; Kimbell, J. S. (1998) Computational fluid dynamics simulations of inspiratory airflow in the human nose and nasopharynx. Inhalation Toxicol. 10: 91-120.
Subramaniam, R. P.; Asgharian, B.; Miller, F. J.; Anjilvel, S.; Freijer, J. I. (2003) Analysis of lobar differences in particle deposition in the human lung. Inhalation Toxicol. 15: 1-21.
Svartengren, K.; Lindestad, P.; Svartengren, M.; Philipson, K.; Bylin, G.; Camner, P. (1995) Added external resistance reduces oropharyngeal deposition and increases lung deposition of aerosol particles in asthmatics. Am. J. Respir. Crit. Care Med. 152: 32-37.
Svartengren, K.; Philipson, K.; Svartengren, M.; Anderson, M.; Camner, P. (1996a) Tracheobronchial deposition and clearance in small airways in asthmatic subjects. Eur. Respir. J. 9: 1123-1129.
Svartengren, K.; Ericsson, C. H.; Svartengren, M.; Mossberg, B.; Philipson, K.; Camner, P. (1996b) Deposition and clearance in large and small airways in chronic bronchitis. Exp. Lung Res. 22: 555-576.
Svartengren, K.; Philipson, K.; Svartengren, M.; Camner, P. (1998) Effect of adrenergic stimulation on clearance from small ciliated airways in healthy subjects. Exp. Lung Res. 24: 149-158.
Svartengren, M.; Svartengren, K.; Aghaie, F.; Philipson, K.; Camner, P. (1999) Lung deposition and extremely slow inhalations of particles. Limited effect of induced airway obstruction. Exp. Lung Res. 25: 353-366.
Sweeney, T. D.; Tryka, A. F.; Brain, J. D. (1990) Effect of exercise on redistribution and clearance of inhaled particles from hamster lungs. J. Appl. Physiol. 68: 967-972.

Sweeney, T. D.; Skornik, W. A.; Brain, J. D.; Hatch, V.; Godleski, J. J. (1995) Chronic bronchitis alters the pattern of aerosol deposition in the lung. Am. J. Respir. Crit. Care Med. 151: 482-488.

Swift, D. L.; Strong, J. C. (1996) Nasal deposition of ultrafine ^{218}Po aerosols in human subjects. J. Aerosol Sci. 27: 1125-1132.

Takahashi, S.; Asaho, S.; Kubota, Y.; Sato, H.; Matsuoka, O. (1987) Distribution of ^{198}Au and ^{133}Ba in thoracic and cervical lymph nodes of the rat following the intratracheal instillation of ^{198}Au-colloid and $^{133}BaSO_4$. J. Radiat. Res. 28: 227-231.

Takahashi, S.; Kubota, Y.; Hatsuno, H. (1992) Effect of size on the movement of latex particles in the respiratory tract following local administration. Inhalation Toxicol. 4: 113-123.

Takenaka, S.; Karg, E.; Roth, C.; Schulz, H.; Ziesenis, A.; Heinzmann, U.; Schramel, P.; Heyder, J. (2001) Pulmonary and systemic distribution of inhaled ultrafine silver particles in rats. Environ. Health Perspect. 109(suppl. 4): 547-551.

Toms, N.; Hasani, A.; Pavia, D.; Clarke, S. W.; Agnew, J. E. (1997) Effect of mucus hypersecretion on initial time course of inert particle clearance from the lung. In: Cherry, N.; Ogden, T., eds. Inhaled Particles VIII: proceedings of an international symposium on inhaled particles organised by the British Occupational Hygiene Society; August 1996; Cambridge, UK. Ann. Occup. Hyg. 41(suppl.): 509-514.

Tran, C. L.; Jones, A. D.; Cullen, R. T.; Donaldson, K. (1999) Exploration of the mechanisms of retention and clearance of low-toxicity particles in the rat lung using a mathematical model. Inhalation Toxicol. 11: 1077-1108.

Tran, C. L.; Buchanan, D.; Cullen, R. T.; Searl, A.; Jones, A. D.; Donaldson, K. (2000) Inhalation of poorly soluble particles. II. Influence of particle surface area on inflammation and clearance. Inhalation Toxicol. 12: 1113-1126.

Tsuda, A.; Butler, J. P.; Fredberg, J. J. (1994a) Effects of alveolated duct structure on aerosol kinetics. I. Diffusional deposition in the absence of gravity. J. Appl. Physiol. 76: 2497-2509.

Tsuda, A.; Butler, J. P.; Fredberg, J. J. (1994b) Effects of alveolated duct structure on aerosol kinetics. II. Gravitational sedimentation and inertial impaction. J. Appl. Physiol. 76: 2510-2516.

Tsuda, A.; Henry, F. S.; Otani, Y.; Haber, S.; Butler, J. P. (1996) Aerosol transport and deposition in the rhythmically expanding pulmonary acinus. J. Aerosol. Med. 9: 389-408.

U.S. Environmental Protection Agency. (1994) Supplement to the second addendum (1986) to air quality criteria for particulate matter and sulfur oxides (1982): assessment of new findings on sulfur dioxide acute exposure health effects in asthmatic individuals. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; report no. EPA-600/FP-93/002. Available from: NTIS, Springfield, VA; PB98-132384.

U.S. Environmental Protection Agency. (1996a) Air quality criteria for particulate matter. Research Triangle Park, NC: National Center for Environmental Assessment-RTP Office; report nos. EPA/600/P-95/001aF-cF. 3v.

U.S. Environmental Protection Agency. (1996b) Air quality criteria for ozone and related photochemical oxidants, v. I-III. Research Triangle Park, NC: Office of Research and Development; report no. EPA/600/P-93/004aF-cF. Available from: NTIS, Springfield, VA; PB96-185582. PB96-185590, and PB96-185608. Available: www.epa.gov/ncea/ozone.htm [25 February 2002].

Venkataraman, C.; Kao, A. S. (1999) Comparison of particle lung doses from the fine and coarse fractions of urban PM-10 aerosols. Inhalation Toxicol. 11: 151-169.

Wagner, E. M.; Foster, W. M. (2001) The role of the bronchial vasculature in soluble particle clearance. Environ. Health Perspect. 109(suppl. 4): 563-565.

Warheit, D. B.; Carakostas, M. C.; Hartsky, M. A.; Hansen, J. F. (1991) Development of a short-term inhalation bioassay to assess pulmonary toxicity of inhaled particles: comparisons of pulmonary responses to carbonyl iron and silica. Toxicol. Appl. Pharmacol. 107: 350-368.

Whitby, K. T. (1978) The physical characteristics of sulfur aerosols. Atmos. Environ. 12: 135-159.

White, F. M. (1974) Viscous fluid flow. New York, NY: McGraw-Hill, pp. 65-72.

Winter-Sorkina, R. de; Cassee, F. R. (2002) From concentration to dose: factors influencing airborne particulate matter deposition in humans and rats. Bilthoven, The Netherlands: National Institute of Public Health and the Environment (RIVM); report no. 650010031/2002. Available: http://www.rivm.nl/bibliotheek/rapporten/650010031.html (13 June 2003).

Wolff, R. K. (1986) Effects of airborne pollutants on mucociliary clearance. Environ. Health Perspect. 66: 223-237.

Wolff, R. K.; Henderson, R. F.; Snipes, M. B.; Griffith, W. C.; Mauderly, J. L.; Cuddihy, R. G.; McClellan, R. O. (1987) Alterations in particle accumulation and clearance in lungs of rats chronically exposed to diesel exhaust. Fundam. Appl. Toxicol. 9: 154-166.

Xu, G. B.; Yu, C. P. (1986) Effects of age on deposition of inhaled aerosols in the human lung. Aerosol Sci. Technol. 5: 349-357.
Yeates, D. B.; Aspin, M. (1978) A mathematical description of the airways of the human lungs. Respir. Physiol. 32: 91-104.
Yeates, D. B.; Aspin, N.; Levison, H.; Jones, M. T.; Bryan, A. C. (1975) Mucociliary tracheal transport rates in man. J. Appl. Physiol. 19: 487-495.
Yeates, D. B.; Pitt, B. R.; Spektor, D. M.; Karron, G. A.; Albert, R. E. (1981) Coordination of mucociliary transport in human trachea and intrapulmonary airways. J. Appl. Physiol. 51: 1057-1064.
Yeh, H.-C.; Schum, G. M. (1980) Models of human lung airways and their application to inhaled particle deposition. Bull. Math. Biol. 42: 461-480.
Yeh, H. C.; Schum, G. M.; Duggan, M. T. (1979) Anatomic models of the tracheobronchial and pulmonary regions of the rat. Anat. Rec. 195: 483-492.
Yu, G.; Zhang, Z.; Lessmann, R. (1998) Fluid flow and particle diffusion in the human upper respiratory system. Aerosol Sci. Technol. 28: 146-158.
Zhang, Z.; Martonen, T. (1997) Deposition of ultrafine aerosols in human tracheobronchial airways. Inhalation Toxicol. 9: 99-110.
Zhang, L.; Asgharian, B.; Anjilvel, S. (1997) Inertial deposition of particles in the human upper airway bifurcations. Aerosol Sci. Tech. 26: 97-110.
Zhang, Z.; Kleinstreuer, C.; Kim, C. S. (2000) Effects of asymmetric branch flow rates on aerosol deposition in bifurcating airways. J. Med. Eng. Technol. 24: 192-202.
Zhang, Z.; Kleinstreuer, C.; Kim, C. S. (2001) Effects of curved inlet tube on air flow and particle deposition in bifurcating lung models. J. Biomechanics 34: 659-669.
Zhang, Z.; Kleinstreuer, C.; Kim, C. S. (2002) Cyclic micron-size particle inhalation and deposition in a triple bifurcation lung airway model. J. Aerosol Sci. 33: 257-281.
Zhu, Y.; Hinds, W. C.; Kim, S.; Shen, S.; Sioutas, C. (2002) Study of ultrafine particles near a major highway with heavy-duty diesel traffic. Atmos. Environ. 36: 4323-4335.

7. TOXICOLOGY OF PARTICULATE MATTER IN HUMANS AND LABORATORY ANIMALS

7.1 INTRODUCTION

The 1997 U.S. Particulate Matter National Ambient Air Quality Standards (PM NAAQS) revisions (Federal Register, 1997) were based, in large part, on new epidemiologic evidence showing associations between (a) ambient PM measured at community monitoring stations and (b) increased risks for mortality and morbidity (especially cardiorespiratory-related) among human populations exposed to contemporary U.S. ambient concentrations. However, very little experimental toxicology data from controlled human or laboratory animal exposure studies were available that provided more direct evidence supporting the plausibility of the observed PM-mortality/morbidity associations being causal at the relatively low ambient PM concentrations studied epidemiologically. The then-limited PM toxicologic data was assessed in Chapter 11 of the 1996 PM Air Quality Criteria Document or PM AQCD (U.S. Environmental Protection Agency, 1996a), which provided scientific assessment inputs supporting the 1997 PM NAAQS decisions.

Since the 1996 PM AQCD, numerous hypotheses have been advanced and extensive new toxicologic evidence generated with regard to possible pathophysiological mechanisms by which PM exposures at ambient or near ambient concentrations might induce increased morbidity and/or mortality. The extensive new PM toxicological research during the past five years or so has focused mainly on addressing several interrelated questions, such as: (1) what types of pathophysiological effects are exerted by ambient PM or constituent substances and what are the potential mechanisms underlying them; (2) what PM characteristics (size, chemical composition, etc.) cause or contribute to health effects; (3) what susceptible subgroups are at increased risk for PM health effects and what factors contribute to increased susceptibility; (4) what types of interactive effects of particles and gaseous co-pollutants have been demonstrated; and (5) are there toxicologic findings on PM-related mutagenic/genotoxic effects that support the plausibility of ambient PM-lung cancer relationships observed epidemiologically in U.S. populations?

7.1.1 Methodological Considerations

Various research approaches have been and continue to be used to address the above questions, including studies of human volunteers exposed to PM under controlled conditions; in vivo studies of laboratory animals including nonhuman primates, dogs, and rodent species; and in vitro studies of tissue, cellular, genetic, and biochemical systems. A wide variety of exposure conditions have been employed, including: whole body, mouth-only, and nose-only inhalation exposures to concentrated ambient particles (CAPs) or laboratory-generated particles; intratracheal, intrapulmonary, and intranasal instillation; and in vitro exposures to test materials in solution or suspension. These research approaches have been targeted mainly to test hypotheses to provide improved understanding of the role of PM in producing those types of health effects identified by PM-related epidemiologic studies. Thus, many of the new toxicological studies have been designed to address the question of biologic plausibility of epidemiologically-demonstrated effects, rather than being explicitly aimed at providing quantification of dose-response relationships for experimentally-induced toxic effects.

Reflecting this, most of the toxicology studies assessed here have generally used exposure concentrations or doses that are relatively high compared to concentrations commonly observed in ambient air. An important consideration contributing to the use of relatively high experimental exposure concentrations is the fact that healthy animals have most typically been used in many controlled-exposure toxicology studies, whereas epidemiologic findings often reflect ambient pollutant effects on compromised humans (e.g., those with one or another chronic disease) or other susceptible groups rendered at increased risk due to other factors. Implicit in the use of relatively high concentrations in experimental studies of healthy subjects is the assumption that increasing the dose somehow makes up for compromised tissue/organ functions that may contribute to observed ambient PM effects. However, this may not be the case, unless the increased susceptibility of an "at risk" group is based on enhanced respiratory tract PM deposition/retention per se. In light of this, there exists a great need for expanded development and use of animal models that more closely mimic important characteristics contributing to increased human susceptibility to ambient PM effects; and some notable progress has been made in this regard, as reflected by the growing number of PM toxicologic studies of compromised animal models published since the 1996 PM AQCD and assessed in this chapter.

Given the relatively high concentrations used, much care should therefore be taken when attempting to interpret and extrapolate effects seen in these studies to provide insight into the biological plausibility and mechanisms of action underlying effects seen in humans under "real world" exposure conditions. Some of the responses might only be seen at the higher concentrations more typical of occupational and experimental laboratory exposures and not necessarily at (usually much lower) ambient particle exposure concentrations. However, the high concentration studies play important roles in generating hypotheses and identifying mechanisms, which can then be tested with more relevant low doses. On the other hand, it is possible that differences between humans and rodents with regard to the inhalability, deposition, clearance, and retention profiles for PM (see Chapter 6 for details) could conceivably make doses to some specific respiratory tract tissues from experimental exposures relatively analogous to doses resulting from human ambient exposures. To help place the toxicologically relevant concentrations/doses into context in relation to ambient conditions, EPA has carried out some illustrative dosimetric/extrapolation modeling analyses to provide comparisons between the high doses typically used in toxicological studies and doses typical of human exposures under ambient conditions. Building upon advances in dosimetric modeling discussed in Chapter 6, these analyses compare PM doses delivered to human or rat lung tissue from experimental exposures and PM doses to the human lung from exposures during normal activities. These analyses and their interpretation of results (described in Appendix 7A) provide context for the exposure concentrations used and results obtained in toxicological studies assessed here. Additionally, it is important to keep in mind that the responses observed in toxicological studies, e.g., inflammatory cell influx, can range from being a normal adaptive or physiological response to a toxic response that is deleterious to the organism.

The effects of controlled exposures to ambient PM have been increasingly investigated since the 1996 PM AQCD by use of particles collected from ambient samplers (e.g., impactors, diffusion denuders, etc.) and, more recently, by the use of aerosol concentrators (e.g., Sioutas et al., 1995a,b, 2000; Gordon et al., 1998; Chang et al., 2000, Kim et al., 2000a,b). In the first type of study, particles from ambient air samplers are first collected on filters or other media, then stored, and later resuspended in an aqueous medium for use in inhalation, intratracheal instillation, or in vitro studies. Some ambient PM has been standardized as a reference material and compared to existing dust and soot standards, e.g., standard materials from the National

Institutes of Standards and Technology (NIST). Both ambient PM extracts and concentrated ambient particles (CAPs) have been used to evaluate effects in healthy and compromised laboratory animals and humans. Particle concentrators provide a technique for exposing animals or humans by inhalation to concentrated ambient particles (CAPs) at levels higher than typical ambient PM concentrations.

The development of particle concentrators has permitted the study of ambient real-world particles under controlled conditions. This strength is offset somewhat by the inability of CAPs studies to precisely control the mass concentration and day-to-day variability in ambient particle composition, and they often lack detailed characterization of variations in chemical composition from one CAPs exposure to another. Because the composition of concentrated ambient PM varies across both time and location, a thorough physical-chemical characterization is necessary to compare results between studies or even among exposures within studies in order to link particle composition to effects. Two other limitations that should be taken into account in interpreting results from CAPs studies are: (1) concentrators in use at the time of many of the studies assessed here could not efficiently concentrate ambient particles $\leq$ 0.1 μm, and (2) gaseous components of PM were not concentrated. Thus, it is likely that a large portion of potentially important combustion-generated particles (e.g, from diesel, gasoline vehicle, wood smoke, coal smoke, etc.) were present only at ambient (not higher concentrated) levels in most or all of the CAPs studies assessed here. A new generation of concentrators is now available that can capture both coarse and ultrafine CAPs, allowing more broadly relevant exposures to be tested. However, the gaseous components are not captured or proportionally concentrated, so potential interactions in the ambient atmosphere are not fully recapitulated.

Controlled human and laboratory animal exposures to particulate material obtained from emission source bag house filters or other emission source collection devices have also been used extensively in recent years to evaluate the in vitro and in vivo respiratory toxicity of complex combustion-related PM. Residual oil fly ash (ROFA) collected from large industrial sources (e.g., oil-fired power plants) has been extensively used, as well as, to a lesser extent, domestic oil furnace ash (DOFA) or coal fly ash (CFA). The major disadvantage associated with the use of such emission source materials derives from questions concerning the potential relevance of results obtained for helping to understand and interpret current ambient PM exposure effects. There is little doubt that in years past, before the extensive implementation of

air pollution controls, U.S. ambient air PM contained mixtures of high concentrations of chemical species analogous to those found in many of the emission-source samples used in toxicologic studies during the past decade or so. It is rare, however, that high concentrations of materials that typify such samples would be found in ambient air PM samples obtained at community monitoring sites in the United States, Canada, and much of Western Europe, which provided aerometric data collected during the past 20 to 30 years that were used to estimate PM exposures in most of the PM epidemiology studies assessed in this document. For example, very high concentrations of metals typify most ROFA samples (especially extremely high nickel and vanadium levels), and experimental exposures to such materials have generally resulted in exposures/doses that are orders of magnitude (100s of times) higher than would be associated with exposures to much lower levels of such metals in ambient PM measured routinely since the 1970s at community monitoring sites across the U.S. (except perhaps at times very near some sources without modern emission control devices or during temporary breakdowns of such). Thus, significant issues arise concerning the extent to which effects of ROFA or other high concentration emission source can be extrapolated to aid in interpretation of ambient air PM exposure effects on humans.

Analogous issues arise in connection with evaluation of the toxicity of PM obtained as emission products from mobile source combustion devices, e.g., diesel and gasoline vehicle engines. The complex combustion-related mixtures in such mobile source emissions include many different types of particles and gaseous compounds in high concentrations which are not necessarily representative of ambient PM derived from such sources after passage through particle traps, catalytic converters, exhaust pipes, etc. For example, ultrafine particles emitted from gasoline and diesel engines are reduced in numbers and concentrations as they agglomerate to form larger, accumulation-mode particles as they cool in passing through exhaust systems and/or as they undergo further physical and chemical transformation as they "age" as ambient air components. Further complicating evaluation of the toxicity of mobile source emission components is: (1) the difficulty in separating out toxic effects attributable to particles versus those of gaseous components in automotive exhausts; and (2) the changing nature of those exhaust mixes as a function of variations in engine operating mode (e.g., cold start versus warm start or "light" versus "heavy" load operation, etc.) and changes in engine technology (e.g., "old diesels" versus "new diesels").

The in vivo studies discussed first and the in vitro studies discussed later have almost exclusively used PM_{10} or $PM_{2.5}$ as particle size cutoffs for studying the adverse effects of ambient PM. Collection of these size fractions has been made easier by widespread availability of ambient sampling equipment for PM_{10} and $PM_{2.5}$. However, the study of other important size fractions, such as the coarse fraction ($PM_{10-2.5}$) and $PM_{1.0}$ has been largely ignored, and only limited toxicology data are now available by which to assess effects of these potentially important particle sizes. Similarly, although organic compounds often comprise 20 to 70% of the dry fine particle mass of ambient PM (see Chapter 3), little research has addressed mechanisms by which such compounds may contribute to ambient PM-related effects. One exception to this has been the evaluation of contributions of diverse organic compounds to mutagenic, genotoxic, and carcinogenic effects discussed later in Section 7.8.

7.1.2 Organization of the Chapter

Ambient PM, as noted above, is comprised of myriad physical and chemical species that can vary widely from one geographic location to another or even from one time to another time at a given location. It is not surprising that only a relatively few ambient air mixes from selected urban areas or subsets or combinations of the diverse variety of physical/chemical species have been investigated in controlled human or laboratory animal studies. However, a full discussion of all types of ambient particles that have been identified (see Chapter 2) is beyond the scope of this chapter. Thus, specific criteria were used to select topics for presentation. High priority was placed on studies that (a) may contribute to enhanced understanding of ambient PM epidemiologic study results and/or (b) elucidate mechanisms of health effects of ambient PM or its major common constituents. Diesel particulate matter (DPM) generally fits the above criteria; however, because it is discussed in great detail in other documents (Health Effects Institute, 1995; U.S. Environmental Protection Agency, 2002), only some aspects are discussed to a limited extent in this chapter. Individual particle species with high inherent toxicity that are of concern mostly because of occupational exposure (e.g., silica) that are discussed in detail in other documents and reports (e.g., U.S. Environmental Protection Agency, 1996b; Gift and Faust, 1997 for silica) are also not assessed in detail in this chapter.

Because of the sparsity of toxicological data on ambient PM at the time of the 1996 PM AQCD (U.S. Environmental Protection Agency, 1996a), the discussion of toxicologic effects

of PM was organized there into specific chemical components of ambient PM or "surrogate" particles (e.g., acid aerosols, metals, ultrafine particles, bioaerosols, "other particle matter"). Many of the newer toxicological studies evaluate potential toxic effects of combustion-related particles. The main reason for this extensive current interest in combustion particles is that these particles, along with materials adsorbed to such particles and secondary aerosols formed from them, are typically among the most dominant components represented in the fine fraction of ambient air PM found in most U.S. urban areas.

This chapter is organized as follows. First, cardiovascular and systemic effects of in vivo PM exposure are discussed in Section 7.2. Next, Section 7.3 discusses respiratory effects of ambient PM, specific components of ambient PM, combustion source-related particle mixes, or other laboratory-generated particles delivered by controlled in vivo exposures of humans or laboratory animals (note that the specific components discussion includes summary points drawn from detailed discussion of ambient bioaerosols in Appendix 7B). In vitro exposure studies are then next discussed (Section 7.4) and are useful in providing information on potential hazardous constituents and mechanisms of PM injury. The next section (Section 7.5) focuses on studies of PM effects in laboratory animal models meant to mimic human disease, as a means for providing information useful in characterizing factors affecting susceptibility to PM cardiovascular and respiratory system effects. Section 7.6 then assesses controlled-exposure studies evaluating health effects of mixtures of ambient PM or specific PM constituents with gaseous pollutants. Section 7.7 discusses exposure/dose-effects relationships for cardiovascular and respiratory effects and comparisons for illustrative health endpoints of experimental exposures/data needed to produce similar effects across species (rats, humans) and/or under ambient conditions (drawing upon extrapolation modeling results presented in Appendix 7A). The ensuing Section (7.8) discusses studies of PM-related mutagenic/genotoxic effects related to evaluation of the relative carcinogenic potential of ambient PM and its constituents, as well as particulate constituents in emissions from various types of combustion sources. Section 7.9 then discusses important new cross-cutting information on airborne particles as carriers of other toxic agents. This organization provides the underlying information used for interpretive summarization (in Section 7.10) of the extensive new findings discussed in the earlier sections with regard to PM-related effects, all of which may individually contribute to and/or combine through intricate interlinkages to mediate ambient PM exposure effects.

7.2 CARDIOVASCULAR AND SYSTEMIC EFFECTS OF IN VIVO PM EXPOSURES IN HUMANS AND LABORATORY ANIMALS

7.2.1 Introduction

A growing number of epidemiology studies are finding (a) associations between ambient PM and increases in cardiac-related deaths and/or morbidity indicators and (b) that the risk of PM-related cardiac effects may be as great or greater than those attributed to respiratory causes (see Chapter 8). Both acute and chronic PM exposures have been implicated in the observed cardiovascular morbidity and mortality effects. These effects appear to be induced via direct particle uptake into the blood and/or via mediation by the nervous system. Figure 7-1 schematically illustrates hypothesized mechanisms thought to be involved in cardiovascular responses to PM exposure. Such effects may be especially deleterious to individuals compromised by disease states such as ischemic heart disease, cardiac arrythmias, and COPD.

As shown in Figure 7-1, the heart receives both parasympathetic and sympathetic inputs, which serve to decrease or increase heart rate, respectively. Vasoconstriction, possibly due to release of endothelin elicited by PM, could cause increased blood pressure (which is detected by baroreceptors). Parasympathetic neural input may then be increased to the heart, slowing heart rate and decreasing cardiac output (which is sensed by aortic and carotid chemoreceptors). These, in turn, may cause a sympathetic response, manifested by increased heart rate and contractile force, thus increasing cardiac output. This arrhythmogenesis and altered cardiac output in either direction can be life-threatening to susceptible individuals. Pathophysiological changes in cardiac function can be detected by electrocardiographic recordings, with certain ECG parameters (e.g., heart rate variability or HRV) recently gaining widening use as indicators of PM-induced cardiac effects.

Heart rate variability (HRV), a measure of the beat-to-beat change in heart rate, is a reflection of the overall autonomic control of the heart. HRV has been used for many years as a research tool to study cardiovascular physiology and pharmacology. Its role as a clinical predictor of outcome for populations with heart disease has been extensively studied. HRV can be divided into time and frequency measures. Frequency measures of variability are more commonly used for mechanistic studies because they resolve parasympathetic and sympathetic influences on the heart better than do time domain measurements. It has been well established that the frequency analysis of heart rate variability is a robust method for measuring the

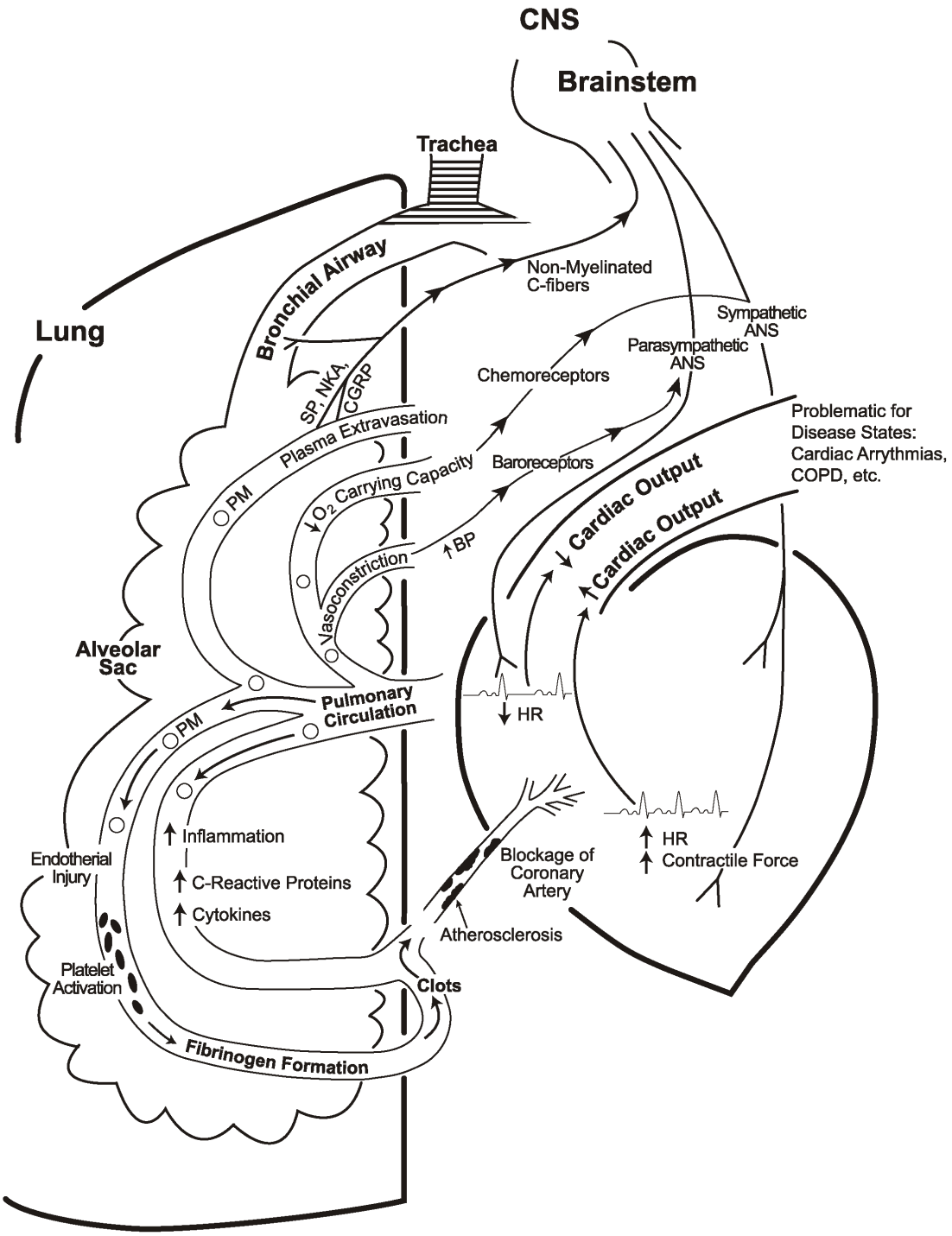

Figure 7-1. Schematic illustration of hypothesized pathways/mechanisms potentially underlying the cardiovascular effects of PM.

autonomic modulation of heart rate. Under certain circumstances, HRV provides insight into sympathetic nervous activity, but more commonly it is a very good measurement of parasympathetic modulation. For prognostication in heart disease, both the time and frequency domain measures of heart rate variability seem equivalent in predicting events. Heart rate variability can be used to judge the relative influences of sympathetic and parasympathetic forces on the heart, as such short-term spectral parameters (i.e., measures averaged over five minute intervals) can vary as much as 4-fold during the course of a 1-h period (Kleiger et al., 1991). Despite the inherent variability of short-term HRV measures during routine daily activity, long-term measures (i.e., measures averaged over 24 h) show excellent day-to-day reproducibility. Given this inherent variability in the minute-to-minute spectral measurements, great care is required in the experimental design of studies utilizing HRV techniques and interpretation of HRV results. When appropriately designed and carefully interpreted, studies utilizing measures of HRV provide insight into the relationship between the perturbation of the internal or external environment and subsequent changes in the modulation of autonomic neural input to the heart.

Heart rate variability has been studied in multiple settings, using different parameters (both time and frequency domain) to determine prognosis in populations. This has been studied most frequently in coronary artery disease populations, particularly in the post-myocardial infarction (post-MI) population. Most reports have dichotomized the study group by HRV parameters and then compared outcomes. To summarize those results, lower time domain as well as frequency domain variables are associated with an increase in cardiac and all-cause mortality. Those variables most closely correlated with parasympathetic tone appear to have the strongest predictive value in heart disease populations. Specifically, acute changes in RR-variability temporally precede and are predictive of increased long-term risk for the occurrence of ischemic sudden death and/or precipitating ventricular arrhythmias in individuals with established heart disease (see for example La Rovere et al., 2003). However, acute changes in HRV parameters do not necessarily occur immediately prior to sudden fatal ventricular arrhythmias (Waxman et al., 1994). The heart rate variability itself is not the causative agent, nor has it been implied to be a causative agent in any of the studies performed to date. Altered HRV, including changes in HRV associated with exposure to PM, is simply a marker for enhanced risk.

Another route by which PM could exert deleterious cardiovascular effects may involve ambient PM effects on endothelial function. In particular, as hypothesized by Seaton et al. (1995), PM exposure could affect blood coagulation, possibly through endothelial injury that results in platelet activation. This then could initiate a cascade of effects, e.g., increased fibrinogen and fibrin formation, leading to increased formation of clots. Figure 7-2 (from Nadziejko, et al., 2002) nicely illustrates physiological events (and applicable timeframes) involved in the blood clotting cascade, as well as denoting important substances released at successive steps which, in turn, stimulate the next step in the clotting cascade and, ultimately, trigger clot lysing events that normally terminate the cascade. Various studies have measured such substances as a means to evaluate possible PM-induced effects on blood coagulation. Another significant effect of PM exposure could be vascular inflammation, which induces release of C-reactive proteins and cytokines. These cause further inflammatory responses that, on a chronic basis, can lead to atherosclerosis. In narrowed coronary arteries, the clots formed in the aforementioned cascade may block blood flow, resulting in acute myocardial infarction.

Nadziejko et al. (2002) further note that small prothrombotic changes in blood coagulation parameters in a large population can have substantial effects on the incidence and prevalence of cardiovascular disease events (Di Minno and Mancini, 1990; Braunwald, 1997; Lowe et al., 1997). In particular, altered coagulation can increase heart attack risk through formation of clots on atherosclerotic plaques in coronary arteries that cut off blood supply to the myocardium or induce ischemic strokes via clots forming or lodging in the carotid arteries and blocking blood flow to cerebral arteries and brain tissue. Also, Nadziejko et al. (2002) note that (a) evidence exists for formation of small thrombi being common in persons with atherosclerosis (Meade et al., 1993) and (b) whether such thrombi lead to more serious effects (heart attack, stroke) depends in part on the balance between thrombogenic factors underlying blood clot formation and fibrinolytic factors that lyse clots. Also, they note that effects of small changes in coagulation on heart attack risk are reflected by the risk of sudden cardiac death being 70% higher between 6:00 a.m. and 9:00 a.m. than the average risk for the rest of the day (Willich, et al., 1987), likely due in part to the circadian rhythm of fibrinolytic factors that are at their lowest levels in the early morning (Andrews et al., 1996). Also, as stated by Nadziejko et al. (2002), sympathetic nervous system activity is increased by standing up after lying prone (Tofler, et al., 1987; Andrews et al., 1996), and increased sympathetic activity causes

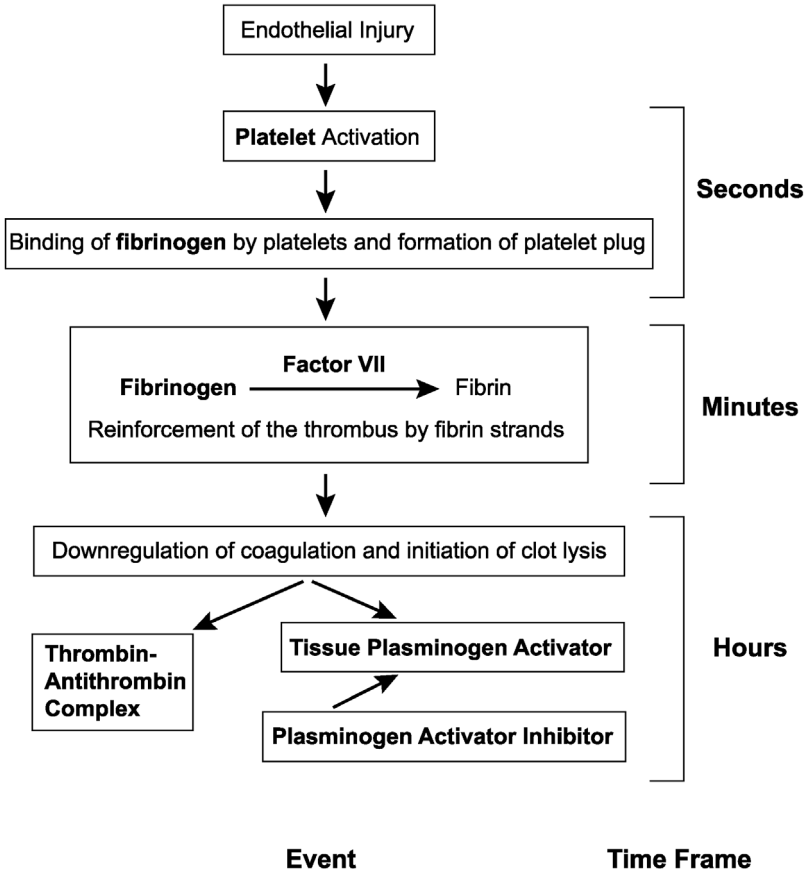

Figure 7-2. Simplified overview of blood coagulation system. The coagulation parameters often measured in the study of PM effects on blood coagulation are indicated by bold type. The relations of these selected parameters with the rest of the coagulation system are outlined.

Source: Nadziejko et al. (2002).

prothrombotic changes in blood coagulation parameters such that even small, homeostatic modulations of coagulation within a normal range could translate into significant increased risk for heart attack.

Thus, potentially dangerous alterations in cardiovascular functions due to PM exposures could be signaled by even small PM-related (a) changes in blood coagulation cascade indicators, e.g., increased blood platelet, fibrinogen, or Factor VII, or decreased tissue plasma activator

(TPA) levels; (b) increased C-reactive protein, or cytokines contributing to increased atherosclerosis plaque formation and/or blood coagulation; c) increased blood pressure; and/or (d) certain alterations in heart rate, heart rate variability, or other ECG indicators indicative of deleterious shifts in parasympathetic/sympathetic neural inputs to the heart or other underlying cardiac pathophysiology.

Another cardiovascular-related effect of PM exposure could be plasma extravasation from post-capillary venules. The mechanisms by which this occurs are thought to include the release of peptides such as neurokinin A, substance P, and calcitonin-gene-related peptide from unmyelinated sensory nerves, near to or on the blood vessels. These peptides bind to receptors on the endothelial cells of vessels and create gaps, allowing leakage of plasma, which is one component of neurogenic inflammation (Piedimonte et al., 1992; Baluk et al., 1992).

There were few studies assessed in the 1996 PM AQCD that evaluated cardiovascular system effects of PM exposures. Since 1996, numerous studies have now become available that evaluated cardiovascular effects of exposures (via inhalation or instillation) of ambient PM, constituent components, complex mixtures from PM emission sources and/or exposures to single PM substances or binary/ternary combinations of particles of varying chemical composition. Also, whereas earlier studies tended to focus on healthy animals, more recent studies have, in addition, begun to focus on evaluation of PM effects in animal models of disease states thought to mimic aspects of pathophysiologic states experienced by compromised humans at increased risk for PM effects.

The toxicological consequences of inhaled particles on the cardiovascular system had not been extensively investigated prior to 1996. Since then, Costa and colleagues (e.g., Costa and Dreher, 1997) have demonstrated that intratracheal instillation of high levels of ambient particles can increase or accelerate death in an animal model of cardiorespiratory disease induced by monocrotaline (MCT) administration in rats. These deaths did not occur with all types of ambient particles tested. Some dusts, such as volcanic ash from Mount Saint Helens, were relatively inert; whereas other ambient dusts, including those from urban sites, were toxic. These early observations suggested that particle composition plays an important role in the adverse health effects associated with episodic exposure to ambient PM, despite an apparent "general particle" effect that seemed to be implied by somewhat similar epidemiologic observations of ambient PM exposure associations with increased mortality and morbidity in

many regions of the United States with varying particle composition. Studies evaluating possible increased susceptibility to the adverse effects of PM in compromised animal models of human pathophysiology provide a potentially important link to epidemiologic observations and are among those discussed below.

Muggenburg et al. (2000a) has described several potential animal models of cardiac disease (MCT-induced pulmonary hypertension, dilated cardiomyopathy, viral and mycoplasmal myocarditis, and ischemic heart disease) and discussed advantages and disadvantages associated with the use of animal models to study cardiac disease and air pollution. The first type of animal model has probably been most extensively used in recent years. Pulmonary hypertension in humans may result from airway and vascular effects due to COPD, asthma, and cystic fibrosis. The MCT-induced vascular disease model exhibits common features of progressive pulmonary hypertension in humans. The injury effects include selective pulmonary endothelial damage and progressive pulmonary arterial muscularization. Pulmonary hypertension develops, the blood flow is impeded, and compensatory right ventricular hypertrophy occurs. To produce pulmonary hypertension, animals are injected subcutaneously with 50-60 mg/kg monocrotaline (MCT). Within two weeks after treatment, experimental animals, primarily rats, develop pulmonary hypertension (Kodavanti et al., 1998a).

A growing number of studies have used extracts of collected/stored ambient PM or real-time generated concentrated ambient particles (CAPs) drawn from various airsheds (e.g., Boston, New York City, etc.) to evaluate cardiovascular and other systemic effects of PM. Numerous other new animal studies have also used metal-associated ROFA as one type of combustion source particle mix; and others have used other types of combustion source materials, e.g., domestic oil fly ash (DOFA), coal fly ash (CFA), or diesel exhaust (DE). The following discussion of cardiovascular/systemic effects of PM first focuses mainly on the ambient PM studies and then discusses findings from the studies using ROFA and other types of particles.

Tables 7-1 and 7-2 summarize newly-available studies (since the 1996 PM AQCD) that evaluated cardiovascular effects of ambient PM mixtures or other types of PM in response to controlled inhalation exposures of humans or laboratory animals. Intratracheal instillation studies are then summarized in Table 7-3, and in vitro exposure studies of cardiovascular effects are discussed in Section 7.4.

TABLE 7-1. CARDIOVASCULAR AND SYSTEMIC EFFECTS OF INHALED AMBIENT PARTICULATE MATTER

Species, Gender, Strain Age, or Body Weight	Particle[a]	Exposure Technique	Mass Concentration	Particle Size	Exposure Duration, PE[b] Time to Analysis	Cardiovascular Effects	Reference
Humans, healthy nonsmokers, 18-40 years old n = 38	CAPs (Chapel Hill)	Inhalation	23.1 to 311.1 μg/m^3	0.65 μm σ_g = 2.35	2 h, analysis at 18 h	Increased blood fibrinogen with CAPs exposure. PM concentration in chamber varied with ambient air PM level. Estimated total dose of 1200 μg.	Ghio et al. (2000a)
Humans, healthy 18-40 years old n = 4	CAPs (Toronto)	Inhalation (face mask)	24 to 124 μg/m^3	0.1 - 2.5 μm		Trend toward increased fibrinogen levels 2 h post high CAPs (124 μg/m^3) exposure, but stat. sig. not specified. Also, no sig. ECG Holter effects.	Petrovic et al. (2000)
Humans, healthy; 19-41 years old n = 4	CAPs (Los Angeles)	Inhalation	148 to 246 μg/m^3	$PM_{2.5}$	2 h	No significant changes in in arterial O_2 saturation or Holter ECGs observed, nor in lung function or symptoms. The maximum steady state fine particle concentration in the breathing zone was typically seven times the ambient concentration.	Gong et al. (2000)
Humans, healthy (n = 12) and asthmatic (n = 12) 18-45 years old, nonsmoking	CAPs (Los Angeles)	Inhalation whole body chamber	99-224 μg/m^3 (mean 174)	80% 0.1 to 2.5 μm	2 h with alternating exercise/rest. Analysis at 0, 4, and 22 h PE.	CAPs-related decrease in Factor VII blood levels, - but no significant changes in blood fibrinogen or serum amyloid A with CAPs. Both healthy and asthmatic subjects had modest increases in HR variability and significant increases in HR during exercise. Some reported cardiac symptoms (faintness, dizziness, pain related to heart, etc) during CAPs exposure.	Gong et al. (2003)
Dogs, female mongrel, 14 to 17 kg	CAPs (Boston)	Inhalation via tracheostomy	3-360 μg/m^3	0.2 to 0.3 μm	6 h/day for 3 days	Peripheral blood parameters were related to specific particle constituents. Factor analysis from paired and crossover experiments showed that hematologic changes were not associated with increases in total CAP mass concentration.	Clarke et al. (2000a)
Dogs, mongrel; Balloon-occluded LAD coronary artery in some, n = 14	CAPs (Boston)	Inhalation via tracheostomy	~100-1000 μg/m^3	0.23 to 0.34 μm σ_g = 0.2 to 2.9	6 h/day for 3 days	Decreased heart and respiratory rate and increased lavage fluid neutrophils in normal dogs. Decreased time to ST segment elevation and increased magnitude in compromised dogs. PM concentration varied depending on ambient PM level and concentrator operation. No dose-response relationship evident.	Godleski et al. (2000)

TABLE 7-1 (cont'd). CARDIOVASCULAR AND SYSTEMIC EFFECTS OF INHALED AMBIENT PARTICULATE MATTER

Species, Gender, Strain Age, or Body Weight	Particle[a]	Exposure Technique	Mass Concentration	Particle Size	Exposure Duration, PE[b] Time to Analysis	Cardiovascular Effects	Reference
Rats	CAPs (Tuxedo, NY)	Inhalation (nose-only)	110-350 µg/m^3	N/A	3 h	Small but consistent increase in HR; increased peripheral blood neutrophils and decreased lymphocytes. No pulmonary injury found. Concentration to chamber varied from 132 to 199 µg/m^3.	Gordon et al. (1998)
Rats, male, F-344, MCT-treated Hamsters, 6-8 months old; Bio TO-2	CAPs (Manhattan)	Inhalation	132-919 µg/m^3	0.2-1.2 µm σ_g = 0.2-3.9	Single 3 h or 3 daily 6 h exposures	No increase in cardiac arrhythmias; inconsistent PM-associated increases in HR, blood cell differential counts, and atrial conduction time of rats. No adverse cardiac or pulmonary effects in hamsters.	Gordon et al. (2000)
Rats, male, F344, 250-275 g	CAPs (NYC)	Inhalation (nose-only)	95-341 µg/m^3	< 2.5 µm	0, 12, and 24 h	No consistent exposure-related effects on platelet count fibrinogen level, factor VII activity, thrombin-anti-thrombin complex, tissue plasminogen activator, or plasminogen activator inhibitor.	Nadziejko et al. (2002)
Rats, Wistar	Ott ambient (EHC-93) (ECH-93L) Diesel soot (DPM) Carbon black (CB)	Inhalation (nose only)	48 mg/m^3 49 mg/m^3 5 mg/m^3 5 mg/m^3	36, 56, 80, 100, and 300 µm	4 h, Analyses at 2, 32, 36, 48 h PE	EHC-93 elevated blood pressure on day 2, ET-1 levels at 32 h, and ET-3 levels at 2, 32, and 48 h postexposure. EHC-93 L had no effect on blood pressure, transient effect on ET-1, -2, -3 levels at 2 h but not 32 h postexposure. DPM had no effect on blood pressure, but elevated ET-3 levels at 36 h PE. CB had no effect.	Vincent et al. (2001)
Humans, male, healthy, age 19-24 years	PM_{10} from S.E. Asian Smoke Haze	Inhalation	~125 µg/m^3 (range = 47 to 216)	N/A	4 weeks, analysis at 3 and 5 weeks PE	Band cell counts were significantly increased during the haze period	Tan et al. (2000)

[a] CAPs = concentrated ambient particles
UAP = urban ambient partciles
DPM = diesel particulate matter
Ott ambient = resuspended UAP from Ottawa, CA

[b] PE = postexposure

TABLE 7-2. CARDIOVASCULAR AND SYSTEMIC EFFECTS OF INHALED ROFA AND OTHER COMBUSTION-RELATED PARTICULATE MATTER

Species, Gender, Strain Age, or Body Weight	Particle[a]	Exposure Technique	Mass Concentration	Particle Size	Exposure Duration, PE[b] Time to Analysis	Cardiovascular Effects	Reference
Dogs, beagles, 10.5 years old, healthy, n = 4	ROFA (Boston)	Oral inhalation	3 mg/m^3	2.22 µm MMAD σ_g = 2.71	3 h/day for 3 days	No consistent changes in ST segment, the form or amplitude of the T wave, or arrhythmias; slight bradycardia during exposure.	Muggenburg et al. (2000b)
Rats, S-D, MCT-treated, 250 g	ROFA (Boston)	Inhalation	580 ± 110 µg/m^3	2.06 µm MMAD σ_g = 1.57	6 h/day for 3 days	Increased expression of the proinflammatory chemokine MP-2 in the lung and heart of MCT-treated rats; less in healthy rats. Significant mortality only in MCT-treated rats.	Killingsworth et al. (1997)
Rats, S-D, SH rats, WKY rats, healthy and MCT-treated	ROFA (location not given)	Inhalation	15 mg/m^3	1.95 µm MMAD	6 h/day for 3 days	Pulmonary hypertensive (MCT-treated S-D) and spontaneously hypertensive (SH) rats exposed to ROFA by inhalation showed similar effects, but of diminished amplitude. There were no lethalities by the inhalation route.	Watkinson et al. (2000a,b)
Rats, male WKY and SH, 12 to 13 weeks old	ROFA (Florida)	Nose-only inhalation	15 mg/m^3	N/A	6 h/day for 3 days	Cardiomyopathy and monocytic cell infiltration, along with increased cytokine expression, was found in left ventricle of SH rats because of underlying cardiovascular disease. ECG showed exacerbated ST segment depression caused by ROFA.	Kodavanti et al. (2000a)
Rats, male, SH and WKY; 12 to 13 weeks old	ROFA (Boston)	Inhalation	15 mg/m^3	1.5 µm σ_g = 1.5	6 h/day, 3 days/week for 1, 2, or 4 weeks	One week exposure increased plasma fibrinogen in SH rats only; longer (2 or 4 week) exposure caused pulmonary injury but no changes in fibrinogen.	Kodavanti et al. (2002a)
Rats, male, S-D, WKY and SH	ROFA (Boston)	Inhalation (nose only)	2, 5, 10 mg/m^3 10 mg/m^3		6 h/day for 4 consec. days 6 h/day 1 day/week, 4 or 16 weeks	No cardiovascular effects see in SD or SH rats with acute or chronic exposure. Cardiac lesions (active chronic inflammatory, multifocal myocardial degeneration, fibrosis, decreases in number of granulated mast cells) seen for WKY rats with chronic (16 week) exposures.	Kodavanti et al. (2003)

TABLE 7-2 (cont'd). CARDIOVASCULAR AND SYSTEMIC EFFECTS OF INHALED ROFA AND OTHER COMBUSTION-RELATED PARTICULATE MATTER

Species, Gender, Strain Age, or Body Weight	Particle[a]	Exposure Technique	Mass Concentration	Particle Size	Exposure Duration, PE[b] Time to Analysis	Cardiovascular Effects	Reference
Rats, male, S-D, healthy and MI	ROFA (Boston) Carbon black	Inhalation	3 mg/m^3	1.81 µm 0.95 µm	1 h	In MI group, with thermocoagulation of left coronary artery, 41% of rats had one or more premature ventricular complexes (PVCs). ROFA but not CB or room air, increased arrhythmia frequency in those with PVCs and decreased heart rate variability.	Wellenius et al. (2002)
Human, healthy, nonsmoking males	Ultrafine carbon particles	Mouthpiece exposure	10 µg/m^3	< 100 nm	2 h exposure; assessment before and immediately, 3.5 h, and 21 h after exposure	No effects on blood coagulability, circulating leukocyte activation, leukocyte expression of activation and adhesion molecules.	Frampton (2001)
Rats, SD, 60 days old	VSO_4 $NiSO_4$	Inhalation	0.3 -2.4 mg/m^3	N/A	6h/day x 4 days	No effects with V at all doses. Ni caused delayed bradycardia, hypothermia and arrhythmogenesis at >1.2 mg/m^3. V+Ni produced delayed effects at 0.5 mg/m^3 and potentiated responses at 1.3 mg/m^3, suggesting synergism of effect.	Campen et al. (2001)
Rats, SH	DE	Whole body	30,100, 300, or 1000 µg/m^3	90% < 1 µm	6 h day, 7 day/week for 1 week	Elevated daytime HR; concentration-dependent prolongation of PQ interval.	Campen et al. (2003)

[a] ROFA = Residual oil fly ash
$NiSO_2$ = Nickel sulfate
$Fe_2(SO_4)_3$ = Iron sulfate
DE = diesel exhaust
VSO_4 = Vanadium sulfate
MCT = monocrotaline
MI = Myocardial infarction

[b] PE = Post Exposure

TABLE 7-3. CARDIOVASCULAR AND SYSTEMIC EFFECTS OF INSTILLED ROFA AND OTHER PARTICULATE MATTER

Species, Gender, Strain Age, or Body Weight	Particle[a]	Exposure Technique	Dose	Particle Size	PE[b] Time to Analysis	Cardiovascular Effects	Reference
Rats, male, S-D, 60 days old, healthy and MCT-treated	ROFA DOFA CFA	Intratracheal instillation	Total mass: 2.5 mg/rat	Emission PM: 1.78- 4.17 µm	Analysis at 24 and 96 h following instillation	ROFA alone induced some mild arrhythmias; MCT-ROFA showed enhanced neutrophilic inflammation.	Costa and Dreher (1997)
	Ambient PM (St. Louis Dusseldorf, Ottawa, Wash. DC)		Total transition metal: 46 µg/rat	Ambient PM: 3.27-4.09 µm		MCT-ROFA animals showed more numerous and severe arrhythmias including S-T segment inversions and A-V block.	
Rats, male, S-D, 60 days old, healthy and MCT-treated, n = 64	ROFA (location not given)	Intratracheal instillation	0.0, 0.25, 1.0, and 2.5 mg/rat	1.95 µm	Analysis at 96 h postexposure	Dose-related hypothermia and bradycardia in healthy rats, potentiated by compromised models at 2.5 mg dose.	Campen et al. (2000)
Rats, male, SD, 60 days old, healthy and MCT-treated	$Fe_2(SO_4)_3$ $NiSO_4$ VSO_4	Intratracheal instillation	105 µg 263 µg 245 µg		Analysis at 96 h postexposure	V caused bradycardia, arrhythmogenesis and hypothermia immediately. Ni caused delayed bradycardia, arrhythmogenesis and hypothermia. Fe had little effect.	Campen et al. (2002)
MCT-treated	$Fe_2(SO_4)_3$ +VSO_4		105 µg 245 µg			Ni exacerbated the immediate effects of V. Fe attenuated them.	
	$Fe_2(SO_4)_3$ + $NiSO_4$		105 µg 263 µg				
	$NiSO_4$ + VSO_4		263 µg 245 µg				
	VSO_4 + $Fe_2(SO_4)_3$ + $NiSO_4$		245 µg 105 µg 263 µg				
Rats, male, S-D; 60 days old	ROFA (Florida) MSH Vol. Ash	Intratracheal instillation	0.3, 1.7, or 8.3 mg/kg	1.95 µm $\sigma_g = 2.19$	Analysis at 24 h	Increased plasma fibrinogen only at 8.3 mg/kg ROFA.	Gardner et al. (2000)

TABLE 7-3 (cont'd). CARDIOVASCULAR AND SYSTEMIC EFFECTS OF INSTILLED ROFA AND OTHER PARTICULATE MATTER

Species, Gender, Strain Age, or Body Weight	Particle[a]	Exposure Technique	Dose	Particle Size	PE[b] Time to Analysis	Cardiovascular Effects	Reference
Rats, male, SD, 60 days old	ROFA (Boston) classified by soluble metals (As, Be, Cd, Co, Cr, Cu, Fe, Mn, Ni, Pb, V, Zn, and sulfate)	Intratracheal instillation	0.83, 3.3 or 8.3 mg/kg	< 3.0 µm MADD	Anaylsis at 24 h postexposure	Dose-dependent increase in BAL protein, LDH, hemoglobin and NAG activity (only high dose data shown). ROFA containing highest concentration of water-leachable Fe, V, and Ni or V and Ni caused largest increase. ROFA with highest V content induced greatest increase in BAL neutrophils. AM chemiluminescence was greatest with ROFA containing primarily soluble V and less with Ni + V.	Kodavanti et al. (1998a)
Rats, male, S-D, MCT-treated	ROFA (Florida)	Intratracheal instillation	0.25, 1.0, or 2.5 mg in 0.3 mL saline	1.95 µm MMAD $\sigma_g = 2.19$	Monitored for 96 h after instillation of ROFA particles	Dose-related increases in incidence and duration of serious arrhythmic events in normal rats. Incidence and severity of arrythmias increased greatly in MCT rats. Changes occurred at all doses ranging from modest effects at the lowest to more serious disturbances at the higher doses. Deaths seen at each instillation level in MCT rats only (6/12 died after MCT + ROFA).	Watkinson et al. (1998)
Rat, SD, 60 d old; 250-300 g healthy or MCT-treated	ROFA (Florida)	Intratracheal instillation	0.83 or 3.33 mg/kg	1.95 µm MMAD, $\sigma_g = 2.19$	Analysis at 24 and 96 h postexposure	Increases in BAL markers of lung injury and inflammation; 58% of MCT rats exposed to ROFA died by 96 h regardless of the dose.	Kodavanti et al. (1999)
Rats, male SH and WKY; 12-13 weeks old	ROFA (Boston)	Intratracheal instillation	1 and 5 mg/kg	1.5 µm $\sigma_g = 1.5$	Analysis at 1, 2, and 4 days	ROFA increased plasma fibrinogen and decreased peripheral lymphocytes in both SH and WKY rats at 5.0 mg/kg dose.	Kodavanti et al. (2002a)
(1) Rats, S-D healthy and MCT, cold-stressed, and ozone-treated	ROFA (location not given)	Intratracheal instillation	0.0, 0.25, 1.0, or 2.5 mg/rat	1.95 µm $\sigma_g = 2.19$	Monitored for 96 h after instillation	(1) Healthy rats exposed IT to ROFA demonstrated dose-related hypothermia, bradycardia, and increased arrhythmias at 2.5 mg dose. Similar response pattern seen at 0.25 and 1.0 mg, but reduced in magnitude and duration. Compromised rats showed exaggerated hypothermia and cardiac responses to IT ROFA at all doses. Mortality was seen only in the MCT-treated rats exposed to ROFA by IT.	Watkinson et al. (2000a,b); Watkinson et al. (2001)

TABLE 7-3 (cont'd). CARDIOVASCULAR AND SYSTEMIC EFFECTS OF INSTILLED ROFA AND OTHER PARTICULATE MATTER

Species, Gender, Strain Age, or Body Weight	Particle[a]	Exposure Technique	Dose	Particle Size	PE[b] Time to Analysis	Cardiovascular Effects	Reference
(2) Rats, SH, 15 months old	OTT ROFA MSH	Intratracheal instillation	2.5 mg 0.5 mg 2.5 mg			(2) Older rats exposed IT to OTT showed a pronounced biphasic hypothermia and a severe drop in HR accompanied by increased arrhythmias. Exposure to ROFA caused less pronounced, but similar effects. No cardiac effects seen with MSH exposure.	Watkinson et al. (2000a,b); Watkinson et al. (2001)
(3) Rats, S-D MCT-treated	$Fe_2(SO_4)_3$ VSO_4 $NiSO_2$	Intratracheal instillation	105 µg 245 µg 262.5 µg			(3) Ni and V showed the greatest toxicity; Fe-exposed rats did not differ from controls.	
Rats, Wistar, male, 200-250g, healthy and ozone-treated	Ottawa EHC-93	Instillation	0.5, 1.5 or 5 mg/rat in 0.3 mL saline	0.5 µm	Analysis at 2,4, or 7 days after exposure	At high doses, 20% increase in plasma fibrinogen at 2 days PE correlated with increases in ET-1 and iNOS mRNA and decrease in ACE.	Ulrich et al. (2002)
Rabbits, female, New Zealand, 2.2 to 3.0 kg	OTT PM_{10} (EHC-93)	Intrapharyngeal instillation	5 mg/dose	4-5 µm mass median diameter	5 mg 2 times per week for 3 weeks	PM_{10} increased circulating band cells and shortened transit time of PMN through postmitotic pool in marrow. Increased bone marrow pool of PNM, esp. in mitotic pool.	Mukae et al. (2001)
Rabbits, female, Watanabe heritable hyperlipidemic 3.2 ± 0.1 kg	OTT PM_{10} (EHC-93)	Intrapharyngeal instillation	5 mg in 1 mL saline	0.8 ± 0.4 µm	5 mg 2 times per week for 4 weeks	Increased circulating PMN band cell counts and size of bone marrow mitotic pools of PMNs. Progression of atherosclerotic lesions. Increase in plaque cell turnover, extracellular lipid pools, and total lipids in aortic lesions.	Suwa et al. (2002)
Rabbits, female, New Zealand White, 1.8 to 2.4 kg	Colloidal carbon	Instillation	2 mL of 1% colloidal carbon (20 mg)	< 1 µm	Examined at 24 to 192 h after instillation	Colloidal carbon stimulated the release of BRDU-labeled PMNs from bone marrow. The supernatant of alveolar macrophages treated with colloidal carbon in vitro also stimulated release of PMNs from bone marrow, likely via cytokines.	Terashima et al. (1997)

TABLE 7-3 (cont'd). CARDIOVASCULAR AND SYSTEMIC EFFECTS OF INSTILLED ROFA AND OTHER PARTICULATE MATTER

Species, Gender, Strain Age, or Body Weight	Particle[a]	Exposure Technique	Dose	Particle Size	PE[b] Time to Analysis	Cardiovascular Effects	Reference
Hamsters, 100-150 g	polystyrene particles (unmodified)	Intravenous (IV) administration and intratracheal instillation	5, 500, 5000 µg/kg	60 nm		IV doses of 5,500 or 5,000 µg/kg b.wt. of unmodified polystyrene particles did not affect thrombus formation.	Nemmar et al. (2002)
	carboxylate-modified polystyrene		50, 100, 500 µg/kg			IV doses of 100 and 500 µg/kg b.wt. carboxylate-modified polystyrene particles decreased ($p < 0.05$) thrombus formation intensity.	
	amine-modified polystyrene		5, 50, 500 µg/kg			IV doses of 100 and 500 µg/kg b.wt. of amine-polystyrene particles increased thrombus formation ($p < 0.01$).	
						Intratracheal instillation of 5,000 µg/kg of amine-polystyrene particles significantly ($p < 0.05$) increased thrombus formation but not 5,000 µg/kg of unmodified- or carboxylate-polystyrene particles.	
						Platelet aggregation (ADP-induced in vitro) was not affected by unmodified-polystyrene up to 100 µg/mL; and was strongly increased by amine-polystyrene particles.	
						Authors attributed observed prothrombic activity of ultrafine paticles, at least, in part, to platelet activation by positively charged amine-modified polystyrene particles.	

[a] ROFA = Residual oil fly ash
$Fe_2(SO_4)_3$ = Iron sulfate
VSO_4 = Vanadium sulfate
CFA = Coal fly ash
DOFA = Domestic oil burning furnace fly ash
OTT = Ottawa urban ambient particles
MSH = Mt. St. Helen's volcanic ash
$NiSO_2$ = Nickel sulfate

[b] PE = Post Exposure

7.2.2 Ambient Particulate Matter Cardiovascular Effects

Epidemiology studies discussed in Chapter 8 suggest that homeostatic changes in the vascular system can occur after episodic exposure to ambient PM. However, very few controlled human exposure studies of ambient PM effects on cardiovascular endpoints have been conducted thus far. In one such study, Ghio et al. (2000a) reported that inhalation of concentrated ambient particles (CAPs) in healthy nonsmokers increased blood fibrinogen levels. They exposed 38 volunteers exercising intermittently at moderate levels of exertion for 2 h to either filtered air (FA) or particles concentrated from the air in Chapel Hill, NC. The CAP exposures ranged from 23 to 311 $\mu g/m^3$, reflecting variations in particles collected outside the facility. Dividing CAPs exposures into three groups, blood fibrinogen levels were somewhat increased for each tritile of exposure (mean = 47 $\mu g/m^3$ for lowest group) in comparison to FA-exposure fibrinogen levels (the CAPs fibrinogen levels being significantly higher for all tritiles combined but not for any one tritile in comparison to FA control values). However, differences between pre- and post-CAPs exposure fibrinogen levels at 18 h postexposure were not significant. Other blood parameters tested in this study (including numbers of RBCs, monocytes, lymphocytes, platelets, or neutrophils) did not change significantly. The blood effects may be associated with mild pulmonary inflammation found 18 h after exposure to such CAPs (see Section 7.2.3).

Two other human CAPs inhalation studies are limited by small numbers of subjects studied. In one, Petrovic et al. (2000) exposed four healthy volunteers (aged 18 to 40 years) under resting conditions to FA and low, mid, and high concentrations (23 to 124 $\mu g/m^3$) of CAPs (0.1 to 2.5 μm) from downtown Toronto for 2 h using a face mask. The low CAP exposures were reflective of typical ambient $PM_{2.5}$ levels and the high ones of maximum $PM_{2.5}$ levels seen in Toronto. On each day prior to exposure, pulmonary function, nasal lavage, nasal acoustic rhinometry, blood collection for plasma fibrinogen and clotting factor VII antigen, and a resting ECG were taken. Pulmonary function measurements were taken every 30 min and ECG readings recorded continuously during exposure, followed by ECG readings after 30 min of postexposure exercise and by nasal lavage, sputum induction, and blood collection at about 2 h and about 24 h postexposure. Review of the ECG data by a cardiologist showed no clinically significant cardiac effects during exposure, the ensuing exercise period, or 24 h postexposure; but 2 of 4 subjects showed 15-20% pre- to postexposure increases in blood fibrinogen levels within 2 h post high CAPs exposure (124 $\mu g/m^3$) versus maximum 5-6% increases after FA

exposures, although there were no statistically significant differences for mean fibrinogen between CAP and FA exposures.

In another small pilot study, reported by Gong et al. (2000), four healthy adult volunteers (2 male, 2 female; aged 19 to 40 years) were exposed for 2 h while at rest in a whole body chamber to FA or to $PM_{2.5}$ CAPs from Los Angeles air. The CAP exposures at mean 2 h concentrations of 148 to 246 $\mu g/m^3$ (the latter approximating likely maximum exposure levels in Los Angeles) resulted in "no meaningful changes" in heart-rate variability, or ECG ST voltages, lung function, or respiratory symptoms, based on data collected during 2-h exposures or 10 or 22 h afterward. These results appear to be suggestive of Los Angeles ambient $PM_{2.5}$ exposures being unlikely to affect cardiorespiratory functions in healthy non-elderly adults. However, such a conclusion must be tempered by several considerations: (a) the small number of subjects tested and only while at rest (versus planned further studies to evaluate larger numbers of both healthy and compromised volunteers with respiratory or vascular disease, presumably to include exposures involving intermittent exercise); and (b) the Harvard model concentrator used did not likely concentrate effectively ambient particles < 0.1 to 0.2 μm MMAD, thus not exposing subjects to concentrated levels of potentially important combustion-derived (from diesel/gasoline vehicles; wood smoke, etc.) ambient particles.

More recently, Gong et al. (2003) exposed 12 healthy and 12 asthmatic subjects (age range 18 to 45 years) to Los Angeles CAPs ($PM_{2.5}$). An exposure to CAPs averaging 174 $\mu g/m^3$ (range 99 to 224) in a whole body chamber for 2 h was alternated with a filtered air (FA) exposure at least 14 days apart. Subjects exercised for 15 min of each half hour at a ventilation rate of 15 to 20 $L/min/m^2$ body surface. Tests were performed just before exposure (pre), just after (immediately post), 3.5 to 4 h after (4 h), and the next day (day 2). No significant CAPS-related changes in routine blood parameters were seen, except for some mediators of blood coagulation and systemic inflammation, (e.g., Factor VII, which declined immediately postexposure and at 4 h later and then rebounded on day 2). However, there were no accompanying changes in fibrinogen or serum amyloid A with CAPs exposure. Both groups exhibited modest increases in HR variability, and both had significant differences in HR during exposure (FA: 76 at rest and 96 at exercise; CAPs: 72 at rest and 92 at exercise). There were no significant differences in diastolic BP and HR-systolic product. Systolic BP increased in healthy subjects after CAP exposure at immediate, 4 h, and 2 days postexposure. Systolic BP decreased in asthmatics

immediately and at day 2 postexposure. Holter ECG data suggested to the authors a CAP-induced increase in parasympathetic input to the heart, about which they are uncertain as to the health significance. During CAPs exposure, some subjects also reported "cardiac symptoms," which included faintness, dizziness, irregular heartbeat, and pain related to the heart.

Godleski and colleagues (2000) have performed a series of experiments examining the cardiopulmonary effects of inhaled CAPs on normal mongrel dogs and on dogs with coronary artery occlusion. Dogs were exposed by inhalation via a tracheostomy tube to Boston CAPs for 6 h/day for 3 consecutive days. The investigators found little biologically-relevant evidence of pulmonary inflammation or injury in normal dogs exposed to CAPs (daily range of mean concentrations was ~100 to 1000 $\mu g/m^3$). The only statistically significant effect was a doubling of the percentage of neutrophils in lung lavage. Despite the absence of major pulmonary effects, a significant increase in heart rate variability (an index of cardiac autonomic activity), a decrease in heart rate, and a decrease in T alternans (an index of vulnerability to ventricular fibrillation) were seen. Exposure assessment of particle composition yielded no indication of which specific components of the CAPs were correlated with the day-to-day variability in response. The significance of these effects is not yet clear, given that the effects did not occur on all exposure days (e.g., changes in heart rate variability were observed on only 10 of the 23 exposure days). Although the HRV increase and the decrease in t-wave alternans might suggest a reduction in cardiovascular risk in response to inhaled concentrated ambient PM, the clinical significance of this effect is unclear. However, the magnitude of the observed changes, while small, are clearly not consistent with increased risk for cardiovascular events.

The most important finding of Godleski et al. (2000) was the observation of a potential increase in ischemic stress of the cardiac tissue from repeated exposure to CAPs from Boston. During coronary occlusion in four dogs exposed to PM, they observed (a) significantly more rapid development of ST elevation of the ECG waveform; and (b) greater peak ST-segment elevation after CAP exposure. Together, these changes are not internally consistent with those noted above. That is, on one hand, the ST segment elevation timing suggests a lower ischemic threshold and a higher risk for serious outcomes in the compromised dog model, but the HRV and T-wave alternans changes in the normal dogs suggest lower cardiac risk. Clearly, much further work in more dogs (and other species) will be necessary to confirm such findings and to better understand their potential significance.

In a series of studies, (Gordon et al., 2000) examined rodent cardiovascular system responses to CAPs derived from New York City air. Particles of 0.2 to 2.5 μm diameter were concentrated up to 10 times their levels in ambient air (~130 to 900 $\mu g/m^3$) to maximize possible differences in effects between normal and cardiopulmonary-compromised laboratory animals. No ECG changes were detected in normal Fischer 344 rats or hamsters exposed by inhalation to the New York City CAPs for a single 3-h exposure or for 3 daily 6-h exposures. Similarly, no deaths or ECG changes were seen in MCT rats or cardiomyopathic hamsters exposed to PM. In contrast to the nonsignificant decrease in heart rate observed in dogs exposed to Boston CAPs (Godleski et al., 2000), statistically significantly heart rate increases (~5%) were observed by Gordon et al. (2000) in both the normal and MCT rats exposed to New York CAPs, but not on all exposure days. Thus, extrapolation of the heart rate changes in these animal studies to human health effects is difficult, although the observed increase in heart rate in rats is similar to that observed in some human population CAPs studies.

Gordon and colleagues (1998) have also reported other cardiovascular effects in animals exposed to inhaled CAPs. Increases in peripheral blood platelets and neutrophils were observed in control and MCT rats at 3 h, but not 24 h, after a 3 h exposure to 150 to 400 $\mu g/m^3$ New York City CAPs. This neutrophil effect did not appear to be dose-related and did not occur on all exposure days, suggesting that day-to-day changes in particle composition may play an important role in the systemic effects of inhaled particles. The number of studies reported was small; and, it is therefore not possible to determine statistically if the day-to-day variability was truly due to differences in particle composition or even to determine the size of this effect.

Nadziejko et al. (2002) exposed healthy rats to concentrated ambient particles (CAPs) from New York City air at concentrations in the range of 95 to 341 $\mu g/m^3$ for 6 h and sampled blood at 0, 12, and 24 h postexposure. They found no consistent differences in counts of platelets, blood cells, or in levels of proteins in the blood coagulation system that included fibrinogen, thrombin-anti-thrombin complex, tissue plasminogen activator, plasminogen activator inhibitor, and factor VII. Nadziejko et al. (2002) present a thorough discussion of the blood coagulation system, demonstrating its complexity, and further discuss limitations of the study that include particle composition and size, the possible blunted response seen in rats compared to humans, the healthy status of the animals compared to a cardiovascular compromised model, and the endpoints chosen.

Studies by Vincent et al. (2001) indicate that very high concentrations (48 mg/m^3) of urban ambient particles from Ottawa ambient air administered by nose-only inhalation for 4 h to laboratory rats can cause a vasopressor response and affect blood levels of endothelin without causing acute lung injury. The authors reported a MMAD of ~4 μm for the EHC93 Ottawa urban ambient particles resuspended from samples from the air purification system of an office building. In this study, they also found that exposure to water-leached Ottawa samples (EHC93L) can modify the potency to influence hemodynamic changes by removal of polar organic compounds and soluble elements from the Ottawa particles. Exposure to DPM (5 mg/m^3) had no effect on blood pressure, but caused elevated endothelin levels, whereas a comparable exposure to 5 mg/m^3 carbon black (CB) had no effects. The authors concluded that their results suggest a novel mechanism by which inhaled particles can affect cardiovascular function, i.e., by causing elevated endothelins, which are among the most potent vasoconstrictors in the systemic circulation and which have been shown to correlate with severity of disease in congestive heart failure and to predict cardiac death (Galatius-Jensen, et al., 1996), possibly due to ET-1 being cardiotoxic by promoting infarct size (Omland et al., 1994). However, the very high exposure concentrations used leave it unclear as to the extent that such effects may be pertinent to ambient PM exposure conditions.

Another study (Ulrich et al., 2002) utilized Ottawa EHC93 and an exposure paradigm consisting of saline control, 5 mg EHC93 only, or ozone (O_3) pretreatment (8 h to 1600 μg/m^3) on the day preceding instillation. Instillations were at concentrations of 0.5, 1.5, or 5 mg/rat (~2.2, 6.7, or 22.2 mg/kg based on reported body weights). At the high doses, both with (170 mg/dl) and without (160 mg/dl) O_3-pretreatment, they observed a 20% increase in plasma fibrinogen at 2 days post exposure compared to saline controls (140 mg/dl). These changes correlated with increases in endothelin (ET)-1 levels and iNOS mRNA and a decrease in angiotensin-converting enzyme (ACE). The authors suggest that the hematological changes seen in this study model heart failure in high-risk groups exposed to PM.

7.2.3 ROFA and Other Combustion Source-Related Particles

Turning to studies evaluating cardiovascular effects of controlled exposures to combustion source-related materials, using the MCT model of cardiorespiratory disease, Killingsworth et al. (1997) examined the effects of a combustion source-related irritant particle mix (residual fuel oil

fly ash [ROFA] from the Boston area). They observed 42% mortality in MCT rats exposed to ~580 μg/m^3 ROFA for 6 h/day for 3 consecutive days but no deaths among MCT rats exposed to filtered air or saline-treated healthy rats exposed to ROFA. The increase in MCT/ROFA group deaths was accompanied by (a) increased neutrophils in lavage fluid and (b) increased immunostaining of macrophage inflammatory protein (MIP-2), from among several proinflammatory chemokines evaluated, in the lungs and hearts of the MCT/ROFA animals. Cardiac immunohistochemical analysis indicated increased MIP-2 in cardiac macrophages. The ROFA-induced deaths did not result from a change in pulmonary arterial pressure, and the cause of death was not identified. The results suggest that MCT treatment and ROFA exposure can produce significant lung inflammation and possible increases in proinflammatory signals in the heart.

Using a similar experimental model, Watkinson et al. (1998) examined the effects of intratracheally instilled Florida area power plant ROFA (0.0, 0.25, 1.0, 2.5 mg in 0.3 mL saline) on ECG measurements in healthy control and MCT rats. They observed a dose-related increase in the incidence and duration of arrhythmic events in control animals exposed to ROFA particles, and these effects appeared to be exacerbated in the MCT animals (the strength of these conclusions and determination of lowest observed effective dose levels being limited due to lack of statistical analyses). Similar to the results of Killingsworth et al. (1997), healthy animals treated with ROFA suffered no deaths, but there were 1, 3, and 2 deaths in the low-, medium-, and high-dose MCT groups, respectively. Further, given that the observed rhythm disturbances were mimicked by infusion of acetylcholine, increased vagal (parasympathetic) input may have contributed to the ROFA-induced increase in arrythmias. Thus, ROFA PM may be linked to conductive and hypoxemic arrhythmias in rats having MCT-induced pulmonary hypertension. However, the specific data and analyses in this study do not establish that relationship with certainty. Such small sampling frequency as was used here does not allow any extrapolation in terms of the total frequency of arrhythmia because of the inherent variability of arrhythmia frequency. Also, since the increased arrhythmia reported by these investigators in this animal model is almost entirely dropped beats, these findings have questionable bearing on the mechanism of potential increased risk of cardiac mortality in humans exposed to PM. It is also possible that the reported mortalities were simply related to the MCT-induced pulmonary hypertension.

In order to help gauge the biological relevance of intratracheal instillation of ROFA particles, Kodavanti et al. (1999) exposed MCT rats to Florida area ROFA by either instillation (0.83 or 3.33 mg/kg) or nose-only inhalation (15 mg/m^3, 6 h/day for 3 consecutive days). Similar to Watkinson et al. (1998), intratracheal instillation of ROFA in MCT rats caused about 50% mortality. However, very notably, no mortality occurred in MCT rats exposed to ROFA by the inhalation route despite the high exposure concentration (15 mg/m^3); nor was there any mortality in healthy rats exposed to ROFA or in MCT rats exposed to clean air. Despite the fact that mortality was not associated with ROFA inhalation exposure of MCT rats, exacerbation of lung lesions and pulmonary inflammatory cytokine gene expression, as well as ECG abnormalities, were evident.

Watkinson and colleagues further examined whether the effects of instilled ROFA would be exacerbated in rodents already under increased stress by being previously exposed to O_3 or being housed in the cold (Watkinson et al., 2000a,b; Watkinson et al., 2001; Campen et al., 2000). The effect of O_3-induced pulmonary inflammation (preexposure to 1 ppm O_3 for 6 h) or housing in the cold (10 °C) on the response to instilled ROFA in rats were similar to that produced with MCT. Bradycardia, arrhythmias, and hypothermic changes were consistently enhanced in the O_3-exposed and cold-stressed animals treated with ROFA (0.25, 1.0, or 2.5 mg/rat); but, unlike for the MCT animals, no deaths occurred. Thus, it appears that preexisting cardiopulmonary disease or increased physiological stress may make rodents more susceptible to cardiovascular changes induced by intratracheal instillation of $\geq$ 0.25 mg of ROFA. While studies of instilled ROFA demonstrated immediate and delayed responses, consisting of bradycardia, hypothermia, and arrhythmogenesis in conscious, unrestrained rats (Watkinson et al., 1998; Campen et al., 2000), further study of instilled ROFA-associated transition metals showed that vanadium (V) induced the immediate responses, while nickel (Ni) was responsible for the delayed effects (Campen et al., 2002). Moreover, Ni, when administered concomitantly, potentiated the immediate effects caused by V.

In another study, Campen et al. (2001) examined responses to these metals in conscious rats by whole-body inhalation exposure. The authors tried to ensure valid dosimetric comparisons with the instillation studies, by using concentrations of V and Ni ranging from 0.3 to 2.4 mg/m^3. The concentrations used incorporated estimates of total inhalation dose derived using different ventilatory parameters. Heart rate (HR), core temperature ($T_{[CO]}$), and

electrocardiographic (ECG) data were measured continuously throughout the exposure. Animals were exposed to aerosolized Ni, V, or Ni + V for 6 h per day for 4 days, after which serum and bronchoalveolar lavage samples were taken. While Ni caused delayed bradycardia, hypothermia, and arrhythmogenesis at concentrations > 1.2 mg/m^3, V failed to induce any significant change in HR or $T_{[CO]}$, even at the highest concentration. When combined, Ni and V produced observable delayed bradycardia and hypothermia at 0.5 mg/m^3 and potentiated these responses at 1.3 mg/m^3 to a greater degree than were produced by the highest concentration of Ni (2.1 mg/m^3) alone. The results are suggestive of a possible synergistic relationship between inhaled Ni and V, albeit these studies were performed at metal concentrations orders of magnitude greater than their typical ambient concentrations.

Watkinson et al. (2000a,b) also sought to examine the relative toxicity of different particles on the cardiovascular system of spontaneously hypertensive (SH) rats. They instilled 2.5 mg of representative particles from ambient (Ottawa) or natural (Mount Saint Helens volcanic ash) sources and compared the response to 0.5 mg ROFA. Instilled particles were either mass equivalent dose or adjusted to produce equivalent metal dose. They observed adverse changes in ECG, heart rate, and arrhythmia incidence that were much greater in the Ottawa ambient PM- and ROFA-treated rats than in the volcanic ash-treated rats. The cardiovascular changes observed with the Ottawa particles were actually greater than with the ROFA particles. These experiments indicate: (a) that instillation of ambient air particles, albeit at a very high concentration, can produce cardiovascular effects; and (b) that exposures of equal mass dose to particle mixes of differing composition did not produce the same cardiovascular effects, suggesting that PM composition rather than just mass was responsible for the observed effects.

Kodavanti et al. (2000a) exposed (via nose-only inhalation) SH and normotensive Wistar-Kyoto (WKY) rats to 15 mg/m^3 ROFA (Florida area) particles for 6 h/day for 3 days. The high exposure concentration (~1,000 times higher than current U.S. ambient PM levels) was selected to produce a frank but nonlethal injury. Exposure to ROFA produced alterations in the ECG waveform of SH but not the normotensive rats. Although the ST segment area of the ECG was depressed in the SH rats exposed to air, further depressions in the ST segment were observed at the end of the 6-h exposure to ROFA on days 1 and 2. The enhanced ST segment depression was not observed on the third day of exposure, suggesting that adaptation to the response may have occurred. Thus, exposure to a very high concentration of ROFA exacerbated an aberrant

variation in the electroconductivity pattern of the heart in an animal model of hypertension. However, this ROFA-induced alteration in the ECG waveform was not accompanied by an enhancement in the monocytic cell infiltration and cardiomyopathy that also develop in SH rats.

Contrary to findings from Godleski's dog study, Muggenburg et al. (2000b) reported that inhalation exposure to high concentrations of Boston area ROFA caused no consistent changes in amplitude of the ST-segment, form of the T wave, or arrhythmias in healthy dogs. In their studies, four beagle dogs were exposed to 3 mg/m^3 ROFA particles for 3 h/day for 3 consecutive days. They noted a slight but variable decrease in heart rate, but the changes were not statistically or biologically significant. The transition metal content of the ROFA used by Muggenburg was ~15% by mass, a value on the order of a magnitude higher than that found in current U.S. urban ambient PM samples. Although the study did not specifically address the effect of metals, it suggests that inhalation of high concentrations of metals may have little effect on the cardiovascular system of a healthy individual. In a second study using dogs with pre-existing cardiovascular disease, Muggenburg et al. (2003) evaluated the effects of short-term inhalation exposure (oral inhalation for 3 h on each of 3 successive days) to aerosols of transition metals. Heart rate and the ECG readings were studied in conscious beagle dogs (selected for having pre-existing cardiovascular disease) that inhaled respirable particles of oxide and sulfate forms of transition metals (Mn, Ni, V, Fe, Cu oxides, and Ni and V sulfates) at concentrations of 0.05 mg/m^3. Such concentrations are 2 to 4 orders of magnitude higher than for typical ambient U.S. levels (usually $\leq$ 0.1 to 1.0 µg/m^3 for such metals). No significant effects of exposure to the transition metal aerosols were observed. The discrepancy between the results of Muggenburg et al. and those of Godleski and colleagues leave open major questions about PM effects on the cardiovascular system of the dog.

Wellenius et al. (2002) developed and tested a model for investigating the effects of inhaled PM on arrhythmias and HRV in rats with acute MI. Left-ventricular MI was induced in Sprague-Dawley rats by thermocoagulation of the left coronary artery, whereas control rats underwent sham surgery. Diazepam-sedated rats were exposed (1 h) to ROFA (Boston area), carbon black (CB), or room air at 12 to 18 h after surgery. Each exposure, at 3 mg/m^3, was immediately preceded and followed by a 1-h exposure to room air (baseline and recovery periods, respectively). Lead-II electrocardiograms were recorded. In the MI group, 41% of rats exhibited one or more premature ventricular complexes (PVCs) during the baseline period.

Exposure to ROFA, but not to CB or room air, increased arrhythmia frequency in animals with preexisting PVCs. Furthermore, MI rats exposed to ROFA, but not to CB or room air, had decreased HRV, but there was no difference in arrhythmia frequency or HRV among sham-operated animals. The limited statistical significance (one MI rat mainly exhibited the reported changes) of the reported results call into question the biological relevance of the change observed in arrhythmia frequency in this myocardial infarction model exposed to ROFA at 3 mg/m^3.

Gardner et al. (2000) examined whether the instillation of particles would alter blood coagulability factors in laboratory animals. Sprague-Dawley rats were instilled with 0.3, 1.7, or 8.3 mg/kg of ROFA (Florida) or 8.3 mg/kg Mount Saint Helens volcanic ash. Because fibrinogen is a known risk factor for ischemic heart disease and stroke, the authors suggested that PM-induced alterations in the blood fibrinogen or other coagulation pathway components could take part in the triggering of cardiovascular events in susceptible individuals. Elevations in plasma fibrinogen, however, were observed in healthy rats only at the highest treatment dose (8.3 mg/kg); and no other changes in clotting function were noted. Because the lower treatment doses are known to cause pulmonary injury and inflammation, albeit to a lesser extent, the absence of plasma fibrinogen changes at the lower doses suggests that only high levels of pulmonary injury are likely to produce an effect in healthy test animals.

To establish the temporal relationship between pulmonary injury, increased plasma fibrinogen, and changes in peripheral lymphocytes, Kodavanti et al. (2002a) exposed SH and WKY rats to Boston ROFA using both inhalation and intratracheal instillation exposure (acute and long-term) scenarios. Increases in plasma fibrinogen and decreases in circulating white blood cells were found for both strains in response to acute ROFA exposure (15 mg/m^3; 6 h/day; 1 week) by inhalation and were temporally associated with acute (1 week post exposure), but not longer-term (2 to 4 week) lung injury. A bolus intratracheal instillation of ROFA at 5 mg/kg body weight increased plasma fibrinogen in both SH and WKY rats; whereas the increase was evident only in SH rats after acute (1 week) ROFA inhalation. The increased fibrinogen in SH rats was associated with greater pulmonary injury and inflammation than was found in the WKY rats. The authors concluded that acute PM exposure can provoke an acute thrombogenic response associated with pulmonary injury/inflammation and oxidative stress in cardiovascular-compromised rats.

Kodavanti et al. (2003) exposed male SD, WKY, and SH male rats to nose-only doses of oil combustion-derived ROFA from Boston, which contained bioavailable zinc (Zn) at doses of 2, 5, or 10 mg/m^3 for 6 h/day for 4 consecutive days. A second exposure paradigm used exposure to 10 mg/m^3 ROFA for 6 h/day, 1 day/week, for 4 or 16 consecutive weeks. Cardiovascular effects were not seen in SD and SH rats with the acute or chronic exposure, but WKY rats from the 16 week exposure group had cardiac lesions consisting of chronic-active inflammation, multifocal myocardial degeneration, fibrosis, and decreased numbers of granulated mast cells. These results suggest that myocardial injury in sensitive rats can be caused by long-term inhalation of high concentrations of ROFA.

Perhaps of more direct relevance to evaluation of ambient PM effects, the effects of diesel emissions (DE) on ECG and HR were evaluated in SH rats, both male and female, exposed to DE generated from a 2000 model diesel engine (Campen et al., 2003). Whole body exposures included dilutions at concentrations of 30, 100, 300, and 1000 μg/m^3 for an exposure period of 6 h/day, 7 days/week, for 1 week. Exposed rats showed a significantly elevated daytime HR (290 ± 7 versus 265 ± 5 for control male rats) throughout the exposure that was not concentration dependent. Additionally, a concentration-dependent prolongation of the PQ interval was observed in exposed rats. The authors suggested that these high level exposures to DE may affect the pacemaking system of rats by means of ventricular arrhythmias. However, the design of the study did not include testing of DPM (versus whole DE) so that one cannot clearly attribute the reported effects to DPM versus associated gases or a combination of both.

Suwa et al. (2002) studied the effect of PM_{10} on the progression of atherosclerosis in rabbits. They exposed Watanabe heritable hyperlipidemic rabbits (with naturally increased susceptibility to atherosclerosis) to 5 mg PM_{10} in 1 mL saline administered by intrapharyngeal instillation (2 times per week for 4 weeks) or to saline vehicle for 4 weeks, and then both (a) measured bone marrow stimulation and (b) used quantitative histologic methods to determine the morphologic features of the atherosclerotic lesions. Exposure to PM_{10} (99% < 3.0 μm) from Ottawa, CN air caused an increase in circulating polymorphonuclear leukocytes (PMN) band cell counts and an increase in the size of the bone marrow mitotic pool of PMNs. Exposure to PM_{10} also caused progression of atherosclerotic lesions toward a more advanced phenotype. The volume fraction (vol/vol) of the coronary atherosclerotic lesions was increased by PM_{10} exposure. The vol/vol of atherosclerotic lesions correlated with the number of alveolar

macrophages that phagocytosed PM_{10}. Exposure to PM_{10} also caused an increase in plaque cell turnover and extracellular lipid pools in coronary and aortic lesions, as well as in the total amount of lipids in aortic lesions.

Terashima et al. (1997) also examined the effect of particles on circulating neutrophils. They instilled rabbits with 20 mg colloidal carbon, a relatively inert particle (< 1 μm), and observed a stimulation of the release of 5'-bromo-2'deoxyuridine (BrdU)-labeled PMNs from the bone marrow at 2 to 3 days after instillation. Because the instilled supernatant from rabbit AMs treated in vitro with colloidal carbon also stimulated the release of PMNs from the bone marrow, the authors hypothesized that cytokines released from activated macrophages may be responsible for this systemic effect. However, this group (Terashima et al., 2001) has determined that the BAL procedure itself has the effect of producing an increase in peripheral blood neutrophils, IL-6, and G-CSF. Bronchoscopy alone does not induce this acute phase response and bone marrow stimulation. The same research group (Tan et al., 2000) looked for increased white blood cell counts as a marker for bone marrow PMN precursor release in humans exposed to very high levels of carbon from biomass burning during the 1997 Southeast Asian smoke-haze episodes. They found a significant association between PM_{10} (1-day lag) and elevated band neutrophil counts expressed as a percentage of total PMNs. The biological relevance of this latter study to more usual urban PM exposure-induced systemic effects is unclear, however, because of the high dose of carbon particles.

Frampton (2001) exposed healthy, nonsmoking subjects (18 to 55 years old) to 10 $\mu g/m^3$ ultrafine carbon while at rest via a mouthpiece for 2 h ½ , with a 10-min break between each hour of exposure. The exposure concentration (10 $\mu g/m^3$) corresponded to 2×10^6 particles/cm^3; and respiratory symptoms, spirometry, blood pressure, pulse-oximetry, blood markers, and exhaled NO were evaluated before, immediately following, and 3.5 and 21 h postexposure. Blood markers focused on parameters related to acute response, i.e., blood coagulation, circulating leukocyte activation (including complete blood leukocyte counts and differentials), IL-6, fibrinogen, and clotting factor VII. Heart rate variability and repolarization phenomena were evaluated by continuous 24-h ECG Holter monitoring. Preliminary findings indicated no particle-related effects, neither for cardiovascular nor respiratory-related endpoints.

Nemmar et al. (2002) studied effects of ultrafine (60 nm) polystyrene particles on thrombus formation in a hamster model after intravenous (IV) administration of unmodified,

carboxylate-polystyrene, or amine-polystyrene particles, which carry a negative or positive charge, respectively. Unmodified particles did not affect thrombosis at IV doses up to 5000 μg/kg; whereas carboxylate-polystyrene particles significantly inhibited thrombus formation at 100 and 500 μg/kg, but not at 50 μg/kg body weight. Thrombosis was significantly enhanced by amine-polystyrene particles at 50 and 500 μg/kg, but not at 5 μg/kg body weight. Intratracheal instillation of 5 mg/kg of amine-polystyrene particles, but not unmodified or carboxylate-modified particles, also increased thrombosis formation. Platelet aggregation (ADP-induced in vitro) was also enhanced significantly by amine-modified polystyrene particles, but not by unmodified or carboxylate-modified particles. Thus, only positively charged ultrafine particles resulted in enhancement of thrombus formation. The authors concluded that (a) the presence of ultrafine particles in the circulation may affect hemostasis and (b) this is dependent on the surface charge of the particles, i.e., positive-charged particles induce prothrombotic effects, at least partly via platelet activation.

7.2.4 Summary of Cardiovascular/Systemic Effects

In summary, experimental controlled exposure studies of cardiovascular-related effects in healthy humans have yielded only very limited evidence for ambient PM effects on cardiac function as indexed by ECG readings or on systemic endpoints (e.g., vasopressor control, blood coagulation control, etc.) linked to more serious cardiovascular events. Probably of most note, the controlled human exposure CAPs study by Ghio et al. (2000a) and another by Petrovic et al. (2000) did find evidence indicating that ambient levels (ranging up to ~125 to 300 $\mu g/m^3$) of inhaled $PM_{2.5}$ can produce some biochemical changes (increased fibrinogen) in blood suggestive of PM-related increased risk for prothrombotic effects. Similarly, Ulrich et al. (2002) found a 20% increase in plasma fibrinogen in rats 2 days after instillation exposure to 6.7 or 22.2 mg/kg of Ottawa EHC93 ambient PM extract. Also, decreased Factor VII levels were observed by Gong et al. (2003) in humans (with 2-h CAPs exposure at ~174 $\mu g/m^3$). The decreased Factor VII levels may be due to that enzyme being consumed in an ongoing coagulation process. On the other hand, the same and many other human and animal studies did not find changes in other factors (e.g., increased platelets or their aggregation) related to blood coagulation control. Overall, then, some available laboratory studies provide limited evidence suggesting that high concentrations/doses of inhaled or instilled particles can exert cardiovascular-related systemic

effects; but many of the studies provide conflicting evidence, especially with regard to heart rate, HRV, or other ECG markers of cardiac function. Thus, although some of the reported changes have been used as clinical "markers" for cardiovascular diseases, the causal relationship between such PM-related changes and potential life-threatening alterations in cardiovascular function remains to be better established.

Among the most salient hypotheses proposed to account for cardiovascular/systemic effects of PM are: alterations in coagulability (Seaton et al., 1995; Sjögren, 1997); cytokine effects on heart tissue (Killingsworth et al., 1997); perturbations in both conductive and hypoxemic arrythmogenic mechanisms (Watkinson et al., 1998; Campen et al., 2000); altered endothelin levels (Vincent et al., 2001); and activation of neural reflexes (Veronesi and Oortgiesen, 2001). Only limited progress has been made in obtaining evidence bearing on such hypotheses (as discussed in later sections of this chapter), and much future research using controlled exposures to PM of laboratory animals and human subjects will clearly be needed to test further such mechanistic hypotheses (as well as others proposed in the future) so as to more fully understand pathways by which low concentrations of inhaled ambient PM may be able to produce life-threatening systemic changes.

7.3 RESPIRATORY EFFECTS OF CONTROLLED IN VIVO PM EXPOSURES OF HUMANS AND LABORATORY ANIMALS

This section assesses the respiratory effects of controlled in vivo exposures of laboratory animals and humans to various types of PM. In vitro studies using animal or human respiratory tract cells are discussed in Section 7.4. Biological responses occurring in the respiratory tract following controlled PM inhalation include changes in pulmonary inflammation and systemic effects that result from direct effects on lung tissue. The observed responses are dependent on the physicochemical characteristics of the PM, exposure parameters (concentration, duration, etc.), and health status of the host.

As noted earlier, data available in the 1996 PM AQCD were derived from studies that evaluated respiratory effects of specific components of ambient PM or laboratory-generated surrogate particles, e.g., metals or pure sulfuric acid droplets. Toxicological studies of various "other" types of PM species were also discussed in the 1996 PM AQCD (U.S. Environmental

Protection Agency, 1996a). These studies included exposures to fly ash, volcanic ash, coal dust, carbon black, and miscellaneous other particles, either alone or in mixtures. Some of the particles discussed were considered to be models of "respirable low toxicity particles" and were used in instillation studies to delineate nonspecific particle effects from effects of known toxicants.

A number of studies on "other PM" examined effects of up to 50,000 $\mu g/m^3$ (50 mg/m^3) of respirable particles with inherently low toxicity. Although there was no mortality, some mild pulmonary function changes after exposure ranging from 1 h to 24 months to 5,000 to 10,000 $\mu g/m^3$ (5 to 10 mg/m^3) of relatively inert particles were observed in rats and guinea pigs. Lung morphology studies revealed focal inflammatory responses, some epithelial hyperplasia, and fibrotic responses after chronic exposure (6 to 7 h/day 5 day/week for 20 to 24 months) of rats to $\geq$ 5,000 $\mu g/m^3$ of coal dust. Changes in macrophage clearance after exposure to > 10,000 $\mu g/m^3$ to a variety of particles over various exposure periods (days to months) were equivocal (no host defense effects). In studies of mixtures of particles and other pollutants, observed effects varied, depending on the toxicity of the associated pollutant. For example, in humans, co-exposure to carbon particles appeared to increase responses to formaldehyde but not to acid aerosol. None of the "other" particles mentioned above are present in ambient air in more than trace quantities.

Thus, it was concluded that the relevance of any of these studies to standard setting for ambient PM may be extremely limited. Newer studies, on the other hand, do provide evidence of likely greater relevance to understanding respiratory effects of ambient PM exposure and underlying mechanisms, as discussed below.

7.3.1 Ambient Particulate Matter

Some new in vivo toxicology studies have employed inhalation exposures to evaluate the respiratory effects of ambient particles in humans and laboratory animals, using either CAPs or resuspended urban ambient PM from various U.S. and Canadian locations. Other new in vivo exposure studies have mainly used intratracheal instillation techniques. The pros and cons of the latter in comparison to inhalation are discussed in Chapter 6 (Section 6.5) and have also been reviewed elsewhere (Driscoll et al., 2000; Oberdörster et al., 1997; Osier and Oberdörster, 1997). In most of the instillation studies, ambient PM samples were first collected on filters; then after

various storage times, PM materials were extracted from the filters and resuspended in a vehicle (usually saline), followed by a small volume of the suspension medium then being instilled intratracheally into the animals. It is important to note that physiochemical characteristics of the collected PM may be altered by deposition and storage on a filter and resuspension in an aqueous medium. Therefore, in terms of use in attempting to extrapolate experimentally observed results to humans exposed under ambient exposure scenarios, greater importance should be placed on inhalation study results. Instillation studies have been most valuable in comparing effects of different types of PM and/or for investigating potential mechanisms by which particles may cause inflammation and lung injury.

7.3.1.1 Ambient Particle Inhalation Exposures

Table 7-4 summarizes newly available studies in which various biological endpoints were measured following inhalation exposures to CAPs or, in the case of one study, resuspended urban ambient particles.

With regard to newly available experimental studies that most directly parallel aspects of ambient PM inhalation exposures, Ghio et al. (2000a) exposed 38 nonsmoking healthy adult volunteers (aged 18 to 40 years) exercising intermittently at moderate levels of exertion (breathing rate = 25 L/min) for 2 h to either filtered air or $PM_{2.5}$ concentrated 6- to 10-fold from Chapel Hill, NC air at the inlet of the exposure chamber. Neither respiratory symptoms nor decrements in pulmonary function (RAW, FVC, $FEV_{1.0}$, PEF measurements) were found immediately after exposure to CAPs. However, analysis of bronchoalveolar lavage (BAL) cells and fluid obtained 18 h after Chapel Hill CAPs exposure (at 23 to 311 $\mu g/m^2$) showed a mild increase in neutrophils in the bronchial and alveolar fractions of BAL in subjects exposed to the highest quartile concentration of concentrated PM (mean of 206.7 $\mu g/m^3$). Lavage protein did not increase, and there were no other indicators of pulmonary injury. The 38 human volunteers reported on by Ghio et al. (2000a) were also examined for changes in host defense and immune parameters in BAL and blood (Harder et al., 2001). There were no changes in the number of lymphocytes or macrophages, subcategories of lymphocytes (according to surface marker analysis by flow cytometry), cytokines IL-6 and IL-8, or macrophage phagocytosis. Similarly, there was no effect of CAPs exposure on lymphocyte subsets in blood. Thus, a mild inflammatory response to Chapel Hill CAPs was not accompanied by any evident effect on

TABLE 7-4. RESPIRATORY EFFECTS OF INHALED AMBIENT PARTICULATE MATTER IN CONTROLLED EXPOSURE STUDIES OF HUMAN SUBJECTS AND LABORATORY ANIMALS

Species, Gender, Strain, Age, etc.	Particle	Exposure Technique	Exposure Concentration*	Particle Size	Exposure Duration; Time to PE[b] Analysis	Particle Effects/Comments	Reference
Humans, healthy nonsmokers; 18 to 40 years old n = 38	CAPs (Chapel Hill)	Inhalation	23.1 to 311.1 µg/m^3	0.65 µm σ_g = 2.35	2 h; analysis at 18 h	Dose-dependent increase in BAL neutrophils in both bronchial and alveolar fractions. Increase noted at all exposure levels. Particles were concentrated 6- to 10-fold at the inlet of the chamber.	Ghio et al. (2000a)
Humans, healthy 18-40 years old n = 4	CAPs (Toronto)	Inhalation (face mask)	24 to 124 µg/m^3	0.1 - 2.5 µm	2 h; analyses pre- & during exposure and about 2 to 24 h postexposure	Only stat. sig. effect on pulmonary function was mean increase of 6.4% in thoracic gas volume after high CAP exposure versus mean 5.6% after filtered air exposure, but not in respiratory symptoms. Trend towards increased nasal neutrophils, but no respiratory inflammatory response.	Petrovic et al. (2000)
Humans, healthy; 19-41 years old n = 4	CAPs (Los Angeles)	Inhalation	148 to 246 µg/m^3	$PM_{2.5}$	2 h	No significant changes in lung function, symptoms, S_aO_2,** or Holter ECGs observed. The maximum steady state fine particle concentration in the breathing zone was typically seven times the ambient concentration.	Gong et al. (2000)
Humans healthy (12) and asthmatic (12) 18-45 years old, nonsmoking	CAPs (Los Angeles)	Inhalation whole body chamber	99-224 µg/m^3 (mean 174)	80% 0.1 to 2.5 µm	2 h with alternating exercise/rest. Analysis at 0, 4, and 22 h PE	CAPs-related decrease in columnar cells in induced sputum at 0 h PE. No significant changes in S_aO_2, FVC, or FEV_1.	Gong et al. (2003)
Mongrel dogs, some with balloon occluded LAD coronary artery n = 14	CAPs (Boston)	Inhalation via tracheostomy	~100-1000 µg/m^3 (variable from day-to-day)	0.23 to 0.34 µm σ_g = up to 2.9	6 h/day × 3 days	Decreased respiratory rate over time and modest increase in lavage fluid neutrophils in normal dogs. Study utilized Harvard ambient particle concentrator. Ambient particles concentrated by approximately 30-fold.	Godleski et al. (2000)
Rats, male S-D 200-225 g, healthy-air, bronchitic-air, healthy-CAPs, bronchitic-CAPs n = 48 (12 per group)	CAPs (Boston)	Inhalation; Harvard/EPA fine particle concentrator; animals restrained in chamber	206, 733, and 607 µg/m^3 for Days 1-3, respectively; 29 °C, 59% RH	0.18 µm σ_g = 2.9	5 h/day for 3 days	Bronchitis induced by pre-treatment with 170 ppm SO_2 for 6 weeks at 5 h/day, 5 days/week. The CAPs-exposed rats had significant increase in TV, increased protein and percent neutrophils and lymphocytes in lavage fluid after CAPs exposure. Responses were greater in bronchitic than healthy rats. Bronchitic CAPs-exposed rats showed evidence of inflammation-related epithelial permeability.	Clarke et al. (1999)

TABLE 7-4 (cont'd). RESPIRATORY EFFECTS OF INHALED AMBIENT PARTICULATE MATTER IN CONTROLLED EXPOSURE STUDIES OF HUMAN SUBJECTS AND LABORATORY ANIMALS

Species, Gender, Strain, Age, etc.	Particle	Exposure Technique	Exposure Concentration*	Particle Size	Exposure Duration; Time to PE[b] Analysis	Particle Effects/Comments	Reference
Rats, male S-D 200-250 g, healthy-air, bronchitic-air, healthy-CAPs, bronchitic-CAPs n = 259 (6 studies, 40-48 per study, 8-10 per group)	CAPs (Boston)	Inhalation; Harvard/EPA fine particle concentrator; animals restrained in chamber	3-day mean CAPs ranged from 187 to 481 µg/m^3 29 °C, 47% RH	0.27 µm σ_g = 2.3	5 h/day for 3 days	Bronchitis induced by pre-treatment with an average of 276 ppm, SO_2 for 5 weeks at 5 h/day, 5 days/week. Increase in neutrophils in both healthy and bronchitic rats associated with CAPs exposure concentration. Specific CAPs components associated with neutrophil increase. In bronchitic rats, CAPs components also associated with lymphocyte increase. Histologic examination suggested bronchial-alveolar junction as the site of greatest inflammation response.	Saldiva et al. (2002)
Rats, male, 90- to 100-day-old S-D, with or without SO_2-induced bronchitis	CAPs (RTP)	Inhalation	650 µg/m^3		6 h/day × 2-3 days	No significant changes in healthy rats. Increased BAL protein and neutrophil influx in bronchitic rats sacrificed immediately afer last CAPs exposure; responses variable between exposure regimens. No CAPs effects seen at 18 h postexposure.	Kodavanti et al. (2000b)
Rats, male F344 Hamsters, male, 8-month-old Bi TO-2	CAPs (NYC)	Inhalation	132 to 919 µg/m^3	0.2 to 1.2 µm σ_g = up to 3.9	1 × 3 h or 3 × 6 h	No inflammatory responses, no cell damage responses, no PFT changes. The PM mean concentration factor (gravimetric) was 19.5 ± 18.6.	Gordon et al. (2000)
Rats, male F344 7-8 months	CAPs (NYC)	Inhalation	100 to 350 µg/m^3 (mean 225 µg/m^3)	0.4 µm σ_g = 2.5	3 h	Basal levels of superoxide ($\bullet O_2^-$) reduced by 90% 72 h postexposure; zymosan-stimulated O_2^- formation increased by > 150% after 24 h; basal level H_2O_2 production by PAM depressed 90% 3 h following exposure and remained 60% below levels at least 24 h; zymosan-stimulated H_2O_2 unaffected. Concentrations tested represents a range over the 3 h exposure period.	Zelikoff et al. (2003)
Rats, male, F-344; 200-250 g	Ottawa ambient	Nose-only Inhalation	40 mg/m^3	4 to 5 µm MMAD	4 h	No acute lung injury; however, lung NO production decreased and macrophage inflammatory protein-2 from lung lavage cells increased after exposure. Increased plasma levels of endothelin-1.	Bouthillier et al. (1998)

*Concentration = range of CAP concentrations at inlet of exposure chamber or in breathing zone of exposed subjects.

**S_aO_2 = arterial oxygen saturation.

[b] PE = Post Exposure

immune defenses, as determined by lymphocyte or macrophage effects. The increase in BAL neutrophils may represent a normal physiological response of the lung to particles, although the presence of activated neutrophils may release biochemical mediators which produce lung injury. Whether this mild inflammatory increase in neutrophils, per se, constitutes a biologically significant injury to the lung is an ongoing controversial issue.

In the small study by Petrovic et al. (2000) described earlier (Section 7.2.2), the four healthy volunteer subjects (aged 18 to 40 years) exposed for 2 h to CAPs (23-124 $\mu g/m^3$ from downtown Toronto were not only evaluated for CAP effects on cardiovascular endpoints, but also several respiratory endpoints (nasal lavage, nasal acoustic rhinometry, pulmonary function). No cellular signs of inflammation were observed in induced sputum samples collected at 2 or 24 h after exposure. The authors said there was a trend toward an increase in nasal lavage neutrophils (but level of statistical significance was not specified). The only statistically significant ($p < 0.01$) change in pulmonary function was a 6.4% decrease in thoracic gas volume after high CAPs exposure to 124 $\mu g/m^3$ PM versus a 5.6% increase after filtered air exposure, but no increase was seen in respiratory symptoms. These results, overall, suggest that acute exposures (~2 h) to Toronto ambient PM are unlikely to exert untoward respiratory effects in healthy adults at $PM_{2.5}$ levels below about 100 $\mu g/m^3$, but may begin to have some mild effects on pulmonary function as $PM_{2.5}$ levels reach or exceed 125 $\mu g/m^3$. However, further evaluations of these possibilities with larger numbers of healthy subjects are needed, as well as analogous studies of compromised human subjects.

As also discussed earlier in Section 7.2.2, Gong et al. (2000) conducted a small pilot study (n = 4 subjects, aged 19 to 41 years) in which healthy adult volunteers were exposed to Los Angeles CAPs (148 to 246 $\mu g/m^3$) for 2 h and evaluated during or immediately after exposure for possible respiratory effects or ECG changes. No significant effects were observed for various lung function measures, respiratory symptoms, oxygen saturation, or in Holter ECG readings, even at $PM_{2.5}$ concentrations (~246 $\mu g/m^3$) approximating likely maximum levels for Los Angeles.

As also noted earlier, the effects of Los Angeles ambient air were studied further by Gong et al. (2003), who exposed 12 healthy and 12 asthmatic subjects (age 18 to 45 years) to Los Angeles CAPS ($PM_{2.5}$). Exposures averaging 174 $\mu g/m^3$ (range 99-224) CAPs in a whole body chamber for 2 h were alternated with filtered air exposure at least 14 days apart. Subjects

exercised for 15 min of each half hour at a ventilation rate of 15 to 20 L/min/m^2 body surface. Tests were performed just before exposure, just after, 3.5 to 4 h after (4 h), and the next day. Ventilation during CAPs exposure was significantly lower in both the healthy and asthmatic groups, and both groups showed a CAPs-related decrease in columnar cells in induced sputum immediately postexposure, but the authors were uncertain as to the health significance of this effect. No significant differences in S_aO_2, FVC, FEV_1, or other respiratory parameters were seen.

Godleski, et al. (2000), in another study noted previously (Section 7.2.2), exposed mongrel dogs to Boston CAPs (ranging from ~100 to 1000 μg/m^3) for 6 h/day for 3 days. The only two respiratory effects reported were a decreased respiratory rate over time and a modest increase in neutrophils in lavage fluid from the lungs of the normal dogs, even with exposures to ambient Boston particles concentrated by 30-fold over ambient levels.

Saldiva et al. (2002) studied the effects of CAPs from Boston on rat lung. The study was designed to: (1) determine whether short-term exposures to CAPs cause pulmonary inflammation in normal rats and in compromised rats with chronic bronchitis (CB); (2) identify the site within the lung parenchyma where CAPs-induced inflammation occurs; and (3) characterize the component(s) of CAPs significantly associated with development of the inflammatory reaction. Chronic bronchitis was induced by exposure to high doses of SO_2 for 5 h/day, 5 days/week during 5 weeks prior to experimental exposures to filtered air or to the Boston CAPs. Thus, four groups of animals were studied: (1) air pre-treated, filtered air-exposed (air-sham); (2) sulfur dioxide pre-treated (CB), filtered air-exposed (CB-sham); (3) air pre-treated, CAPs-exposed (air-CAPs); and (4) SO_2 pre-treated, CAPs-exposed (CB-CAPs). Normal and CB rats were exposed by inhalation either to filtered air or to CAPs during 3 consecutive days (5 h/day). The Boston CAPs concentrations varied considerably (73.5 to 733 μg/m^3), with 3-day mean CAPs mass = 126 to 481 μg/m^3. The average MMAD of the CAPs particles was 0.27 μm (σ_g = 2.3). CAPs mass (as a binary exposure term) and CAPs mass (in regression correlations) induced a significant increase in BAL neutrophils and in both normal and CB animals. Numerical density of neutrophils in alveolar walls significantly increased with CAPs in normal animals only, with greater neutrophils seen in central, compared to peripheral, regions of the lung. Significant dose-dependent associations were observed between various CAPs components and BAL neutrophils or lymphocytes; however, only vanadium and bromine

concentrations were significantly associated with both BAL neutrophils and neutrophils in CAPs-exposed groups analyzed together. The authors concluded that (a) short-term exposures to CAPs from Boston induce a significant inflammatory reaction in rat lungs and (b) the reaction is influenced by particle composition.

In another study of Boston CAPs, Clarke et al. (1999) exposed healthy normal rats and (SO_2-induced) bronchitic rats by inhalation via tracheostomy for 5 h/day for 3 days to filtered air or concentrated Boston ambient $PM_{2.5}$ particles averaging 206, 773, and 607 $\mu g/m^3$ on the three different days. Significantly increased tidal volume (TV) was observed with CAPs exposures for both the normal rats and, even greater, for the chronic bronchitic rats. Bronchiolar lavage performed 24-h after the final day of exposure revealed evidence for significant pulmonary inflammation following CAPs exposures, especially in chronic bronchitic rats, as indexed by significant increases in neutrophils, lymphocytes, and total lavage protein. The authors concluded that these results suggested two distinct mechanistic responses to inhaled particles: (1) a stressor-type pulmonary function reaction (typified by increases in air flow and volume) and (2) acute pulmonary inflammation characterized by cellular influx (especially neutrophils).

Zelikoff et al. (2003) reported effects on pulmonary or systemic immune defense mechanisms in Fischer rats exposed by inhalation to filtered air or to New York City CAPs (90 to 600 $\mu g/m^3$; mean = 345 $\mu g/m^3$) for 3 h prior to the IT instillation of *Streptococcus pneumoniae* ($2 - 4 \times 10^7$ organisms delivered dose). The number of lavageable cells (AM and PMN) increased in both control and experimental groups, but were elevated faster and were twice as high in the CAPs-exposed group, as well as staying elevated longer. Lymphocyte values and white blood cell (WBC) counts were significantly increased 24 and 72 h postinfection in both groups. CAPs exposure resulted in a decline in TNF-α and IL-6 levels three days postinfection compared to bacteria-only exposed rats; but the differences were not significant. The New York City CAPs exposure significantly increased bacterial burdens at 24 h after infection. Thereafter, CAPs-exposed animals exhibited significantly lower bacterial burdens. In another study, Zelikoff et al. (2003) also evaluated the effects of New York City CAPs exposure (65 to 150 $\mu g/m^3$; mean = 107 $\mu g/m^3$) in rats following a single 5 h exposure to IT instilled *Streptococcus pneumoniae*. The CAPs exposure significantly reduced percentages of lavageable PMN 24 h following CAPs exposure and remained well below control levels for up to 3 days, but lavageable AM was significantly increased in the CAPs-exposed animals. CAPs

exposure also reduced the levels of TNF-α, IL-1, and IL-6. The bacterial burden decreased in both exposed groups over time; however, CAPs exposed animals had a significantly greater burden after 24 h than did control rats. Lymphocyte and monocyte levels were unaffected by the CAPs exposures.

Bouthillier et al. (1998) reported that a 4-h exposure of rats by nose-only inhalation to 40 mg/m^3 of resuspended Ottawa ambient PM (MMAD = 4 to 5 μm) produced no evident acute lung injury. However, lung NO production decreased and macrophage inflammatory protein-2 from lung lavage cells increased at 4 h after exposure, as did plasma levels of endothelin-1 (a powerful cardiac cytotoxic agent). The lack of acute lung injury demonstrated may be due, in part, to only 60% of the PM being inhalable (see Figure 7A-4) and too much of the PM being trapped in the nose.

7.3.1.2 Intratracheal and Intrabronchial Instillation of Ambient Particulate Matter

Other newly-available studies (Table 7-5) that evaluated acute effects of intratracheal or intrabronchial instillation of ambient PM extracts from filters obtained from various locations have found evidence indicating that exposures to such ambient PM materials can cause lung inflammation and injury.

Costa and Dreher (1997) showed that instillation in rats of relatively high doses of PM samples from four ambient airsheds (St. Louis, MO; Washington, DC; Dusseldorf, Germany; and Ottawa, Canada) and from three combustion sources (two oil and one coal fly ash) resulted in acute inflammatory responses, as indexed by increases in lung PMNs and eosinophils 24 h after instillation. Biomarkers of permeability (total protein and albumin) and cellular injury, lactic dehydrogenase (LDH), were also increased. Animals were dosed with (1) an equal dose by mass (nominal 2.5 mg/rat) of each PM mixture or with (2) doses based on normalization of each PM mass to a metal content of 46 μg/dose and 35.5 μg of total metals (Cu, Fe, V, Zn) for the ambient PM and ROFA comparison. The relative potencies of the combustion-source particles in producing the acute inflammatory effects ranked in the order: DOFA > ROFA >> CFA = saline vehicle, reflecting closely the much higher amounts of bioavailable metals in the oil fly ash than in the coal-derived fly ash. Analogously, the ambient PM extracts exhibited, on a per mass basis, much less potency in inducing inflammatory responses than the oil fly ash extracts (e.g., ROFA), with the Ottawa extract exerting notably stronger effects than ambient

TABLE 7-5. RESPIRATORY EFFECTS OF INSTILLED AMBIENT PARTICULATE MATTER IN LABORATORY ANIMALS AND HUMAN SUBJECTS[a]

Species, Gender, Strain, Age, etc.	Particle	Exposure Technique	Concentration	Particle Size	Exposure Duration; Time to PE[b] Analysis	Particle Effects/Comments	Reference
Humans, healthy nonsmokers; 21 M, 3 F; 26.4 ± 2.2 years old	Provo, UT PM_{10} filters (10 ys old)	Intrabronchial instillation	500 µg of PM extract in 10 mL saline	N/A	24 h BAL	Inflammation (PMN) and pulmonary injury produced by particles collected during steel mill operation was greater than during period of mill closure.	Ghio and Devlin (2001)
Rats, male S-D 60 days old	Provo, UT TSP filters (10 ys old)	Intratracheal instillation	0.25, 1.0, 2.5, 5.0 mg of PM extract in 0.3 mL saline	N/A	24 h	Dose-dependent increase in inflammation (PMN) and pulmonary injury produced by particles collected during steel mill operation was greater than for during period of mill closure for all exposed groups.	Dye et al. (2001)
Rats, S-D 60 days old n = 8/fraction	Provo, UT TSP filters (10 ys old), soluble and insoluble extracts	Intratracheal instillation	100, 150, 500, and 1000 µg of PM extract in 0.5 mL saline	N/A	24 h	Dose-dependent increase in inflammation (PMN) and lavage fluid protein. Effect was greater with the soluble fraction containing more metal (Zn, Fe, Cu) except for the 100 µg exposed group.	Ghio et al. (1999a)
Rats, male, S-D 60 days old	Provo, UT TSP. Collected 1982.	Intratracheal Instillation	100, 500, 1500 µg PM in 0.5 mL saline	N/A	24 h BAL	Increased BAL protein and PMN at ≥ 500 µg dose. Also proliferation of bronchiolar epithelium and intraalveolar hemorrhage at 500 µg dose.	Kennedy et al. (1998)
Rats, Wistar (HAN strain)	Edinburgh PM_{10} filters Carbon black (CB) Ultrafine CB	Intratracheal instillation	Range of 50 to 125 µg in 0.2 mL phosphate buffered saline	PM_{10} CB = (200-500 nm) UCB = 20 nm	Sacrificed at 6 h	Increased PMN, protein, and LDH following 50-125 µg PM_{10}; greater response with ultrafine CB but not CB; decreased GSH level in BAL; free radical activity (deplete supercoil DNA); leukocytes from treated animals produced greater NO and TNF.	Li et al. (1996, 1997)
Hamsters, Syrian golden, male, 90-125 g	Kuwaiti oil fire particles; urban particles from St. Louis, MO	Intratracheal instillation	0.15, 0.75, and 3.75 mg/100 g	Oil fire particles: < 3.5 µm, 10 days of 24-h samples	Sacrificed 1 and 7 days postinstillation	Dose-dependent increases in PMN, albumin, LDH, and β-N-acetylglucosaminidase and myeloperoxidase, decrease in AM. Acute toxicity of the particles found in smoke from Kuwaiti oil fires roughly similar to that of urban particles.	Brain et al. (1998)

[a] LDH = lactate dehydrogenase
PMN = polymorphonuclear leukocytes

[b] PE = Post Exposure

PM extracts from the other cities. However, when the exposures were normalized to match metal content, there was little difference between the ambient PM and ROFA effects. Interestingly, the most potent ambient PM (Ottawa) both was the freshest one collected (3 years versus 10 years old) and had the highest bioavailable metal content of the ambient PM. Thus, this study demonstrated, overall, that the lung dose of bioavailable transition metals, not just instilled PM mass, was the primary determinant of the acute inflammatory response.

Kennedy et al. (1998) reported a similar dose-dependent inflammation (i.e., increase in protein and PMN in lavage fluid, proliferation of bronchiolar epithelium, and intraalveolar hemorrhage) in rats instilled with water-extracted particles in TSP samples collected from Provo, UT in 1982. The particulate extract mixture was comprised of 1.0 mg/g Zn, 0.04 mg/g Ni, 2.2 mg/g Fe, 0.01 mg/g V, 1.4 mg/g Cu, 1.7 mg/g Pb, and 78 mg/g SO_4^{2+} in 500 mL saline solution. Doses of 0, 150, 500, and 1500 μg were instilled; and effects were seen at ≥ 500 μg. This study also indicated that the metal constituent, in this case PM-associated Cu, was a plausible cause of the outcome based on IL-8 secretion and enhanced activation of the transcription factor NF-kB in cultured epithelium.

Toxicological studies of ambient PM collected from around Provo, UT (Utah Valley) in the late 1980s are also particularly interesting (Ghio and Devlin, 2001; Dye et al., 2001). Earlier epidemiologic studies by Pope (1989, 1991) showed that exposures to PM_{10} during closure of an open-hearth steel mill over a 13-mo period beginning in 1987 were associated with reductions in several health endpoints, e.g., hospital admissions for respiratory diseases, as discussed in the 1996 PM AQCD. Ambient PM was collected near the steel mill during the winter of 1986 (before closure), throughout 1987 (during closure), and again in 1988 (after plant reopening). The fibrous glass hi-vol filters were stored, folded PM-side inward, in plastic sleeves at room temperature and humidity (Dye et al., 2001). A description of the in vivo toxicological studies follows; pertinent in vitro studies (e.g., Wu et al., 2001; Soukup et al., 2000; Frampton et al., 1999) are discussed in Section 7.4.2.1.

Ghio and Devlin (2001) investigated biologic effects of PM from the Utah Valley to determine if the biological responses mirrored the epidemiologic findings, with greater injury occurring after exposure to an equal mass of particles from those years when the mill was in operation. Aqueous extracts of the filters collected prior to temporary closure of the steel mill, during the closure, and after its reopening were instilled (500 μg of extract in 10 mL of sterile

saline) through a bronchoscope into the lungs of nonsmoking human volunteers. Twenty-four hours later, the same subsegment was lavaged. Exposure to aqueous extracts of PM collected before closure and after reopening of the steel mill provoked a greater inflammatory response than PM extracts from filters taken during the plant shutdown. These results are suggestive of pulmonary effects of experimental exposure of humans to Utah Valley PM that parallel health outcomes observed in epidemiologic studies of the human population exposed under ambient conditions.

Dye et al. (2001) also examined effects of Utah Valley ambient PM on respiratory health in laboratory animals. Sprague-Dawley rats were intratracheally instilled with equivalent masses of aqueous extracts (0, 0.83, 3.3, 8.3, or 16 mg extract/kg body weight in 0.3 mL saline) from filters originally collected during the winter before, during, and after closure of the steel mill. Twenty-four hours after instillation, rats exposed to extracts of particles collected when the plant was open developed significant pulmonary injury and neutrophilic inflammation. Additionally, 50% of rats exposed to these extracts had increased airway responsiveness to acetylcholine, compared to 17 and 25% of rats exposed to saline or the extracts of particles collected when the plant was closed. By 96 h, these effects were largely resolved, except for increases in lung lavage fluid neutrophils and lymphocytes in rats exposed to PM extracts from prior to the plant closing. Analogous effects were observed with lung histologic assessment. Chemical analysis of extract solutions demonstrated that nearly 70% of the mass in all three extracts appeared to be sodium-based salts derived from the glass filter matrix (Ca^{2+}). However, extracts of particles collected when the plant was open contained more sulfate, cationic salts (e.g., Ca, K, Mg), and certain metals (e.g., Cu, Zn, Fe, Pb, As, Mn, Ni). Although total metal content was $\leq$ 1% of the extracts by mass, the greater quantity detected in the extracts of particles collected when the plant was open suggested that metals may be among the important determinants of the observed pulmonary toxicity. The authors concluded that the pulmonary effects induced in rats by exposure to aqueous extracts of local ambient PM filters were in good accord with the epidemiologic reports of adverse respiratory health effects in Utah Valley residents and with results from the Molinelli et al. (2002) in vitro study of Utah Valley PM filter extract effects on human epithelial cells (discussed later in Section 7.4). As with use of other ambient PM, the use in the Utah Valley studies of dust collected more than 10 years earlier introduces uncertainties associated with the age and handling of the filters.

Also of interest are some other new instillation study results. For example, Li et al. (1996, 1997) reported that instillation of ambient PM_{10} (50-125 μg in 0.2 mL buffered saline) collected in Edinburgh, Scotland, also caused pulmonary injury and inflammation in rats. In addition, Brain et al. (1998) examined the effects of instillation of particles (< 3.5 μm) that resulted from the Kuwaiti oil fires in 1991 compared to effects of urban PM collected in St. Louis (NIST SRM 1648, collected in a bag house in the early 1980s). Brain et al. (1998) showed that, on an equal mass basis, the acute toxicity of the Kuwaiti oil fire particles was similar to that of urban particles collected in the United States. At all exposure levels (0.15, 0.75, and 3.75 mg/100 g body weight), both the Kuwaiti oil fire and St. Louis urban particles significantly increased BAL neutrophils, macrophages, and levels of albumin and other biomarkers (LDH, MPO) of lung inflammation.

The fact that instillation of ambient PM collected from different geographical areas has been shown to cause pulmonary inflammation and injury tends to support epidemiologic studies that report increased PM-associated respiratory effects in populations living in some of the same geographical areas (e.g., Utah Valley). On the other hand, the potential exists that lower, more "realistic" doses associated with ambient PM exposures may activate cells and signaling pathways not observed with much higher than ambient experimental doses, such that lower-dose mechanisms may be overwhelmed. Thus, high-dose instillation studies may actually produce different effects on the lung than inhalation exposures at lower concentrations or doses more closely paralleling those seen with ambient PM exposures.

7.3.2 ROFA and Other Combustion Source-Related Particles

Because combustion emission sources contribute to the overall ambient air particulate burden (Spengler and Thurston, 1983), a number of the studies investigating the response of laboratory animals to particle exposures have used combustion source-related particles (see Tables 7-6 and 7-7). For example, the residual oil fly ash (ROFA) samples used in many toxicological studies have been collected from a variety of sources, e.g., boilers, bag houses used to control emissions from power plants, and from particles emitted downstream of such collection devices. ROFA has a high content of water soluble sulfate and metals, accounting for 82 to 92% of water-soluble mass, while the water-soluble mass fraction in ambient air varies from low teens to more than 60% (Costa and Dreher, 1997; Prahalad et al., 1999). More than

TABLE 7-6. RESPIRATORY EFFECTS OF INTRATRACHEALLY INSTILLED ROFA AND OTHER COMBUSTION SOURCE-RELATED PARTICULATE MATTER IN HEALTHY LABORATORY ANIMALS[a]

Species, Gender, Strain, Age, etc.	Particle	Dose	Particle Size	Time to PE[b] Analysis	Particle Effects/Comments	Reference
Mice, female, NMRI, 28-32 g	Coal fly ash (CFA) Copper smelter dust (CMP) Tungsten carbide (TC)	CMP: 20 µg arsenic/kg, or CMP: 100 mg particles/kg, TC alone (100 mg/kg), CFA alone (100 mg/kg [i.e., 20 µg arsenic/kg]), CMP mixed with TC (CMP, 13.6 mg/kg [i.e., 20 µg arsenic/kg; TC, 86.4 mg/kg]) and $Ca_3(AsO_4)_2$ mixed with TC (20 µg arsenic/kg; TC 100 mg/kg)	N/A	1, 6, 30 days post-treatment lavage for total protein content, inflammatory cell number and type, and TNF-α production	Mild inflammation for TC; $Ca_3(AsO_4)_2$ caused significant inflammation; CMP caused severe but transient inflammation; CFA caused persistent alveolitis. Cytokine production was upregulated in TC-and $Ca_3(AsO_4)$ treated animals after 6 and 30 days, respectively; a 90% inhibition of TNF-α production was still observed at day 30 after CMP administration and CFA; a significant fraction persisted (10-15% of the arsenic administered) in the lung of CMP- and CFA-treated mice at day 30. Suppression of TNF-α production is dependent on the slow elimination of the particles and their metal content from the lung.	Broeckaert et al. (1997)
Rats, male, S-D, 60 days old	ROFA (Florida), DOFA (Boston), CFA (RTP, NC) Ambient PM (St. Louis; Wash, DC; Ottawa; Dusseldorf)	Total mass: 2.5 mg/rat or Total transition metal: 46 µg/rat	Combustion source PM: 1.78-4.17 µm Ambient PM: 3.27-4.09 µm	Analysis at 24 and 96 h following instillation	Increases in eosinophils, PMNs, albumin, and LDH following exposure to ambient and combustion source (ROFA, DOFA, CFA) particles; induction of injury by test samples was determined primarily by constituent metals and their bioavailability in both ambient and combustion source PM.	Costa and Dreher (1997)
Rats, male, S-D, 65 days old	ROFA (Florida)	2.5 mg (8.3 mg/kg)	1.95 µm	Analysis at 24, 96 h PE	Increased PMNs, protein, LDH at both time points; bioavailable metals were causal constituents of pulmonary injury.	Dreher et al. (1997)
Rats, S-D, 65 days old	ROFA (Florida)	500 µg/rat ROFA 500 µg/rat ROFA plus DMTU	1.95 µm	Analysis at 24 h PE	ROFA-induced increased neutrophilic inflammation was inhibited by DMTU treatment, indicating role to reactive oxygen species.	Dye et al. (1997)

TABLE 7-6 (cont'd). RESPIRATORY EFFECTS OF INTRATRACHEALLY INSTILLED ROFA AND OTHER COMBUSTION SOURCE-RELATED PARTICULATE MATTER IN HEALTHY LABORATORY ANIMALS[a]

Species, Gender, Strain, Age, etc.	Particle	Dose	Particle Size	Time to PE[b] Analysis	Particle Effects/Comments	Reference
Rats, male, S-D, 60 days old	Two ROFA (Florida) samples (R1, R2) also R2s (supernatant)	2.5 mg (9.4 mg/kg)	R1: 1.88 µm R2: 2.03 µm	Analysis at 4 days PE	Four of 24 animals treated with R2 or R2s died; none of R1s animals; more AM, PMN, eosinophils protein, and LDH in R2 and R2s animals; more focal alveolar lesions, thickened alveolar septae, hyperplasia of type II cells, alveolar fibrosis in R2 and R2s animals; baseline pulmonary function and airway hyperreactivity worse in R2 and R2s groups. R1 had twice the saline-leachable sulfate, Ni, and V and 40 times Fe as R2; R2 had 31 times higher Zn.	Gavett et al. (1997)
Mice, female, BALB/cJ 7-15 weeks	ROFA, #6 lo-S (Florida)	60 µg in saline (dose 3 mg/kg)	< 2.5 µm	Analysis at 1, 3, 8, 15 days postexposure	ROFA caused increases in eosinophils, IL-4 and IL-5 and airway responsiveness in ovalbumin-sensitized and challenged mice. Increased BAL protein and LDH at 1 and 3 days but not at 15 days postexposure. Combined OVA and ROFA challenge increased all damage markers and enhanced allergen sensitization. Increased methacholine response after ROFA.	Gavett et al. (1999)
Rats, male, S-D	ROFA (Florida)	500 µg	3.6 µm	Analysis at 4 and 96 h postexposure	Ferritin and transferrin were elevated; greatest increase in ferritin, lactoferrin, transferrin occurred 4 h postexposure.	Ghio et al. (1998a)
Mice, normal and Hp, 105 days old	ROFA (Florida)	50 µg	1.95 µm	Analysis at 24 h PE	Diminished lung injury (e.g., decreased lavage fluid ascorbate, protein, lactate dehydrogenase, inflammatory cells, cytokines) in Hp mice lacking transferrin; associated with increased metal storage and transport proteins.	Ghio et al. (2000b)
Rats, male, S-D, 60 days old	ROFA (Florida)	1.0 mg in 0.5 mL saline	1.95 µm	Analysis at 24 h PE	Increased PMNs, protein.	Kadiiska et al. (1997)
Rats, male, S-D and F-344 (60 days old)	ROFA (Florida)	8.3 mg/kg	1.95 µm $\sigma_g = 2.14$	Sacrificed at 24 h PE	Increase in neutrophils in both S-D and F-344 rats; a time-dependent increase in eosinophils occurred in S-D rats but not in F-344 rats.	Kodavanti et al. (1996)

TABLE 7-6 (cont'd). RESPIRATORY EFFECTS OF INTRATRACHEALLY INSTILLED ROFA AND OTHER COMBUSTION SOURCE-RELATED PARTICULATE MATTER IN HEALTHY LABORATORY ANIMALS[a]

Species, Gender, Strain, Age, etc.	Particle	Dose	Particle Size	Time to PE[b] Analysis	Particle Effects/Comments	Reference
Rats, male, S-D, WISTAR, and F-344 (60 days old)	ROFA (Florida)	8.3 mg/kg	1.95 μm σ_g = 2.14	Sacrificed at 6, 24, 48, and 72 h; 1, 3, and 12 weeks	Inflammatory cell infiltration, as well as alveolar, airway, and interstitial thickening in all three rat strains; a sporadic incidence of focal alveolar fibrosis in S-D rats, but not in WISTAR and F-344 rats; cellular fibronectin (cF_n) mRNA isoforms EIIIA(+) were up-regulated in S-D and WIS rats but not in F-344 rats. Fn mRNA expression by macrophage, alveolar and airway epithelium, and within fibrotic areas in S-D rats; increased presence of Fn EIIIA(+) protein in the areas of fibrotic injury and basally to the airway epithelium.	Kodavanti et al. (1997b)
Rats, male, S-D, 60 days old	ROFA (Florida) $Fe_2(SO_4)_3$, VSO_4, $NiSO_4$	8.3 mg/kg ROFA-equivalent dose of metals	1.95 μm σ_g = 2.14	Analysis at 3, 24, and 96 h, postinstillation	ROFA-induced pathology lesions were as severe as those caused by Ni. Metal mixture caused less injury than ROFA or Ni alone; Fe was less pathogenic. Cytokine and adhesion molecule gene expression occurred as early as 3 h after exposure. V-induced gene expression was transient, but Ni caused persistent expression and injury.	Kodavanti et al. (1997a)
Rats, male, S-D, 60 days old	10 compositionally different ROFAs from Boston area power plant	0.83, 3.3, 8.3 mg/kg	1.99-2.67 μm	Sacrificed at 24 h	ROFA-induced increases in BAL protein and LDH, but not PMN, associated with water-leachable total metal, Ni, Fe, and S; BALF neutrophilic inflammation was correlated with V but not Ni or S. Chemiluminescence signals in vitro (AM) were greatest with ROFA containing soluble V and less with Ni + V. Only data for the 8.3 mg/kg dosed group were reported.	Kodavanti et al. (1998a)
Rats, male, S-D 60-day-old treated with MCT (60 mg/kg)	ROFA (Florida)	0, 0.83, 3.3 mg/kg	1.95 μm σ_g = 2.19	24-96 h	Dose-dependent increase in BALF protein and LDH activity and neutrophilic inflammation. Effects were variable due to high mortality. 58% of rats exposed to ROFA died within 96 h.	Kodavanti et al. (1999)
Rats, male, WKY and SH, 11-13 weeks old	ROFA (Florida) VSO_4, $NiSO_4$, or saline	3.3 mg/mL/kg 1.5 μmol/kg	1.95 μm σ_g = 2.14	1 and 4 days; postinstillation analysis at 6 or 24 h	Increased BALF protein and LDH alveolitis with macrophage accumulation in alveoli; increased neutrophils in BAL. Increased pulmonary protein leakage and inflammation in SH rats. Effects of metal constituents of ROFA were strain specific; vanadium caused pulmonary injury only in WKY rats; nickel was toxic in both SH and WKY rats.	Kodavanti et al. (2001)

TABLE 7-6 (cont'd). RESPIRATORY EFFECTS OF INTRATRACHEALLY INSTILLED ROFA AND OTHER COMBUSTION SOURCE-RELATED PARTICULATE MATTER IN HEALTHY LABORATORY ANIMALS[a]

Species, Gender, Strain, Age, etc.	Particle	Dose	Particle Size	Time to PE[b] Analysis	Particle Effects/Comments	Reference
Rats, female, Brown Norway 8-10 weeks old	ROFA (Florida) and HDM	200 µg or 1000 µg	1.95	N/A	ROFA enhanced the response to house dust mite (HDM) antigen challenge. Eosinophil numbers and LDH were increased in highest exposed groups. BAL protein and IL-10 were increased in both ROFA groups + HDM versus HDM alone.	Lambert et al. (1999)
Rats, male, S-D, 60 days old	ROFA #6 (Florida)	1000 µg in 0.5 mL saline	1.95 ± 0.18 µm	15 min to 24 h	Production of acetaldehyde increased at 2 h postinstillation.	Madden et al. (1999)
	DOFA (NC)	1000 µg in 0.5 mL saline		15 min to 24 h	ROFA induced production of acetaldehyde with a peak at about 2 h. No acetaldehyde was seen in plasma at any time. DOFA increased acetaldehyde, as did V, Fe.	
Rats, male, S-D; 60 days old	ROFA #6 (Florida) $NiSO_4$ VSO_4	3.3 mg/mL/kg; ROFA equivalent dose of metals	1.9 µm $\sigma_g = 2.14$	3 or 24 h	Inflammatory and stress responses were upregulated; the numbers of genes upregulated were correlated with metal type and ROFA	Nadadur et al. (2000); Nadadur and Kodavanti (2002)
Rats, male, S-D, 60 days old	ROFA (Cayman Chemical, Ann Arbor, MI)	400 and 1000 µg/mL (200 and 500 µg ROFA in 0.5 mL saline)	N/A	12 h post-IT	ROFA increased PGE_2 via cycloxygenase expression in the 400 µg/mL group. PGE_2 depressed in 1000 µg/mL group by COX2 inhibitor.	Samet et al. (2000)
Rats, male, S-D, 60 days old	ROFA, #6 LoS (Florida)	500 µg in 0.5 mL saline	3.6 µm	1, 4, or 24 h	Mild and variable inflammation at 4 h; no pronounced inflammation until 24 h when there were marked increases in P-Tyr and P-MAPKS.	Silbajoris et al. (2000)
Rats, S-D	DPM	500 µg in 0.5 mL saline	N/A	3 times/week, 2 weeks	Decreased concentration of lavage ascorbate. Urate and glutathione concentrations unchanged; elevated MIP-2 and TNF; total cell count increased; lavage protein and LDH increased; increased total lavage iron concentration.	Ghio et al. (2000b)

[a] CFA = Coal fly ash
CMP = Copper smelter dust
DOFA = Domestic oil-burning furnace fly ash
ROFA = Residual oil fly ash
TC = Tungsten carbide
$Fe_2(SO_4)$ = Iron sulfate
VSO_4 = Vanadium sulfate
$NiSO_4$ = Nickel sulfate
LoS = low sulfur
MCT = Monocrotaline
OVA = Ovalbumin

[b] PE = Post Exposure

TABLE 7-7. RESPIRATORY EFFECTS OF INHALED AND INSTILLED ROFA AND OTHER COMBUSTION SOURCE-RELATED PARTICULATE MATTER IN COMPROMISED LABORATORY ANIMAL MODELS[a]

Species, Gender, Strain, Age, etc.	Particle	Exposure Technique	Concentration/ Dose	Particle Size	Exposure Duration; Time to PE[b] Analysis	Particle Effects/Comments	Reference
Inhalation							
Rats, male, WISTAR Bor:WISW strain n = 20	Coal fly ash (CFA)	Inhalation (chamber)	0, 11, 32, and 103 mg/m^3	1.9-2.6 µm σ_g = 1.6-1.8	6 h/day, 5days/week, for 4 weeks	At 103 mg/m^3, type II cell proliferation, mild fibrosis and increased perivascular lymphocytes seen. At lowest concentration, main changes seen were particle accumulation in AM and mediastinal lymph nodes. Lymphoid hyperplasia observed at all concentrations. Effects increased with exposure duration.	Dormans et al. (1999)
Mice, BALB/C, 2-day-old, sensitized to ovalbumin (OVA)	Aerosolized ROFA leachate	Nose-only inhalation	50 mg/mL	N/A	30 min	Increased airway response to methylcholine and to OVA in ROFA exposed mice; increased airway inflammation also.	Hamada et al. (1999)
Rats, S-D, 250 g MCT	ROFA (Boston)	Inhalation	580 ± 110 µg/m^3	2.06 µm σ_g = 1.57	6 h/day for 3 days	Mortality seen only in MCT rats exposed to ROFA. Neutrophils in lavage fluid increased significantly in MCT rats exposed to ROFA versus filtered air. MIP-2 mRNA expression induced in lavage cells in normal animals exposed to fly ash.	Killingsworth et al. (1997)
Rats, male, S-D 60-day-old treated with MCT (60 mg/kg)	ROFA (Florida)	Nose-only inhalation	15 mg/m^3	1.95 µm σ_g = 2.14	6 h/day for 3 days analysis at 0 or 18 h	No mortality occurred by inhalation. ROFA exacerbated lung lesions (edema, inflammation, alveolar thickening) and gene expression in MCT rats. Rats showed inflammatory responses (IL-6, MIP-2 genes upregulated).	Kodavanti et al. (1999)

TABLE 7-7 (cont'd). RESPIRATORY EFFECTS OF INHALED AND INSTILLED ROFA AND OTHER COMBUSTION SOURCE-RELATED PARTICULATE MATTER IN COMPROMISED LABORATORY ANIMAL MODELS[a]

Species, Gender, Strain, Age, etc.	Particle	Exposure Technique	Concentration/ Dose	Particle Size	Exposure Duration; Time to PE[b] Analysis	Particle Effects/Comments	Reference
Inhalation (cont'd)							
Rats, male, WKY and SH, 11-13 weeks old	ROFA (Florida)	Nose-only Inhalation	15 mg/m^3	1.95 µm $\sigma_g = 2.14$	6 h/day × 3 days, analysis at 0 or 18 h	More pulmonary injury in SH rats. Increased RBCs in BAL of SH rats. ROFA increased airway reactivity to acetylcholine in both SH and WKY rats. Increased protein, albumin, and LDH in BAL after ROFA exposure (SH > WKY). Increased oxidative stress in SH rats. SH rats failed to increase glutathione. Inflammatory cytokine gene expression increased in both SH and WKY rats.	Kodavanti et al. (2000b)
Mice, male, Swiss-Webster, 6-8 weeks old (A/J, AKR/J, B6C3F1/J, BALB/cJ, C3H/HeJ-C3, C3HeOuJ, CSTBL/6J-B6, SJL/J, SWR/J, 129/J) strains raised in a pathogen free laboratory	Carbon black Regal 660 Carbon-associated $SO_4^=$	Nose only inhalation	10 mg/m^3 (carbon) 10 ppm SO_2 285 $\mu g/m^3$ (average concentration of particle-associated sulfates)	0.29 µm ± 2.7 µm	4 h	Differences in inflammatory responses (PMN) across strains. Appears to be genetic component to the observed differences in susceptibility.	Ohtsuka et al. (2000a,b)
Rats, F-344 8 weeks, 20 months old Mice, TSK 14-17 months old	Carbon	Inhalation	100 $\mu g/m^3$ and/or 1.0 ppm O_3 following exposure to endotoxin (12 min to 70 EU)	UF	6 h	Small effect on lung inflammation and activation of inflammatory cells. Effects enhanced in compromised lung and in older animals. Greatest effect in compromised lung exposed to UF carbon and O_3.	Elder et al. (2000a,b)
Rats, male, S-D, MCT-treated	Fluorescent microspheres	Inhalation	3.85 ± 0.81 mg/m^3	1.38 ± 0.10 µm $\sigma_g = 1.8 \pm 0.28$	3 h/day × 3 days	MCT-treated animals had fewer microspheres in their macrophages, probably because of impaired chemotaxis.	Madl et al. (1998)

TABLE 7-7 (cont'd). RESPIRATORY EFFECTS OF INHALED AND INSTILLED ROFA AND OTHER COMBUSTION SOURCE-RELATED PARTICULATE MATTER IN COMPROMISED LABORATORY ANIMAL MODELS[a]

Species, Gender, Strain, Age, etc.	Particle	Exposure Technique	Concentration/ Dose	Particle Size	Exposure Duration; Time to PE[b] Analysis	Particle Effects/Comments	Reference
Instillation							
Rats, male, S-D; 60-day-old; WKY and SH; cold-stressed SH; O_3-exposed SH; MCT-treated SH	ROFA (source not specified), Ottawa dust, MSH Vol. Ash	Intratracheal instillation	0, 0.25, 1.0, and 2.5 mg/rat	1.95 µm	96 h post-IT	ROFA instillation caused acute, dose-related increase in pulmonary inflammation. Data on Ottawa dust and volcanic ash not reported.	Watkinson et al. (2000a,b)
Rats, male, S-D (200 g)	Diesel, SiO_2, carbon black	Intratracheal instillation	1 mg in 0.4 mL.	DEP collected as TSP-disaggregated in solution by sonication (20 nm); SiO_2 (7 nm); carbon black	Necropsy at 2, 7, 21, 42, and 84 days postinstillation	Amorphous SiO_2 increased permeability and neutrophilic inflammation. Carbon black and DEP translocated to interstitum and lymph nodes by 12 weeks.	Murphy et al. (1998)

[a] CFA = Coal fly ash
CMP = Copper smelter dust
DOFA = Domestic oil-burning furnace fly ash
ROFA = Residual oil fly ash
TC = Tungsten carbide
$Fe_2(SO_4)$ = Iron sulfate
VSO_4 = Vanadium sulfate
$NiSO_4$ = Nickel sulfate
LoS = low sulfur
MCT = Monocrotaline
OVA = Ovalbumin

[b] PE = Post Exposure

90% of the metals in ROFA are transition metals; whereas these metals typically represent only a very small subfraction of the total ambient PM mass of U.S. monitoring samples. Thus, the dose of bioavailable metal that is delivered to the lung when ROFA is instilled into a laboratory animal can be orders of magnitude greater than an ambient PM dose, even under a worst-case scenario. Transition metals generate reactive oxygen species (ROS) pertinent to understanding of one proposed mechanism of PM toxicity and of PM components possibly contributing to toxic responses.

Intratracheal instillation of various doses of ROFA suspension has been shown to produce severe inflammation, an indicator of pulmonary injury that includes recruitment of neutrophils, eosinophils, and monocytes into the airway. The biological effects of ROFA in rats have been shown to depend on aqueous leachable chemical constituents of the particles (Dreher et al., 1997; Kodavanti et al., 1997a). A leachate prepared from ROFA, containing predominantly Fe, Ni, V, Ca, Mg, and sulfate, produced lung injury similar to that induced by the complete ROFA suspension (Dreher et al., 1997). Depletion of Fe, Ni, and V from the ROFA leachate eliminated its pulmonary toxicity. Correspondingly, minimal lung injury was observed in animals exposed to saline-washed ROFA particles. A surrogate transition metal sulfate solution containing Fe, V, and Ni largely reproduced the lung injury induced by ROFA. Interestingly, ferric sulfate and vanadium sulfate antagonized the pulmonary toxicity of nickel sulfate. Interactions between different metals and the acidity of PM were found to influence the severity and kinetics of lung injury induced by ROFA and its soluble transition metals.

To further investigate the response to ROFA with differing metal and sulfate composition, Kodavanti et al., (1997a) instilled male Sprague-Dawley rats (60 days old) intratracheally with ROFA (2.5 mg/rat) or metal sulfates (Fe – 0.54 μmole [105 μg]/rat, V – 1.7 μmole [245 μg]/rat, and Ni – 1.0 μmole [263 μg]/rat, individually or in combination). Transition metal sulfate mixtures caused less injury than ROFA or Ni alone, suggesting metal interactions. This study also showed that V-induced effects were less severe than that of Ni and were transient. Ferric sulfate was least pathogenic. Cytokine gene expression was induced prior to the pathology changes in the lung, and the kinetics of gene expression suggested persistent injury by nickel sulfate. Another study by the same investigators was performed using 10 different ROFA samples collected at various sites within a power plant burning residual oil (Kodavanti et al., 1998a). Animals received intratracheal instillations of either saline (control), or a saline

suspension of whole ROFA (< 3.0 μm MMAD for all ground PM) at three doses (0.83, 3.33, or 8.33 mg/kg). This study showed that ROFA-induced PMN influx was associated with its water-leachable V content; but protein leakage was associated with water-leachable Ni content. ROFA-induced in vitro activation of AMs was highest with ROFA containing leachable V but not with Ni plus V, suggesting that the potency and the mechanism of pulmonary injury may differ between emissions containing bioavailable V and Ni.

Other studies have shown that soluble metal components play an important role in the toxicity of emission source particles. Gavett et al. (1997) investigated the effects of two ROFA samples of equivalent diameters, but having different metal and sulfate content, on pulmonary responses in Sprague-Dawley rats. ROFA sample 1 (R1; the same emission particles used by Dreher et al. [1997]) had approximately twice as much saline-leachable sulfate, Ni, and V, and 40 times as much Fe as ROFA sample 2 (R2), whereas R2 had a 31-fold higher Zn content. Rats were instilled with suspensions of 2.5 mg R2 in 0.3 mL saline, the supernatant of R2 (R2s), the supernatant of 2.5 mg R1 (R1s), or saline only. By 4 days after instillation, 4 of 24 rats treated with R2s or R2 had died. None treated with R1s or saline died. Pathological indices, such as alveolitis, early fibrotic changes, and perivascular edema, were greater in both R2 groups. In surviving rats, baseline pulmonary function parameters and airway hyperreactivity to acetylcholine were significantly worse in the R2 and R2s groups than in the R1s groups. Other than BAL neutrophils, which were significantly higher in the R2 and R2s groups, no other inflammatory cells (macrophages, eosinophils, or lymphocytes) or biochemical parameters of lung injury were significantly different between the R2 and R2s groups and the R1s group. Although (a) soluble forms of Zn had been found in guinea pigs to produce a greater pulmonary response than other sulfated metals (Amdur et al., 1978) and (b) the level of Zn was 30-fold greater in R2 than R1, the precise mechanisms by which Zn may induce such responses are unknown. Still, these results show that the composition of soluble metals and sulfate is critical in the development of airway hyperractivity and lung injury produced by ROFA, albeit at very high instilled doses.

Dye et al. (1997) pretreated rats with an intraperitoneal (IP) injection of 500 mg/kg dimethylthiourea (DMTU) or saline, followed 30 min later by intratracheal instillation of either acidic saline (pH = 3.3) or an acidified suspension of ROFA (500 μg/rat). Dimethylthiourea reduces the activity of the reactive oxygen species. The systemic administration of DMTU

impeded development of the cellular inflammatory response to ROFA but did not ameliorate biochemical alterations in BAL fluid. In a subsequent study, it was determined that oxidant generation, possibly induced by soluble V compounds in ROFA, is responsible for the subsequent rat tracheal epithelial cells gene expression, inflammatory cytokine production (MIP-2 and IL-6), and cytotoxicity (Dye et al., 1999).

In parallel work on the potential importance of metals in mediating ambient PM effects, Kodavanti et al. (2002b) studied the role of Zn in PM-induced health effects in several animal models. Male Sprague-Dawley (SD) rats were instilled IT with ROFA in saline (0.0, 0.8, 3.3, or 8.3 mg/kg) from a Boston area power plant. Also, in order to evaluate the potential role of leachable Zn, additional rats were instilled with either saline, whole ROFA suspension, the saline leachable fraction of ROFA, the particulate fraction of ROFA (8.3 mg/kg, soluble Zn = 14.5 μg/mg ROFA), or $ZnSO_4$ (0.0, 33.0, or 66.0 μg/kg Zn). Three rat strains that differ in PM susceptibility, i.e., male SD, normotensive WKY, and spontaneously hypertensive (SH) rats, were exposed at age 90 days nose-only to either filtered air or ROFA (2, 5, or 10 mg/m^3 for 6 h/day × 4 days/week × 1 week; or 10 mg/m^3 for 6 h/day × 1 day/week for 1, 4, or 16 weeks) and assessed at 2 days postexposure. Intratracheal exposures to whole ROFA suspensions produced a dose-dependent increase in protein/albumin permeability and neutrophilic inflammation. Pulmonary protein/albumin leakage and neutrophilic inflammation caused by the leachable fraction of ROFA and $ZnSO_4$ were comparable to effects of the whole suspension. However, protein/albumin leakage was not associated with the particulate fraction, although significant neutrophilic inflammation did occur after instillation. With ROFA nose-only inhalation, acute exposures (10 mg/m^3 only) for 4 days resulted in small increases BAL protein and N-acetyl glucosaminidase activities (~50% above control); but, unlike with IT exposures, no neutrophilic influx was detectable in BAL from any of the inhalation groups. The only major effect of acute and long-term ROFA inhalation was a dose- and time-dependent increase in alveolar macrophages (AM), regardless of rat strain. Histological evidence also showed dose- and time-dependent accumulations of particle-loaded AM. Particles were also evident in interstitial spaces and in the lung-associated lymph nodes following the inhalation exposures (SH > WKY = SD). There were strain-related differences in peripheral WBC counts and plasma fibrinogen, but no major ROFA inhalation effect. The authors attributed the differences in pulmonary responsiveness to ROFA between IT and inhalation exposures to the dose of

bioavailable zinc; the IT ROFA exposures, but not acute and long-term inhalation of up to 10 mg/m^3, caused neutrophilic inflammation.

In addition to transition metals, other components in fly ash also may cause lung injury. The effects of arsenic compounds in coal fly ash or copper smelter dust on the lung integrity and on the ex vivo release of TNF-α by alveolar phagocytes were studied by Broeckaert et al. (1997). Female NMRI mice were instilled with different particles normalized for arsenic content (20 μg/kg body weight [i.e., 600 ng arsenic/mouse]) and particle load (100 mg/kg body weight [i.e., 3 mg/mouse]). Mice received tungsten carbide (TC) alone, coal fly ash (CFA) alone, copper smelter dust (CMP) mixed with TC, and $Ca_3(AsO_4)_2$ mixed with TC (see Table 7-6 for concentration details). Copper smelter dust caused a severe but transient inflammatory reaction; whereas a persisting alveolitis (30 days postexposure) was seen after treatment with coal fly ash. Also, TNF-α production in response to lipopolysaccharide (LPS) by alveolar phagocytes was significantly inhibited at day 1, but was still observed at 30 days after administration of CMP and CFA. Although arsenic was cleared from the lung tissue 6 days after $Ca_3(AsO_4)_2$ administration, a significant fraction persisted (10 to 15% of the As administered) in the lung of CMP- and CFA-treated mice at day 30 postexposure. Hence, suppression of TNF-α production may be dependent on the slow elimination of particles and their metal content from the lung.

Antonini et al. (2002) investigated effects of preexposure to ROFA on lung defenses and injury after pulmonary challenge with *Listeria monocytogenes*, a bacterial pathogen. Male SD rats were dosed IT at day 0 with saline (control) or ROFA (0.2 or 1 mg/100 g body weight). Three days later, both groups of rats were instilled IT with a low (5×10^3) or high (5×10^5) dose of *L. monocytogenes*. Chemiluminescence (CL) and nitric oxide (NO) production, two indices of AM function, were measured for BAL cells from the right lungs. The left lungs and spleens were homogenized, cultured, and colony-forming units were counted after overnight incubation. Exposure to ROFA and the high dose of *L. monocytogenes* led to marked lung injury and inflammation as well as to an increase in mortality, compared with rats treated with saline and the high dose of *L. monocytogenes*. Preexposure to ROFA significantly enhanced injury and delayed pulmonary clearance of *L. monocytogenes* at both bacterial doses when compared to the saline-treated control rats. ROFA had no effect on AM CL but caused a significant suppression of AM NO production. The authors concluded that acute exposure to ROFA slowed pulmonary

clearance of *L. monocytogenes* and altered AM function, changes that could lead to increased susceptibility to lung infection in exposed populations.

In summary and as indicated in Table 7-6, intratracheally instilled high doses of ROFA produced acute lung injury and inflammation. Water soluble metals in ROFA appear to play a key role in the acute effects of instilled ROFA through the production of reactive oxygen species. These ROFA studies clearly show that combustion-generated particles with a high metal content can cause substantial lung injury; but how well such effects can be extrapolated to help understand ambient PM exposure effects in humans remains to be more fully established.

Results listed in Table 7-7 indicate that in a few cases both normal and compromised animals have similar responses to ROFA and other combustion source-related PM. However, most studies show that responses are seen at lower concentrations/doses in compromised animals. Additionally, ROFA has been shown to exacerbate lesions and inflammation created by MCT-pretreatment and to induce more pulmonary injury in SH rats. Strain-specific differences have also been noted in inflammatory responses to carbon and ROFA, indicating a genetic component to the differences in susceptibility.

7.3.3 Metals

Results from occupational and laboratory animal studies reviewed in the 1996 PM AQCD indicated that acute exposures to very high levels (hundreds of $\mu g/m^3$ or more) or chronic exposures to lower levels (as low as 15 $\mu g/m^3$) of metallic particles could affect the respiratory tract. It was concluded, on the basis of data available at that time, that the metals at typical concentrations present in the ambient atmosphere (1 to 14 $\mu g/m^3$) were not likely to have a significant acute effect in healthy individuals. This included metals such as As, Cd, Cu, Ni, V, Fe, and Zn. Other metals found at concentrations less than 0.5 $\mu g/m^3$ were not reviewed in the 1996 PM AQCD.

More recently published data from controlled experimental exposure studies, however, are suggestive of particle-associated metals possibly being among PM components contributing to health effects attributed to ambient PM. Included among such studies are a number of the "ambient PM," ROFA, and other "combustion-source" studies assessed in the preceding two sections which included analyses of potential contributions of metals to observed effects. Other

new studies on effects of laboratory-generated metals/metal compounds are summarized in Table 7-8.

Iron is the most abundant of the elements capable of catalyzing oxidant generation and is also present in ambient urban particles. Lay et al. (1998) and Ghio et al. (1998b) tested the hypothesis that the human respiratory tract will attempt to diminish the added, iron-generated oxidative stress. They examined cellular and biochemical responses of human subjects instilled, via the intrapulmonary route, with a combination of iron oxyhydroxides that introduced an oxidative stress to the lungs. Saline alone and iron-containing particles suspended in saline were instilled into separate lung segments of human subjects. Subjects underwent bronchoalveolar lavage at 1 to 91 days after instillation of 2.6-μm diameter iron oxide (~5 mg or 2.1×10^8 particles) agglomerates. Lay and colleagues found iron oxide-induced inflammatory responses in both the alveolar fraction and the bronchial fraction of the lavage fluid at 1 day after instillation. Lung lavage 24 h after instillation revealed decreased transferrin concentrations and increased ferritin and lactoferrin concentrations, consistent with a host-generated response to decrease the availability of catalytically reactive iron (Ghio et al., 1998b). Normal iron homeostasis returned within 4 days of the iron particle instillation. The same iron oxide preparation, which contained a small amount of soluble iron, produced similar pulmonary inflammation in rats. In contrast, instillation of rats with two iron oxide preparations that contained no soluble iron failed to produce injury or inflammation, thus suggesting that soluble iron was responsible for the observed intrapulmonary changes.

In a subsequent inhalation study, Lay et al. (2001) studied the effect of iron oxide particles on lung epithelial cell permeability. Healthy, nonsmoking human subjects inhaled 12.7 mg/m^3 low- and high-solubility iron oxide particles (MMAD = 1.5 μm and $\sigma_g = 2.1$) for 30 minutes. Neither pulmonary function nor alveolar epithelial permeability, as assessed by pulmonary clearance of technetium-labeled DPTA, was changed at 0.5 or 24 h after exposure to either type of iron oxide particle. Ghio et al. (2001) reported a case study, however, in which acute exposure to oil fly ash from a domestic oil-fired stove produced diffuse alveolar damage, difficulty in breathing, and symptoms of angina. Elemental analyses revealed high metal content (Fe, V, etc.) in fly ash samples; and other evaluations suggested that the high metal content of oil fly ash altered the epithelial cell barrier in the alveolar region.

TABLE 7-8. RESPIRATORY EFFECTS OF INHALED AND INSTILLED METAL PARTICLES IN HUMAN SUBJECTS AND LABORATORY ANIMALS

Species, Gender, Strain, Age, etc.	Particle	Exposure Technique	Concentration	Particle Size	Exposure Duration/Time to Analysis	Particle Effects/Comments	Reference
Inhalation							
Humans, healthy nonsmokers; 8 M, 8 F; 18-34 years old	Fe_2O_3	Inhalation	12.7 mg/m^3	1.5 µm $\sigma_g = 2.1$	30 min	No significant difference in $^{98m}T_c$-DTPA clearance half-times, D_LCO, or spirometry	Lay et al. (2001)
Rats, SD; 60 days old	VSO_4 $NiSO_4$	Inhalation	0.3 - 1.7 mg/m^3 0.37 - 2.1 mg/m^3	N/A	6h/day x 4 days	V did not induce any significant changes in BAL or HR. Ni caused delayed bradycardia, hypothermia, and arrhythmogenesis at > 1.3 mg/m^3. Possible synergistic effects were found.	Campen et al. (2001)
Instillation							
Humans, healthy nonsmokers; 12 M, 4 F; 18-35 years old	Colloidal iron oxide	Bronchial instillation	5 mg in 10 mL	2.6 µm	1, 2, and 4 days after instillation	L-ferritin increased after iron oxide particle exposure; transferrin was decreased. Both lactoferrin and transferrin receptors were increased.	Ghio et al. (1998b)
Humans, healthy nonsmokers; 27 M, 7 F; 20-36 years old.	Fe_2O_3	Intrapulmonary instillation	3×10^8 microspheres in 10 mL saline.	2.6 µm	N/A	Initially-induced transient inflammation (neutrophils, protein, LDH, IL-8) resolved by 4 days postinstillation.	Lay et al. (1998)
Mice, NMRI; Mouse peritoneal macrophage	MnO_2	Intratracheal instillation; in vitro	0.037, 0.12, 0.75, 2.5 mg/animal	surface area of 0.16, 0.5, 17, 62 m^2/g	Sacrificed at 5 days	LDH, protein and cellular recruitment increased in a dose-related manner with increasing surface area for particles with surface areas of 17 and 62 m^2/g; freshly ground particles with surface areas of 0.5 m^2/g had enhanced cytotoxicity.	Lison et al. (1997)

TABLE 7-8 (cont'd). RESPIRATORY EFFECTS OF INHALED AND INSTILLED METAL PARTICLES IN HUMAN SUBJECTS AND LABORATORY ANIMALS

Species, Gender, Strain, Age, etc.	Particle	Exposure Technique	Concentration	Particle Size	Exposure Duration/Time to Analysis	Particle Effects/Comments	Reference
Instillation (cont'd)							
Rats, Female, CD	$NaVO_3$ $VOSO_4$ V_2O_5	Intratracheal instillation	21 or 210 µg V/kg ($NaVO_3$, $VOSO_4$ soluble) 42 or 420 µg V/kg (V_2O_s) less soluble	N/A	1 h or 10 days following instillation	PMN influx was greatest following $VOSO_4$, lowest for V_2O_5 (no effect at lowest concentration); $VOSO_4$ induced inflammation persisted longest; MIP-2 and KC (CXC chemokines) were rapidly induced as early as 1 h postinstillation and persisted for 48 h; Soluble V induced greater chemokine mRNA expression than insoluble V; AMs have the highest expression level.	Pierce et al. (1996)
Mice, Swiss	EHC-93 soluble metal salts	Intratracheal instillation	1 mg in 0.1 mL H_2O	0.8 ± 0.4 µm	3 days	Solution containing all metal salts (Al, Cu, Fe, Pb, Mg, Ni, Zn) or ZnCl alone increased BAL inflammatory cells and protein.	Adamson et al. (2000)
Rats, M, F344, 175-225 g	TiO_2	Intratracheal inhalation and Intratracheal instillation	Inhalation at 125 mg/m^3 for 2 h; Instillation at 500 µg for fine, 750 µg for ultrafine	Fine: 250 nm Ultrafine: 21 nm	Inhalation exposure, 2 h; sacrificed at 0, 1, 3, and 7 days postexposure for both techniques	Inflammation produced by intratracheal inhalation (both severity and persistence) was less than that produced by instillation; ultrafine particles produced greater inflammatory response than fine particles for both dosing methods.	Osier and Oberdörster (1997)
Rats, M, F344, 175-225 g	TiO_2	Intratracheal inhalation and Intratracheal instillation	Inhalation at 125 mg/m^3 for 2 h; Instillation at 500 µg for fine, 750 µg for ultrafine	Fine: 250 nm Ultrafine: 21 nm	Inhalation exposure, 2 h; sacrificed at 0, 1, 3, and 7 days postexposure for both techniques	MIP-2 increased in lavage cells but not in supernatant in those groups with increased PMN (more in instillation than in inhalation; more in ultrafine than in fine); TNF-α levels had no correlation with either particle size or dosing methods.	Osier et al. (1997)

CdO = Cadmium oxide
Fe_2O_3 = Iron oxide
MgO = Magnesium oxide
MnO_2 = Manganese oxide
$NaVO_3$ = Sodium metavanadate
TiO_2 = Titanium oxide
$VOSO_4$ = Vanadyl sulfate
V_2O_5 = Vanadium pentoxide
ZnO = Zinc oxide
BAL = Bronchoalveolar lavage
CMD = Count median diameter
IL = Interleukin
LDH = Lactate dehydrogenase
MIP-2 = Macrophage inflammatory protein-2
mRNA = Messenger RNA (ribonucleic acid)
N/A = Data not available

Several of the other studies summarized in Table 7-8 provide evidence that several different metal salts (when instilled intratracheally in rats or mice at relatively high doses) can produce inflammatory responses in the lung as indicated by various markers (e.g., increased BAL PMNs or other inflammatory cells, induction of cytokines, etc). Two of the studies (by Osier and Oberdörster, 1997; Osier et al., 1997) further indicate that (a) ultrafine metal particles are more effective than fine particles in producing the inflammation and (b) intratracheal inhalation is less effective than instillation in producing the inflammation. Analogously, Campen et al. (2001) did not observe any significant changes in BAL markers with 6 h/day inhalation exposure of rats for 4 days to $VOSO_4$ at concentrations ranging up to 2.1 mg/m^3. The results of these metal studies and their potential significance are elaborated on further in later sections (e.g., Section 7.4.4.1) of this chapter.

7.3.4 Acid Aerosols

Extensive earlier studies (conducted up to the early 1990s) on the effects of controlled exposures to aqueous acid aerosols on various aspects of lung function in humans and laboratory animals were reviewed in an EPA Acid Aerosol Issue Paper (U.S. Environmental Protection Agency, 1989) and in the 1996 PM AQCD. Methodology and measurement methods for controlled human exposure studies were also reviewed elsewhere (Folinsbee et al., 1997).

The studies summarized in the 1996 PM AQCD illustrate that aqueous acidic aerosols have minimal effects on symptoms and mechanical lung function in young healthy adult volunteers at concentrations as high as 1000 $\mu g/m^3$. Asthmatic subjects appear to be more sensitive to the effects of acidic aerosols on mechanical lung function. Responses have been reported in adolescent asthmatics at concentrations as low as 68 $\mu g/m^3$, and modest bronchoconstriction has been seen in adult asthmatics exposed to concentrations $\geq$ 400 $\mu g/m^3$, but the available data are not consistent. However, at levels as low as 100 $\mu g/m^3$, acid aerosols can alter mucociliary clearance. Brief exposures ($\leq$ 1 h) to low concentrations ($\approx$ 100 $\mu g/m^3$) may accelerate clearance while longer (multihour) exposures to higher ones (> 100 $\mu g/m^3$) can depress clearance.

Some earlier acid aerosol studies not assessed in the 1996 PM AQCD or published more recently are summarized in Table 7-9. For example, Frampton et al. (1992) found that acid aerosol exposure in humans (1000 $\mu g/m^3$ H_2SO_4 for 2 h) did not result in airway inflammation and there was no evidence of altered macrophage host defenses. Also, Leduc et al. (1995) found

TABLE 7-9. RESPIRATORY EFFECTS OF ACID AEROSOLS IN HUMANS AND LABORATORY ANIMALS [a]

Species, Gender, Strain, Age, etc.	Particle	Exposure Technique	Concentration	Particle Size	Exposure Duration	Particle Effects/Comments	Reference
Humans, healthy nonsmokers; 10 M, 2 F; 20-39 years old	H_2SO_4 aerosol NaCl (control)	Inhalation	1000 µg/m^3	0.8-0.9 µm MMAD	2 h; analysis 18 h	No inflammatory responses; slight increase in BAL protein and slight decrease in albumin in H_2SO_4 subjects compared to NaCl. No effect on bacterial killing by macrophages was found.	Frampton et al. (1992)
Humans, asthmatic; 13 M, 11 F	H_2SO_4 aerosol NH^+_4/SO^{-2}_4 aerosol	Inhalation by face mask	500 µg/m^3	9 µm MMAD 7 µm MMAD	1 h	Exposure to simulated natural acid fog did not induce bronchoconstriction nor change bronchial responsiveness in asthmatics.	Leduc et al. (1995)
Rabbits, New Zealand white Humans, healthy nonsmokers; 10 M, 21-37 years old	H_2SO_4	Inhalation	1000 µg/m^3	0.8 µm σ_g 1.6	2 h	No inflammatory response; LDH activity in BAL elevated in both species; effect on bacterial killing by humans was inconclusive.	Zelikoff et al. (1997)
Rats, female, F-344; Guinea Pigs, female, Hartley	H_2SO_4 aerosol	Inhalation	94 mg/m^3 43 mg/m^3	0.80 σ_g 1.89 0.93 σ_g 2.11	4 h	Acid aerosol increased surfactant film compressibility in guinea pigs.	Lee et al. (1999)
Dogs, beagle, healthy; n = 16	Neutral sulfite aerosol	Inhalation	1.5 mg/m^3	1.0 µm MMAD σ_g = 2.2	16.5 h/day for 13 months	Long-term exposure to particle-associated sulfur and hydrogen ions caused only subtle respiratory responses and no change in lung pathology.	Heyder et al. (1999)
	Acidic sulfate aerosol	Inhalation	5.7 mg/m^3	1.1 µm MMAD σ_g = 2.0	6 h/day for 13 months		
Mice, BALB/c, 6-8 weeks old, normal and sensitized to OVA (ovalbumin)	Ammonium Bisulfite ($NH_4HSO_{4)}$	Inhalation, nose only	78 µg/m^3 972µg/m^3 235 µg/m^3	0.53 µm 0.45 µm 0.085 µm (MMD)	4 h/day for 3 days, analyzed at 1 or 4 days PE	No changes in BAL NAG, LDH, or protein with any of the particles. Small, non-relevant changes IL-4, IL-6 and TNFα. No treatment related effects on lung histopathology or serum IgE levels. Suggest that increases in asthma are not due to $NH_4HSO_{4)}$	Cassee et al. (1998a)

TABLE 7-9 (cont'd). RESPIRATORY EFFECTS OF ACID AEROSOLS IN HUMANS AND LABORATORY ANIMALS [a]

Species, Gender, Strain, Age, etc.	Particle	Exposure Technique	Concentration	Particle Size	Exposure Duration	Particle Effects/Comments	Reference
Mice, BALB/c, 6-8 weeks old, normal and sensitized to OVA	Ammonium Ferrosulfate $(NH_4)_2Fe(SO_4)_2 \bullet 6H_2O$	Inhalation, nose only	250 μg/m^3	0.459 μm (MMD)	4 h/day for 3 days, analyzed at 1 day PE	No changes in BAL NAG, LDH, or protein. Marginal, nonsignificant changes in TNFα and cell differential. No indications of enhanced allergic response with $(NH_4)_2Fe(SO_4)_2 \bullet 6H_2O$.	Cassee et al. (1998b)
Mice, BALB/c, 6-8 weeks old, normal and sensitized to OVA	Ammonium Nitrate ($NH_4NO_{3)}$	Inhalation, nose only	140 μg/m^3 250 μg/m^3	0.3 μm 0.03 μm (CMD)	4 h/day for 3 days, analyzed at 1 day PE	Increases in BAL NAG with 0.3 μm particle only. Increased neutrophils and decreased AMs with 0.03 μm particle only. No other exposure-related effects. Authors concluded that both mass concentration and specific size of the particles determine adverse effects of NH_4NO_3 exposure.	Cassee et al. (1998c)
Rats, SD, 6-8 weeks old, normal and MCT-treated	Ammonium Bisulfite, Ammonium Ferrosulfate, Ammonium Nitrate, or Fine CB	Inhalation, nose only	70-420 275-410 μg/m^3 2-9 mg/m^3	0.070-0.1 0.57-0.64 0.6 MMD	4 h/day for 3 days, analyzed at 1 day PE	No significant exposure-related changes in BAL NAG, LDH, protein, cytokines, lung histopathology or phagocytic activity with any of the particles.	Cassee et al. (2002)

[a] H_2SO_4 = Sulfuric acid
BAL = Bronchoalveolar lavage
LDH = Lactate dehydrogenase
MMAD = Mass median aerodynamic diameter
MMD = Mass median diameter
σ_g = Geometric standard deviation
CMD = Count median diameter

no increase in bronchoconstriction or bronchial responsiveness among asthmatic human adults exposed for 1 h via facemask to 500 μg/m^3 of simulated acid fog containing ammonium sulfate or H_2SO_4 aerosol.

Zelikoff et al. (1997) compared the responses of rabbits and humans exposed for 3 h to similar concentrations (i.e., 1000 μg/m^3) of H_2SO_4 aerosol. For both rabbits and humans, there was no evidence of PMA infiltration into the lung and no change in BAL fluid protein level, although there was an increase in LDH in rabbits but not in humans. Macrophages showed somewhat less antimicrobial activity in rabbits; but insufficient data were available for humans. Superoxide production by macrophages was somewhat depressed in both species. Macrophage phagocytic activity was also slightly reduced in rabbits but not in humans.

Ohtsuka et al. (2000a,b) also showed that a single 4 h exposure of mice to acid-coated carbon particles at a high mass concentration of 10,000 μg/m^3 carbon black caused decreased phagocytic activity of alveolar macrophages, even in the absence of lung injury. However, in another study, Lee et al. (1999) found little effect on female rats or guinea pigs of an inhalation exposure for 4 h to very high concentrations (43 or 94 mg/m^3) of H_2SO_4 aerosol.

In another study, Heyder et al. (1999) exposed healthy beagle dogs by inhalation to 1.5 mg/m^3 of acidic neutral sulfate aerosol for 16.5 h/day for 13 months or to acidic sulfate aerosol at 5.7 mg/m^3 for 6 h/day for 13 months. Interestingly, such chronic exposure to particle-associated hydrogen and sulfur ions at very high concentrations resulted in only some subtle respiratory responses, but no evident lung pathology.

Cassee and colleagues, in reports for the National Institute of Public Health and the Environment, Bilthoven, the Netherlands (Cassee et al., 1998a,b,c), have examined the effects of sulfate and nitrate aerosols in several compromised animal models. They used mice sensitized to OA as a model of allergic asthma and compared them to normal mice. One study (Cassee et al., 1998a) used exposures consisting of either fine ammonium bisulfate at 78 μg/m^3 (0.53 μm MMD) or 972 μg/m^3 (0.45 μm MMD), or ultra fine particles at 235 μg/m^3 (0.085 μm MMD), for exposure periods of 4 h/day for 3 consecutive days. Animals were analyzed at 1 or 4 days PE for various cellular, biochemical, and immunological endpoints. No changes were seen in BAL NAG, LDH, or protein with any of the particles. Only small changes were seen in the cytokines IL-4, IL-6 and TNF-α, which were not considered relevant. Additionally there were no treatment related effects on lung histopathology or serum IgE levels. The authors conclude that

ammonium bisulfate exerts only marginal responses in this compromised model, and suggest that the finding of increases in asthma in epidemiological studies is not due to this component of PM.

A second study by this group (Cassee et al, 1998b) using the same exposure regimen, but with ammonium ferrosulfate at a concentration of 250 $\mu g/m^3$ (0.459 μm MMD), found only marginal changes in TNF-α and cell differential, which were not significant. A third study (Cassee et al., 1998c), again using the asthmatic mouse model, assessed exposures of 140 $\mu g/m^3$ (0.3 μm CMD) or 250 $\mu g/m^3$ (0.03 μm CMD) ammonium nitrate aerosols. This particulate exposure differed from the sulfates in that it caused increases in BAL NAG with exposure to the smaller particle, and increased neutrophils and decreased AMs with exposure to the larger particle. Other parameters showed no exposure-related effects. The authors stated that, as the effects were mostly seen after exposure to the fine, rather than ultrafine, particle, both mass concentration and specific size of the particles determine adverse effects.

Subsequent studies (Cassee et al., 2002) utilized an animal model of pulmonary hypertension, MCT treatment, to study the effects of ammonium bisulfate, ammonium ferrosulfate, and ammonium nitrate exposure. Exposures lasting 4 h/day for 3 consecutive days used concentrations of ultrafines at 70+ $H_2O/\mu g/m^3$ (0.070 to 0.1 μm MMD), concentrations of fine particles at 275 to 410 $\mu g/m^3$ (0.57 to 0.64 MMD) and fine CB aerosol at 2 to 9 mg/m^3 (0.6 μm). Animals were examined at 1 day PE, using the same endpoints as in the three previous studies in addition to phagocytic activity. As with the asthma model, no significant exposure-related effects were seen with any of the particles.

Schlesinger and Cassee (2003) reviewed the literature on nitrate and sulfate secondary inorganic particles. They concluded that, in healthy humans and animals and in the limited number of compromised animal models studied, exposure to environmentally relevant levels of these particles has little biological potency. They also discussed the chemical basis of toxicity of these secondary inorganic particles and state that acidic particles, upon contact with epithelial lining fluid (ELF), can be neutralized by the endogenous ammonia present. Additionally, the mucus lining the airway buffers the acidic particles. This neutralization and buffering modulate the effect of the particles, but the capacity of these systems may be reduced in compromised individuals (Holma, 1989). Sarangapani and Wexler (1996) have modeled this defense system

and predict greater neutralization for small particles (< 0.1 μm) than for larger particles (> 1.0 μm).

Schlesinger and Cassee (2003) also stated that the available data indicate an acute exposure of > 1000 $\mu g/m^3$ is necessary to affect pulmonary function in healthy humans. The dosage for adverse effects in asthmatics is 68 to 100 $\mu g/m^3$, although the data are inconsistent. Transient effects on mucociliary clearance are seen at sulfuric acid aerosol concentrations of 100 mg/m^3, with no differences observed between asthmatics and normal individuals. Their evaluation of chronic exposure studies shows that concentrations of 100 to 250 $\mu g/m^3$ elicit changes in secretory cell function, mucociliary clearance, and nonspecific airway hyperresponsiveness. The review also stated that, with acute exposures, effects seen are a function of exposure concentration (C) and duration or time (T) and that a threshold appears to exist for both C and T.

There is little evidence linking direct acute or chronic exposures to aqueous acid aerosols to acute respiratory effects or chronic long pathology, except at much higher than current ambient levels.

7.3.5 Diesel Particulate Matter

Studies of controlled exposures to diesel exhaust (DE) and/or diesel particles (DPM) were previously evaluated in detail in two prior assessment documents, one by the Health Effects Institute (1995) and the other by the U.S. Environmental Protection Agency (2002). As noted in these documents, in addition to carcinogenic effects of exposure to diesel exhaust (DE), there are significant noncancer health effects observed with high levels of exposure.

Acute (short-term exposure) effects in both humans and laboratory animals include eye, throat, and bronchial irritation; neurophysiological symptoms include lightheadedness and nausea; respiratory effects include cough and phlegm; and immunologic effects such as exacerbation of allergenic responses to allergens. Chronic (long-term exposure) effects, as determined mainly from animal studies, include a spectrum of dose-dependent inflammation and histopathological changes in lung.

The most salient findings of the EPA 2002 Health Assessment Document for Diesel Engine Exhaust noncancer health effects are first briefly recapitulated (at times verbatim) below. Then some of these findings are elaborated upon further and the results of additional new studies are discussed.

7.3.5.1 Salient Findings from U.S. EPA 2002 Diesel Document

The EPA 2002 Diesel Document (U.S. Environmental Protection Agency, 2002) indicated that acute human exposure to DE elicits subjective complaints of eye, throat, and bronchial irritation and neurophysiological symptoms including headache, lightheadedness, nausea, vomiting, and numbness and tingling of limbs. With increasing concentrations of DE, the odor is detected more rapidly and the severity of symptoms increase. Studies of occupationally-exposed workers demonstrated that there are minimal, generally not statistically significant, increases in respiratory symptoms and decreases in lung function (FVC, FEV_1, PEFR, and FEF_{25-75}) during the course of the work shift. Smokers showed greater decrements in respiratory functions and increased incidence of respiratory symptoms with DE exposure compared to nonsmokers. Taken as a whole, both experimental and epidemiologic studies were not found to show any consistent pattern of acute DE exposure effects on human pulmonary function or respiratory symptoms. On the other hand, controlled human exposure studies were found to have shown that acute exposures to DE induce airway inflammation (Rudell et al., 1990, 1994) and to cause changes in peripheral blood (Salvi et al., 1999) in healthy humans, as further elaborated on below.

As for chronic exposure effects, epidemiologic studies of chronic DE exposures which occur in occupationally-exposed workers such as bus garage workers, miners, and railroad yard workers were found to indicate an absence of excess risk of chronic respiratory disease associated with exposure. Some respiratory symptoms, (primarily cough, phlegm, or chronic bronchitis) were seen in a few studies; and two studies found statistically significant decrements in baseline pulmonary functions, though most studies did not find changes in these parameters. There was little evidence detected for adverse effects of DE on other organ systems, including the cardiovascular system. The 2002 Diesel Document cautioned that interpretation of these epidemiologic studies is difficult because of some methodological problems that include incomplete information regarding effects of potentially confounding variables (smoking and exposure to other toxicants concurrently) and the short durations and low intensity of the exposures.

The 2002 EPA Diesel Document further noted that acute exposure of laboratory animals to DE had been shown to cause mild functional effects, but only at high concentrations ($\geq$ 6 mg/m^3 DPM) and durations (20 h/day; Pepelko et al., 1980a). However, short-term exposures to even

low levels of DE were found to elicit pathophysiological effects such as accumulation of DPM in lung tissue, inflammation, AM aggregation and accumulation near the terminal bronchioles, Type II cell proliferation, and thickening of the alveolar walls adjacent to AM.

Chronic DPM exposures were found to have little effects on survival in rodents. Some evidence of reduced body weight in rats was seen with exposure concentrations of $\geq$ 1.5 mg/m^3 DPM and durations of 16 to 20 h/day, 5 days/week for 104 to 130 weeks (Heinrich et al., 1995; Nikula et al, 1995). Species-specific changes in organ weights were reported with cats having decreased lung and kidney weights with exposure and rodents having increased lung weights, lung to body-weight ratios, and heart to body-weight ratios. The LOEL for these effects in rats was 1 to 2 mg/m^3 DPM for 7h/day, 5 days/week for 104 weeks (Brightwell et al., 1986; Heinrich et al., 1986a,b).

Chronic exposures were also found to impair pulmonary function in rodents, cats, and monkeys. Parameters affected by DE exposure included lung compliance, resistance, diffusing capacity, volume and ventilatory performance. The exposure levels at which pulmonary function was affected differed among species: 1.5 and 3.5 mg/m^3 DPM in rats (Gross, 1981; Mauderly et al., 1988; McClellan et al 1986), 4.24 and 6 mg/m^3 PDM in hamsters (Vinegar et al, 1980, 1981a,b), 11.7 mg/m^3 in cats (Pepelko et al, 1980b, 1981), and 2 mg/m^3 in cynomolgus monkeys (only level tested in this species; Lewis et al, 1989). Exposures were typically 7 to 8 h/day, 5 days/week for 104 to 130 weeks and resulted in restrictive lung disease in all species except monkeys. Gross (1981) estimated that observed changes in expiratory flow rates in rats indicated a LOEL of 1.5 mg/m^3 for chronic exposures. Obstructive airway disease was evidenced in monkeys exposed chronically to 2 mg/m^3 DE. This disparity with other species tested is probably due to differences in anatomy and physiology, dose delivered, dose retained, site of deposition, and effectiveness of clearance and repair mechanisms.

Histopathological effects have also been reported with chronic DE exposures. These typically included alveolar histiocytosis, AM aggregation, tissue inflammation, increase in PMNs, hyperplasia of bronchiolar and alveolar Type II cells, thickened alveolar septa, edema, fibrosis, emphysema, and lesions of the trachea and bronchi. These were accompanied by histochemical changes in lung including increases in lung DNA, total protein, alkaline and acid phosphatase, and glucose-6-phosphate dehydrogenase. Additionally, increased synthesis of collagen and release of inflammatory mediators have also been observed with chronic exposures.

There appears to be a threshold of exposure to DPM below which these histopathologic effects are not observed. Reported no observed effect levels (NOELs) include: 0.11 to 0.35 mg/m^3 for rats (Ishinishi et al., 1986, 1988); 0.25 mg/m^3 for guinea pigs (Barnhart et al., 1981, 1982); and 2 mg/m^3 for cynomolgus monkeys (only level tested in this species; Lewis et al., 1989) for exposures of 7 to 20 h/day, 5 to 5.5 days/week for 104 to 130 weeks.

Chronic exposures to DPM were further found to have an effect on airway clearance, which in large part determines the pathological effects. Alveolar macrophages phagocytose DPM as part of a multiphasic process of clearance. Exposures of $\geq$1 mg/m^3 DPM were shown to have a detrimental effect on clearance (Wolff et al, 1987; Wolff and Gray, 1980), the net effect being focal aggregations of particle-laden AMs in the peribronchiolar and alveolar regions and also the hilar and mediastinal lymph nodes. As mentioned above, species differences exist in anatomy, physiology, rate of uptake, deposition, clearance, size of AM population, rate of influx of AM and leukocytes, and the relative efficiencies for removal of particles by the mucociliary escalator and lymphatic transport system. Any decrease in AM function tends to reduce clearance. It is mostly particles that are persistently retained in the lungs that impair clearance and this occurs in F344 rats at a PM burden of 0.1 to 1 mg/g lung tissue (Health Effects Institute, 1995). Morrow (1988) estimated that AM loading of $\geq$60 μm^3 PM impairs clearance and $\geq$ 600 μm^3 causes clearance to cease. This results in agglomerated particle-laden AMs remaining in the alveolar region and particles translocating to the pulmonary interstitium.

Consistent with impairment of AM function and clearance, reduction of an animal's resistance to respiratory infection was found with exposure to DPM. This effect was seen after an acute exposure of 5 to 8 mg/m^3 for as little as 2 or 6 h. The effect is thought not to be due to direct impairment of the lymphoid or splenic immune systems. Both animal and human acute exposure data also suggest that DPM is a factor in the increasing incidence of allergic hypersensitivity. Both the nonextractable carbon core and the organic fraction of DPM were implicated in the effect. It was noted that synergies with DPM may increase the potency of known airborne allergens, and DPM was posited to act as an adjuvant in immune responses.

Chronic DE exposures in rats lasting from birth to 28 days of age were also shown to have behavioral effects on spontaneous locomotor activity and decrements in learning in adulthood (Laurie et al, 1980). These findings were corroborated by physiological evidence of delayed neuronal maturation (Laurie and Boyes, 1980, 1981). These studies, published in the early

1980s, used exposures of 6 mg/m^3 DPM for 8 h/day, 7 days/week. No recent studies have added to this literature. Also, based on the weight of evidence of a number of studies, essentially no effects were noted for reproductive and teratogenic effects in mice, rats, rabbits, and monkeys; for clinical chemistry and hematology in rat, cat, hamster, and monkeys; and for enzyme induction in the rat and mouse.

Key conclusions arrived at, based on the studies assessed in the U.S. EPA 2002 Health Assessment Document for Diesel Engine Exhaust, included: (1) short-term exposure to the DPM component of DE can result in allergenic inflammatory disorders of the airway; (2) acute occupational exposures to DE can cause respiratory symptoms of cough, phlegm, chest tightness and wheezing (all suggestive of an irritant mechanism) but do not generally cause pulmonary function decrements; and (3) pulmonary histopathology (principally fibrosis) and chronic inflammation are noncancer effects seen in laboratory animals, but noncancer effects in humans from long-term chronic exposures to DPM are not evident. Also, current knowledge indicates that the carbonaceous core of DPM is probably the causative agent of lung effects. Further, progressive impairment of AM is a factor in the extent of lung injury. Lung effects occur in response to DE exposures in several species and occur in rats at doses lower than those inducing particle overload and a tumorigenic response.

It is important to note that several DE toxicity studies cited in the EPA 2002 Diesel Document compared the effects of whole, unfiltered exhaust to those produced by the gaseous components of the exhaust. A comparison of the toxic responses in laboratory animals exposed to whole exhaust or filtered exhaust containing no particles demonstrates across studies that, when the exhaust is sufficiently diluted to limit the concentrations of gaseous irritants (NO_2 and SO_2), irritant vapors (aldehydes), CO, or other systemic toxicants, the diesel particles are clearly contributors to noncancer health effects, although additivity or synergism with the gases cannot be ruled out. These toxic responses are both functional and pathological and represent a cascading sequelae of lung pathology based on concentration and species. The diesel particles plus gas exposures produced biochemical and cytological changes in the lung that are much more prominent than those evoked by the gas phase alone. Such marked differences between whole and filtered DE are also evident from general toxicological indices, such as decreases in body weight and increases in lung weights, pulmonary function measurements, and pulmonary histopathology (e.g., proliferative changes in Type II cells and respiratory bronchiolar epithelium

fibrosis). Hamsters, under equivalent exposure regimens, have lower levels of retained DPM in their lungs than rats and mice and, consequently, less pulmonary function impairment and pulmonary pathology. These differences may result from lower DPM inspiration and deposition during exposure, greater DPM clearance, or lung tissue less susceptible to the cytotoxicity of deposited DPM.

The above past assessment findings, on the whole, tend to suggest the potential importance of DPM contributing to at least some ambient PM-related toxic effects, particularly in urban micro-environments with heavy diesel traffic. The findings of some DE- or DPM-related controlled human exposure studies are elaborated on below and then are further interrelated to pertinent laboratory animal studies discussed later in Section 7.5.3 (Particulate Matter Effects on Allergic Hosts).

Pulmonary function and inflammatory markers (as assayed in induced sputum samples or BAL) have been studied in human subjects exposed to either resuspended or freshly generated and diluted DPM. In one controlled human exposure study, Sandstrom and colleagues (Rudell et al., 1994) exposed eight healthy subjects in an exposure chamber to diluted exhaust from a diesel engine for 1 h with intermittent exercise. Dilution of the DE was controlled to provide a median NO_2 level of ~1.6 ppm. Median particle number was 4.3×10^6 /cm^3, and median levels of NO and CO were 3.7 and 27 ppm, respectively (particle size and mass concentration were not provided). There were no effects on spirometry or on airway closing volume. Five of eight subjects experienced unpleasant smell, eye irritation, and nasal irritation during exposure. BAL performed 18 h after exposure was compared with a control BAL performed 3 weeks prior to exposure. There was no control air exposure. Small, yet statistically significant, reductions were seen in BAL mast cells, AM phagocytic function, and lymphocyte CD4 to CD8+ cell ratios, along with a small increase in neutrophils. These findings suggest that DE may induce mild airway inflammation in the absence of spirometric changes. Although this study generated some potentially important information on the effect of DE exposure in humans, only one exposure level was used, the number of subjects was low, a limited range of endpoints was reported, and no comparisons to clean control exposures were provided. Several follow-up studies have been done by the same and other investigators.

Rudell et al. (1996) later exposed 12 healthy volunteers to DE for 1 h in an exposure chamber. Light work on a bicycle ergometer was performed during exposure. Random, double-

blinded exposures included exposures to clean air, DE, or DE with particle numbers reduced 46% by a particle filter. The engine used was a new Volvo model 1990, a six-cylinder direct-injection turbocharged diesel with an intercooler, run at a steady speed of 900 rpm during the exposures. It is hard to compare this study with others, because neither exhaust dilution ratios nor particle concentrations were reported. Based on concentrations of 27 to 30 ppm CO and of 2.6 to 2.7 ppm NO, however, estimated DPM concentrations likely equaled several mg/m^3. The most prominent symptoms during exposure were irritation of the eyes and nose, accompanied by an unpleasant smell. Both airway resistance and specific airway resistance increased significantly during the exposures. Despite the 46% reduction in particle numbers by the filter, effects on symptoms and lung function were not significantly reduced. A follow-up study on the usefulness of a particle filter confirmed the lack of effect of the filter on DE-induced symptoms (Rudell et al., 1999). In this study, 10 healthy volunteers also underwent BAL 24 h after exposure. Exposure to DE produced inflammatory changes in BAL, as evidenced by increases in neutrophils and decreases in macrophage phagocytic function in vitro. A 50% reduction in the particle number concentration by the particle filter did not alter these BAL cellular changes.

As reported in a series of studies (Rudell et al., 1990, 1996, 1999; Blomberg et al., 1998; Salvi et al., 1999), significant increases in neutrophils and B lymphocytes, as well as in histamine and fibronectin in airway lavage fluid, were not accompanied by decrements in pulmonary function. Salvi et al. (1999) exposed healthy human subjects to diluted DE (DPM = 300 $\mu g/m^3$) for 1 h with intermittent exercise. Bronchial biopsies obtained 6 h after DE exposure showed a significant increase in neutrophils, mast cells, and CD4+ and CD8+ T lymphocytes, along with upregulation of the endothelial adhesion molecules ICAM-1 and vascular cell adhesion molecule-1 (VCAM-1) and increases in the number of leukocyte function-associated antigen-1 (LFA-1+) in the bronchial tissue. Importantly, extra-pulmonary effects were observed in these subjects. Significant increases in neutrophils and platelets were found in peripheral blood following exposure to DE.

In a follow-up investigation of potential mechanisms underlying the DE-induced airway leukocyte infiltration, Salvi et al. (2000) exposed healthy human volunteers to diluted DE of 300 $\mu g/m^3$ on two separate occasions for (1 h each) in an exposure chamber. Fiber-optic bronchoscopy was performed 6 h after each exposure to obtain endobronchial biopsies and bronchial wash (BW) cells. These workers observed that diesel exhaust (DE) exposure enhanced

gene transcription of interleukin-8 (IL-8) in the bronchial tissue and BW cells and increased growth-regulated ontogeny-α protein expression and IL-8 in the bronchial epithelium; there was also a trend toward an increase in interleukin-5 (IL-5) mRNA gene transcripts in the bronchial tissue. Whether these effects were due to DPM or associated DE gaseous components (or both) could not be disentangled with the study design used.

Nightingale et al. (2000) reported inflammatory changes in healthy volunteers exposed to 200 $\mu g/m^3$ resuspended DPM for 2 h under resting conditions in a double-blinded study. Small but statistically significant increases in neutrophils and myeloperoxidase (an index of neutrophil activation) were observed in sputum samples induced 4 h after exposure to DPM in comparison to air. Exhaled CO was measured as an index of oxidative stress and was found to increase maximally at 1 h after exposure. These biochemical and cellular changes occurred in the absence of any decrements in pulmonary function, thus confirming that markers of inflammation are more sensitive than pulmonary function measurements.

Because of the concern about inhalation of ambient particles by sensitive subpopulations, (Nordenhäll et al., 2001) also studied the effect of a 1 h exposure to DE (containing 300 $\mu g/m^3$ DPM, 1.2 ppm NO_2, 3.4 ppm NO, 2.6 ppm HC, and 9.1 ppm CO) on 14 atopic asthmatics with stable disease and on inhaled corticosteroid treatment. At 6 h after exposure, there was a significant increase in airway resistance ($p < 0.004$) and in IL-6 in induced sputum ($p < 0.048$) following exposure to DE versus filtered air. At 24 h after exposure, there was a significant increase in the nonspecific airway responsiveness to inhaled methacholine. Although the DPM exposure level was high relative to ambient PM levels, these findings may be important, as noted by the authors, in terms of supporting epidemiologic evidence for increased asthma morbidity associated with episodic exposure to ambient PM.

The IL-6 increase seen here 6 h after DE exposure in asthmatic subjects parallels similar significant IL-6 increases in sputum 6 h after DE exposure of healthy subjects, suggesting that the IL-6 release represents an acute response of both healthy and asthmatic persons to DE exposures. Other work by Steerenberg, et al. (1998) showed that DE particles are effective in inducing release of IL-6 from human bronchial epithelial cells (see Section 7.4).

The role of antioxidant defenses in protecting against acute DE exposure has also been studied. Blomberg et al. (1998) investigated changes in the antioxidant defense network within the respiratory tract lining fluids of human subjects following diesel exhaust exposure. Fifteen

healthy, nonsmoking, asymptomatic subjects were exposed to filtered air or DE (containing 300 mg/m^3 DPM) for 1 h on two separate occasions at least 3 weeks apart. Nasal lavage fluid and blood samples were collected prior to, immediately after, and 5.5 h postexposure. Bronchoscopy was performed 6 h after the end of DE exposure. Nasal lavage ascorbic acid concentration increased 10-fold during DE exposure, but returned to basal levels 5.5 h postexposure. Diesel exhaust had no significant effects on nasal lavage uric acid or GSH concentrations and did not affect plasma, bronchial wash, or BAL antioxidant concentrations or malondialdehyde or protein carbonyl concentrations. The authors concluded that the acute increase in ascorbic acid in the nasal cavity induced by DE may help prevent further oxidant stress in the upper respiratory tract of healthy individuals.

Seagrave et al. (2002) evaluated the inflammation and cytotoxicity created by exposure to exhaust from a number of vehicles including automobiles, SUVs, and pickup trucks from 1976 to 2000. Both PM and vapor-phase semivolatile organic compound (SVOC) fractions were collected, both at room temperature and in a cold environment. The PM and SVOC fractions were recombined and tested for toxicity in male F344/CrlBR rats at age ~11 weeks. The emission samples were intratracheally instilled at doses of 0.1 to 3 mg/rat. BAL was collected at 4 h for cytokine endpoints and collected at 24 h for examination of histopathology and lavage parameters. Three different assays, histopathology, LDH and protein, were used to determine the cytotoxicity of the emission samples. Total protein in BAL and LDH similarly ranked cytotoxicity of the samples, and histology results created similar rankings, except for gasoline, which was ranked least toxic by LDH and protein and fourth by histopathology. The authors uniformly scaled the potencies and ranked the cytotoxicity as: gasoline engine emitting white smoke > gasoline engine emitting black smoke > high emitter diesel > normal diesel 72 °F > current diesel at 30 °F > normal gasoline 30 °F > normal gasoline 72 °F. Inflammatory endpoints examined were total leukocytes, macrophages, PMNs/mL BALF , MIP-2, TNF-α, and histopathology. There was good agreement among data for total leukocytes, PMNs, and macrophages for which the three highest emissions were ranked: gasoline engine emitting white smoke > gasoline engine emitting black smoke = high emitter diesel. These three exhausts as had equally high inflammatory effects (as indicated by increases in MIP-2, but were less consistent for effects on TNF-α, it being suppressed in some samples and slightly increased in others. Uniformly scaled potencies for inflammation using total leukocytes, PMA, macrophages,

histopathology, and MIP-2 endpoints were: gasoline engine emitting white smoke > gasoline engine emitting black smoke > high emitter diesel > current diesel at 30 °F > normal gasoline 72 °F > normal gasoline 30 °F > normal diesel 72 °F.

7.3.6 Ambient Bioaerosols

Bioaerosols are airborne particles consisting of large molecules or volatile compounds that are living, contain living organisms, or have been released from living organisms. Major types of bioaerosol particles encountered in ambient (outdoor) air, indoor air, and/or in contaminated indoor or outdoor dusts that can be resuspended into air include: (1) intact pollen and pollen fragments; (2) fungi, their spores, and other fungal byproducts; (3) humic-like substances (HULIS), which include bioaerosols, biomass combustion generated and secondary organic compounds and other plant debris; (4) certain animals or associated debris, e.g., dust mites or their excreta, shed mammalian or avian skin cells, etc.; (5) bacteria or fragments thereof, e.g., endotoxins consisting of proteins and lipopolysaccharides (LPS) that comprise portions of cell walls of Gram-negative bacteria; (6) (1→3)-β-D-glucan, a polyglucose compound in the cell walls of Gram-positive bacteria, fungi, and plants; and (7) viruses.

Such particles are suspended and/or transported in air as distinct separate entities or adhered to other organic and nonorganic particles or in water droplets. Biological particles can range in size from 0.01 μm (viruses) to > 20 μm (some pollen), with the smaller ones < 10.0 μm being inhalable and, upon inhalation, being capable of penetrating into tracheobronchial (TB) and alveolar (A) regions of the lower respiratory tract — thus creating potentially serious health problems for sensitive human populations.

The relationship between bioaerosol exposure and illness is complex. Numerous studies published since the 1996 PM AQCD have produced extensive new information which has greatly enhanced our knowledge regarding environmental occurrence of such biological aerosols, their health effects, and possible combined influences of their being copresent along with other biological and/or nonbiological particles in ambient air. In particular, there is growing recognition that bioaerosols may contribute to health effects related to ambient PM exposures partly through their own direct toxic effects and/or in combination with other PM that carries biologically-derived materials which may elicit untoward effects.

Appendix 7B recapitulates a number of key points regarding ambient bioaerosols derived from the 1996 PM AQCD and goes on to update and integrate information derived from newer studies, as well. This includes background information on types and sources of ambient bioaerosols, factors affecting their dispersal and airborne concentrations, and both epidemiologic and toxicologic evaluations of health effects associated with different classes of them. As such, some of the materials discussed may have been touched on in other chapters, but are brought together in Appendix 7B and summarized here to provide a coherent overall picture related to bioaerosols as potentially important contributors to ambient PM-related health effects.

A large number of studies show relationships between exposure to bioaerosols and airways inflammation and other signs/symptoms of allergic/asthmatic responses. Generally these exposures are most often associated with: certain occupational settings (cotton milling, grain workers, feed mill employees, farmers); humid and poorly ventilated indoor environments where moisture/dampness can harbor these organisms; and households having domestic animals/pets (Wheatley and Platts-Mills, 1996).

Bioaerosols mainly tend to be in the coarser fraction of ambient PM, but some (e.g., fungal spores, pollen fragments) are in the fine fraction as well. Flowering plants, trees, and grasses produce pollen, the species and quantity being determined by region, season, and meteorological factors (especially humidity/moisture levels). For example, increased levels of grass pollen allergens following thunderstorms have been linked to increased levels of asthma attacks i.e., "thunderstorm asthma" (Bellomo et al., 1992; Ong, 1994; Rosas et al., 1998; Schäppi et al., 1999). Wind-pollinated plants produce large grains >10-20 μm, which when intact, deposit in upper airways, inducing allergic rhinitis. However, rupture of these grains following rain events generates allergen-containing cytoplasmic pollen fragments that constitute respirable particles (~0.1 to 5.0 μm) associated with exacerbation of asthma.

Very importantly, it is now known that interactions between aerosolized allergen-laden pollen debris and other types of ambient airborne particles occur. Pollen, in addition to containing cytoplasmic allergens, has also been shown to be a carrier of other allergenic materials. Several different types of immunoactive, allergenic materials (e.g., Gram−negative and Gram-positive bacteria; endotoxin, fungi) have been shown to be associated with grass and tree pollens in Poland (Spiewak, 1996a,b). Also, Taylor et al. (2002) suggest that the polycyclic hydrocarbon component of diesel exhaust may interact with allergen-laden pollen debris in a

synergistic combination to explain, in part, the notable increase in the prevalence of pollen-induced asthma during the past 50 years. Ormstad et al. (1998) and Knox et al. (1997) demonstrated that DPM (especially < 2.5 μm) can act as a carrier for plant (and animal) allergens and, further, may act as a mechanism whereby plant allergens can become concentrated in air and trigger asthma attacks. Additionally, evidence from Behrendt et al. (1992, 1995, 1997, 2001) show that pollen grains may incorporate other atmospheric pollutants that alter the pollen surface, leading to exocytosis of proteinaceous material and increased allergen release. As for health-related studies of pollen effects (see Table 7B-2), Hastie and Peters (2001) evaluated in vivo ragweed allergen exposure (via bronchoscopic segmented ragweed challenge) effects on ciliary activity of bronchial epithelial cells harvested 24 h after challenge in nonallergic human adults and in allergic subjects with severe inflammatory response. Allergic subjects with mild inflammatory changes showed slight increases in albumin and doubling of bronchoalveolar cell levels whereas allergic subjects with severe inflammatory changes showed a 12-fold increase in albumin and a 9-fold increase in bronchoalveolar cell levels.

In another study of mice, a mixture of DPM and Japanese cedar pollen caused increased IgE and IL-4 production compared to pollen alone (Fujimaki et al., 1994). Synergistic relationships were also observed with DPM and ragweed allergen in the production of specific cytokines (Diaz-Sanchez et al., 1997).

In an epidemiologic study in the Netherlands, Brunekreef et al. (2000) found a positive correlation between mortality rates and pollen concentration, suggesting that pollen-associated acute exacerbation of allergic inflammation may cause death among some compromised individuals. Increases in hospitalizations for asthma have also been reported to be correlated with pollen exposure in Mexico City (Rosas et al., 1998) and London (Celenza et al., 1996), as have increased asthma incidence and medication use (Delfino et al., 1996, 1997).

In summary, newly available information indicates release of allergen-laden material from pollen-spores in respirable-sized aerosols; suggests possible ways by which binding of such material to other airborne particles (e.g., DPM) may concentrate such allergens in ambient air or, once inhaled, jointly exacerbate allergic reactions in susceptible human populations; and indicates that pollen itself may act as a carrier for other allergenic materials. Thus, new information about the synergistic relationship between plant allergens and other forms of PM

suggest a possible mechanism which may explain, in part, the increased morbidity (especially asthma) and mortality associated with increased pollen levels.

In addition to pollen, other plant-related bioaerosols are generated by human activities such as the storage, handling and transport of plant material; and they, too, can cause adverse health effects. A growing database suggests that plant debris is a significant contributor to organic aerosols at continental sites. This debris has a considerable component that is insoluble. Humic-like substances (HULIS), originating from biomass fires and secondary atmospheric reactions, comprise up to 24% of organic carbon in some aerosol samples. In many areas in the western United States there are episodic or seasonal increases in plant-derived bioaerosol material from biomass burning emissions. These controlled agricultural burns, forest fires and domestic wood burning all contribute to ambient PM in these regions.

Fungi, growing on dead organic matter, are ubiquitous and produce huge quantities of aerosols, including spores, body fragments, and fragments of decomposed substrate material. Fungal spores, ranging in size from 1.5 μm to > 100 μm, form the largest and most consistently present component of outdoor bioaerosols. These cause allergic rhinitis and asthma, while allergic fungal sinusitis and allergic bronchopulmonary mycoses are caused by fungi colonizing thick mucus in the sinuses or lungs of allergic individuals. Yang and Johanning (2002) have shown that, once an individual is sensitized to the fungi, small concentrations can trigger an asthma attack or other allergic response.

Several studies have found relationships between exposure to fungi and their byproducts in respiratory illnesses and immune pathology (Hodgson et al., 1998; Tuomi et al., 2000; Yang and Johanning, 2002). Larsen et al. (1996) showed non-immunological histamine release from leukocytes exposed to a suspension of fungal spores and hyphal fragments. Some fungal byproducts have also been shown to stop ciliary activity in vitro and may act to produce general intoxication by macroorganisms through the lung tissue or to enhance bacterial or viral infection (Piecková and Kunová, 2002; Yang and Johanning, 2002).

Fungal concentrations in most parts of the world have a pattern of peak levels in the summer and early fall, but low levels in the winter months. Outdoor air fungal composition affects culturable fungal propagules indoors, but it appears that the levels of fungi inside do not just reflect the outdoor levels. Analogous to pollen exposures, fungal spore exposures have been

positively correlated with asthma hospital admissions of children in Mexico City (Rosas et al., 1998) and with asthma deaths in Chicago (Targonski et al., 1995). Airborne fungal concentrations of $\geq$1000 spores/m^3 were reported to be associated with asthma deaths among 5- to 34-year-old persons in Chicago between 1985 and 1989 (Targonski et al., 1995). The odds of death occurring on days with airborne fungal concentrations of $\geq$1000 spores/m^3 were 2.16 times higher than mortality on other days.

All classes of animals including humans, house pets, wild and domesticated birds, and insects produce bioaerosols capable of producing hypersensitivity diseases. Dust mites and cockroaches are prolific insects from which fecal material and shed body parts create allergens that are a major causes of sensitization in children (Burge, 1995).

Bacteria and viruses are infectious agents that are released from hosts in droplets exhaled from the respiratory tract. The antigenic component of bacteria can be the whole living bacteria or enzymes or cell wall components of the bacteria. Viruses, composed of either DNA or RNA surrounded by a protein coat, utilize living cells for reproduction. Virus are extremely small ($<<$1 μm), but the infectious droplets are usually larger (1 to 10 μm).

Endotoxins are present in the outer cell membrane of gram-negative (Gram -) bacteria. Heederik et al. (2000) noted that animal feces and plant materials contaminated with bacteria contribute most to organic dust-related endotoxin exposure. Although there is strong evidence that inhaled endotoxin plays a major role in the toxic effects of bioaerosols encountered in the work place (Castellan et al., 1984, 1987; Rose et al., 1998; Vogelzang et al., 1998; Zock et al., 1998), it is not clear as to what extent typical ambient concentrations of endotoxin are sufficient to produce toxic pulmonary or systemic effects in healthy or compromised individuals.

Endotoxins act on cells in the respiratory system by binding to receptors and triggering production of cytokines, which initiates a cascade of inflammation, smooth muscle constriction, and vasodilation (Young et al., 1998). Table 7B-3 summarizes studies of the respiratory effects of inhaled endotoxin-laden ambient bioaerosols. Some new occupational exposure studies suggest declines in lung function due to exposure to endotoxins in pig farm waste (Vogelzang et al., 1998) and potato processing (Zock et al., 1998). Also, increases in BAL lymphocytes were observed in life guards exposed to endotoxins at a swimming pool (Rose et al., 1998). However, these studies do not rule out the effects of other agents in the complex airborne

organic aerosols that may contribute to the functional and cellular effects observed. Still, the authors noted that their results support the selection of the lower of two proposed (Clark, 1986; Palchak et al., 1988) occupational exposure threshold levels of 30 or 100 ng/m^3 for airborne endotoxin.

Two German cities 80 km apart with a differing prevalence of hay fever and allergic sensitization in children were studied for the possible effects of endotoxin (Heinrich et al., 2002a,b), but the researchers could not attribute observed differences between the towns in respiratory disease prevalence to endotoxin levels. Later work by this group showed higher concentration and absolute mass of endotoxin in coarse-mode particles versus fine particles. Levels of endotoxin were also seasonal, demonstrating increased levels in late spring/summer and lower levels in winter.

Dose-response studies in healthy human adults exposed to doses ranging up to 50 μg endotoxin, by the inhalation route, suggested a threshold for pulmonary and systemic effects for endotoxin between 0.5 and 5.0 μg (Michel et al., 1997). Inhalation in heterodisperse droplets with a MMAD of 1 to 4 μm of 5 or 50 μg of LPS, but not 0.0 or 0.5 μg increased PMNs in blood and sputum. Another controlled human exposure study of endotoxin, involving inhalation of lipopolysaccharide (LPS: the purified derivative of endotoxin) by known smokers showed increases in myeloperoxidase and eosinophilic cationic protein, decreases in FEV_1 and FVC, and irritation, dry cough, breathlessness, and tiredness at a LPS dose of 40 μg (Thorn and Rylander, 1998a).

Also, Monn and Becker (1999) also examined effects of size fractionated outdoor PM on human monocytes and found cytokine induction characteristic of endotoxin activity in the coarse-size fraction but not in the fine fraction.

Certain gram-positive bacteria, fungi, and plants contain the polyglucose compound (1→3)-β-D-glucan in their cells walls, which has been shown to induce stimulation of the reticuloendothelial system, activation of PMNs, AMs, and complement. Heederik et al. (2000) found T-lymphocyte activation and proliferation with glucan exposure of experimental animals. In homes in Sweden where (1→3)-β-D-glucan levels ranged between 0 and 19 ng/m^3, Thorn and Rylander (1998b) found that there was a significantly larger number of atopic subjects in the > 65 year old group exposed to > 3 ng/m^3 (1→3)-β-D-glucan in their homes. Rylander (1996) also found that an acute exposure to (1 → 3)-β-D-glucan can produce symptoms of airway

inflammation in normal human subjects without a history of airway reactivity after exposing subjects to 210 ± 147 ng/m^3 (1 → 3)-β-D-glucan for 3 separate 4 h sessions 5 to 8 days apart.

Douwes et al. (1998) examined the relationship between exposure to (1 → 3)-β-D-glucan and endotoxins and peak expiratory flow (PEF) in children (ages 7 to 11 years) with and without chronic respiratory symptoms. As indicated by linear regression analysis, peak expiratory flow variability in the children with chronic respiratory symptoms was strongly associated with (1→3)-β-D-glucan levels in dust from living room floors. The association was strongest for atopic children with asthma.

Thus, new research is focusing on the bioaerosol component of ambient PM. Findings include a greater-than-realized impact of pollen on asthma, and synergistic associations between pollen and other PM, with the potential for increased risk of adverse health effects. Fungi, and especially the spores, are the largest component of outdoor bioaerosols and have been linked to allergic rhinitis, asthma, sinusitis, and allergic bronchopulmonary mycoses. Much research is being directed at characterizing the mechanism by which bacterial endotoxins and (1→3)-β-D-glucan cause adverse health effects, especially in compromised individuals.

Of much importance are the seasonal variations in ambient air concentrations of all types of airborne allergens (both plant- and animal-derived) typically observed in temperate climate areas. Typically, (given that warmer, humid conditions tend to facilitate pollen, fungal and bacterial growth) outdoor levels of pollen fragments, fungal materials, endotoxins, and glucans all tend to increase in the spring/summer months and decrease to low ambient levels in late fall/winter months in most U.S. and other temperate areas. Also of much importance are increased levels of cellulose and other plant debris in respirable size fractions of ambient aerosols during the spring and summer months — plant materials that can act as carriers for allergenic materials (bacterial, fungal, etc.). The copresence in ambient air of other biological particles capable of acting as carriers of such allergens would probably enhance the risk of allergic/asthmatic reactions to them. Pertinent to this, it is of interest to note, that endotoxin concentrations tend to be higher in coarse fraction ambient PM samples than in fine (< 2.5 μm) ambient PM samples; but endotoxin concentrations are typically very low, rarely exceeding 0.5 EU/m^3.

7.3.7 Summary of Respiratory Effects

The respiratory effects of PM having varying physical and chemical characteristics have been extensively studied for more than 30 years using a wide range of techniques and with exposure durations ranging from brief periods to months. The most extensively studied materials have been sulfates and acid aerosols formed as secondary pollutants in the atmosphere. Fly ash from coal-fired power plants or other coal-combustion sources has been less extensively studied. The toxicological data available today provide little basis for concluding that these specific PM constituents have substantial respiratory effects at current ambient levels of exposure. Recently, ROFA, a very specific kind of PM, has been studied extensively and found to produce a range of respiratory effects, especially lung inflammation at higher concentrations or doses.

Recent studies evaluating controlled human exposures to concentrated ambient particles (CAPs) from diverse locations (e.g., Boston, New York City , Los Angeles, Toronto, and Chapel Hill, NC) have found little or no effects on pulmonary function or respiratory symptoms in healthy human adults acutely exposed (for 2 h) to CAPs concentrations that ranged from about 25 up to about 300 $\mu g/m^3$. Some indications of mild lung inflammation were reported with such exposures in some of the studies, but not others. Analogous controlled exposures to CAPs of rats, hamsters, and dogs at concentrations varying across a range of ~100 to 1000 $\mu g/m^3$ for 1-6 h/day for 1 to 3 days yielded similar minimal effects on respiratory functions, but some signs of mild inflammation in normal healthy animals and somewhat enhanced indications of lung inflammation in at least one compromised animal model of chronic bronchitis. Another study found some indications of mild impairment of lung immune defense functions and exacerbation of bacterial infection with an acute (3 h) exposure of rats to New York City CAPs (at 100-350 $\mu g/m^3$). There is also new evidence for the transition metal components of ROFA and ambient PM from diverse locations having a mediating role in producing injury.

There still remains, however, a critical need for the systematic conduct of studies of the potential respiratory effects of major components of PM from different regions of the U.S., in recognition that PM of different composition and from different sources can vary markedly in its potency for producing different respiratory effects.

7.4 CARDIOVASCULAR AND RESPIRATORY PATHOPHYSIOLOGY AND TOXICITY: IN VITRO PM EXPOSURES

7.4.1 Introduction

Toxicological studies play an important role in providing evidence by which to evaluate the biological plausibility of health effects associations with ambient PM exposure observed in epidemiologic studies. At the time of 1996 PM AQCD (U.S. Environmental Protection Agency, 1996a) little was known about potential mechanisms that could explain associations between morbidity and mortality and ambient airborne PM observed in human populations studies. One of the difficulties in trying to sort out possible mechanisms is the nature of ambient PM mixes. Ambient PM has diverse physicochemical properties, ranging from physical characteristics of the particles to chemical components in or on the surface of the particles. Any one of these properties could change at any time in the ambient exposure atmosphere, making it difficult to duplicate actual properties of ambient PM in a controlled experiment. As a result, controlled exposure studies have as yet neither clearly identified those particle properties nor specific mechanisms by which ambient PM may affect biological systems. However, new in vitro toxicologic studies that have become available since the 1996 PM AQCD have provided additional information useful to help explain how ambient particles may exert toxic effects on the respiratory and cardiovascular systems. Such studies are summarized in Tables 7-10 (ambient PM) and 7-11 (ROFA and other combustion source PM) and are discussed in the next several subsections.

In vitro exposure is a useful technique by which to obtain information on potentially hazardous PM constituents and mechanisms of PM injury, especially when only limited amounts of PM test material are available. For example, respiratory epithelial cells lining the airway lumen have been featured in numerous studies involving airborne pollutants and show inflammatory responses similar to that of human primary epithelial cultures. Also, alveolar macrophage cells from humans, rats, or other species have been employed in vitro to evaluate effects on phagocytosis and various other aspects of lung defense mechanisms. Limitations of in vitro studies include possible alterations in physiochemical characteristics of PM because of collection and resuspension processes, exposure conditions that do not fully simulate air-cell interface conditions within the lungs, and difficulties in estimating comparable dosage delivered to target cells in vivo. Also, doses delivered in vitro, like intratracheal administration, can be

TABLE 7-10. IN VITRO EFFECTS OF AMBIENT PARTICULATE MATTER AND PARTICULATE MATTER CONSTITUENTS

Species, Cell Type, etc. [a]	Particle or Constituent [b]	Cell Count	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
BEAS-2B Primary culture human tracheal and bronchial epithelial cells	TSP (Provo, Utah)	2×10^5 cells/mL	TSP filter samples (36.5 mg/mL) agitated in deionized H_2O_2 for 96 h, centrifuged at 1200 g for 30 min, lyophylized and resuspended in deionized H_2O_2 or saline 100 - 500 µg/well	N/A (TSP samples, comprised 50 to 60% PM_{10})	Sacrificed at 24 h	Provo particles caused cytokine-induced neutrophil-chemoattractant-dependent inflammation of rat lungs; Provo particles stimulated IL-6 at 500 µg/mL and IL-8 at ≥ 200 µg/mL, increased IL-8 mRNA at 500 µg/mL and ICAM-1 at 100 µg/mL in BEAS-2B cells, and stimulated IL-8 secretion at ≥ 125 µg/mL in primary cultures of human tracheal and bronchial epithelial cells; cytokine secretion was preceded by activation of NF-κB and was reduced by SOD, DEF, or NAC; quantities of Cu^{2+} found in Provo particles replicated the effects	Kennedy et al. (1998)
BEAS-2B	PM_{10} extract (Provo, UT)		125, 250, 500 µg/mL	PM_{10}	2 and 24 h	Dose-dependent increase in IL-6 and IL-8 induced at all doses after 24 h for cells by particles collected while steel mill in operation (years 1 and 3). Increase noted for year 2 for particles taken during plant closure, but not dose-dependent; and particles collected during plant closure had the lowest concentrations of soluble Fe, Cu, and Zn. Cytotoxicity seen at 500 µg/mL.	Frampton et al. (1999)
BEAS-2B	(Provo, UT) TSP soluble and insoluble extract		500 µg/mL	TSP	24 h	Water soluble fraction caused greater release of IL-8 than insoluble fraction. The effect was blocked by deferoxamine and presumably because of metals (Fe, Cu, Zn, Pb).	Ghio et al. (1999a)
NHBE BEAS-2B	Utah Valley PM_{10} extract		50, 100, 200 µg/mL	PM_{10}	24 h	Dose-dependent increase in expression of IL-8 produced at ≥ 50 µg/mL by particles collected when the steel mill was in operation; effects seen at lowest dose tested.	Wu et al. (2001)

TABLE 7-10 (cont'd). IN VITRO EFFECTS OF AMBIENT PARTICULATE MATTER AND PARTICULATE MATTER CONSTITUENTS

Species, Cell Type, etc. [a]	Particle or Constituent[b]	Cell Count	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
Human AM	PM_{10} extract (Provo, UT)	2×10^5 cells/mL	500 µg/mL	PM_{10}	24 h	AM phagocytosis of (FITC)-labeled Saccharomyces cerevisiae inhibited 30% by particles collected before steel mill closure.	Soukup et al. (2000)
Human and rat AM	Four urban air particles (UAP): St. Louis; Wash, DC; Ottawa ERC–93; Dusseldorf). ROFA (Florida) MSH Vol. Ash DPM Silica	2.5×10^5 cells/mL	Urban and DPM: 12, 27, 111, 333, or 1000 µg/mL SiO_2 and TiO_2: 4, 12, 35, 167, or 500 µg/mL Fe_2O_3: 1:1, 3:1; 10:1 particles/cell ratio	Urban particles: 0.3-0.4 µm DPM: 0.3 µm ROFA: 0.5 µm MSH Vol. Ash: 1.8 µm Silica: 05-10 µm TiO_2: < 5 µm Latex: 3.8 µm	2 h for cytotoxicity, 16-18 h for cytokine assay; chemiluminescence at 30 minutes	UAP-induced cytokine production (TNF, IL-6) in AM of both species that is not related to respiratory burst or transition metals but may be related to LPS (blocked by polymyxin B but not DEF). The effects were seen in human AM at UAP concentrations of ≥ 56 µg/mL and in rat AM at all exposures. ROFA induced strong chemiluminescence (all conc. in humans and ≥ 35 µg/mL in rats) but had no effects on TNF production.	Becker et al. (1996)
Human AM and blood monocytes M and F 20 - 35 year	Urban air particles (UAP): St. Louis SRM 1648; Washington, DC, SRM 1649; Ottawa, Canada, EHC-93 ROFA (Florida #6) MSH Vol. Ash	2×10^5 cells/mL	33 or 100 µg/mL	0.2 to 0.7 µm	3, 6, or 18-20 h	AM and MO phagocytosis inhibited by exposure to 100 µg/mL UAP for 18 h. UAP caused decreased expression of β_2-integrins involved in antigen presentation and phagocytosis in the AMs exposed to 100 µg/mL.	Becker and Soukup (1998)
Human lung epithelial (A549) cells ØX174 RFI DNA	Urban particles: SRM 1648, St. Louis SRM 1649, Washington, DC	20,000 cells/cm^2	100 µg/cm^2 for Fe mobilization assay	SRM 1648: 50% < 10 µm SRM 1649: 30% < 10 µm	Up to 25 h	Single-strand breaks in DNA were induced by PM only in the presence of ascorbate, and correlated with amount of Fe that can be mobilized; ferritin in A549 cells was increased with treatment of PM suggesting mobilization of Fe in the cultured cells.	Smith and Aust (1997)

TABLE 7-10 (cont'd). IN VITRO EFFECTS OF AMBIENT PARTICULATE MATTER AND PARTICULATE MATTER CONSTITUENTS

Species, Cell Type, etc. [a]	Particle or Constituent[b]	Cell Count	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
Rat AM	UAP (St. Louis) DPM	1×10^6 for TNF-α secretion; 3×10^6 cells/mL for gene egression	25 to 200 µg/mL	DPM: 1.1–1.3 µm	2 h incubation; supernatant collected following 18 h of culture	Dose-dependent increase in TNF-α, IL-6, CINC, MIP-2 gene expression by UAP but not DPM (TNF-α increase at all doses with peak at 200 µg/mL). Cytokine production not related to ROS but inhibited by polymyxin B; LPS detected on UAP but not DPM. Endotoxin responsible for cytokine gene expression induced by UAP in AM. Increase in gene expression determined semiquantitatively.	Dong et al. (1996)
Rat AM	PM_{10} (from Mexico City 1993); MSH Vol. Ash		10 µg/cm^2	< 10 µm	24 h	PM_{10} stimulated AMs to induce up-regulation of PDGF ∝ receptor on myofibroblasts. Endotoxin and metal components of PM_{10} stimulate release of IL-β. This is a possible mechanism for PM_{10}-induced airway remodeling.	Bonner et al. (1998)
Human erythrocytes; mouse monocyte-macrophage cell RAW 264.7	$PM_{10\text{-}2.5}$; $PM_{2.5}$ (Rome, Italy)	1×10^6 cells/mL Raw cells	5 doses across range of 0 to 80 µg/mL saline solution	$PM_{2.5}$ $PM_{10\text{-}2.5}$	1 h for hemolysis 24 h for oxidative stress	Increased hemolysis of erythrocytes linearly related to $PM_{2.5}$ doses across 0 to 80 µg/mL range, but not to $PM_{10\text{-}25}$ below 50 µg/mL. However, little difference seen between $PM_{2.5}$ and $PM_{10\text{-}2.5}$ effects based on surface per volume unit of suspension, suggesting that oxidative stress on cell membranes is related to PM surface area. $PM_{2.5}$ also caused dose-dependent decrease in viability and increased markers of inflammation in RAW 264.7 cells, but significance levels not reported..	Diociaiuti et al. (2001)
Peripheral blood monocytes	Organic extract of TSP, Italy	1×10^4 cells/mL	5, 10, 21, 42, 85, 340 µg	N/A, collected from high-volume sampler (60 m^3/h)	2 h	Superoxide anion generation was inhibited at a particulate concentration of 0.17 mg/mL (340 µg) when stimulated with PMA; dose-dependent increase in LDH; at 0.17 mg/mL LDH increased 50%; disintegration of plasma membrane.	Fabiani et al. (1997)
ØX174 RF1 DNA	PM_{10} (Edinburgh, Scotland)		3.7 or 7.5 µg/assay	PM_{10}	8 h	Significant free radical activity on degrading supercoiled DNA at both concentrations; mainly because of hydroxyl radicals (inhibited by mannitol); Fe involvement (DEF-B conferred protection); more Fe^{3+} was released compared to Fe^{2+}, especially at pH 4.6 than at 7.2.	Gilmour et al. (1996)

TABLE 7-10 (cont'd). IN VITRO EFFECTS OF AMBIENT PARTICULATE MATTER AND PARTICULATE MATTER CONSTITUENTS

Species, Cell Type, etc. [a]	Particle or Constituent[b]	Cell Count	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
Supercoiled DNA	PM_{10} from Edinburgh, Scotland		996.2 ± 181.8 µg/filter in 100 µL	PM_{10}	8 h	PM_{10} caused damage to DNA; mediated by hydroxyl radicals (inhibited by mannitol) and iron (inhibited by DEF). Clear supernatant has all of the suspension activity. Free radical activity is derived either from a fraction that is not centrifugeable on a bench centrifuge or that the radical generating system is released into solution.	Donaldson et al. (1997)
Human AM from smokers (mean age 68) and nonsmokers (mean age 72), male and female	EHC-93 (Ottawa) ROFA latex beads carbon particles	0.5×10^6 cells/mL	0.01-0.1 mg/mL	< 10 µm 0.1,1, and 10 µm	2, 4, 8, 12, and 24 h (only 24 h data shown)	TNF-α increased at 0.01 to 0.1 mg/mL EHC-93 and at 0.1 mg/mL latex, carbon and ROFA. EHC93 at 0.1 mg/mL increased levels of IL6, IL-1β, MIP-1 α, and GM-CSF	Van Eeden, et al. (2001)
Human AM from age 62 ± 5 smokers Rabbit AM, 6 weeks old	EHC-93 (Ottawa)	0.5×10^6 cells/mL	0.01-0.1 mg/mL	4-5 µm mass median diameter	2, 4, 8, 12, and 24 h (only 24 h data shown)	0.1 mg/mL produced significant increase in TNF-α. Instillation of supernatants from human and rabbit PM-exposed AMs into the lungs of rabbits caused increases in circulating PMNs and circulating band cells and shortening the transit time of PNMs through mitotic and postmitotic bone narrow pools.	Mukae et al. (2000)
Rat AM and AM primed with LPS	$PM_{2.5}$ (Boston) Indoor and outdoor	1×10^6 cells/mL	100 µg/mL	< 2.5 µm	20 h	Increased TNF production in both indoor and outdoor exposures. LPS-primed AMs had greater responses. Indoor $PM_{2.5}$ caused significantly more TNF production than outdoor $PM_{2.5}$.	Long et al. (2001)
Rat AM and AM primed with LPS	Boston CAPS, separated in soluble/insoluble fractions SRM1649, iron oxide, carbon black, diesel dust	2.4×10^6 cells/mL	100 µg/mL	Fe, CV and DD all < 1 µm, UAP was 30% larger	20 h	Priming enhanced AM release of TNF and MIP-2 in response to UAP and some CAPs samples. Other CAPs and CB, DD, Fe did not induce cytokines. Toxicity associated with insoluble fractions. The activation state of the AM determines which particle-associated components are most bioactive.	Imrich et al. (2000)
Mouse AM	Boston CAPs	1×10^6 cells/mL	~5-120 µg/mL	≤ 2.5 µm	5 h	Soluble and insoluble CAPs caused MIP-2 and TNF-α production. Cytokine induction and endotoxin content was associated with the insoluble fraction. PB neutralization of endotoxin abrogated > 80% of TNF-α induction, but inhibited MIP-2 production by only 40%.	Ning et al. (2000)

TABLE 7-10 (cont'd). IN VITRO EFFECTS OF AMBIENT PARTICULATE MATTER AND PARTICULATE MATTER CONSTITUENTS

Species, Cell Type, etc. [a]	Particle or Constituent [b]	Cell Count	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
Rat AM	Switzerland PM collected during the four seasons.	4×10^5/mL		< 10 µm	40 h	All exposures produced significant toxicity in MTT assay. Spring and summer samples induced the most TNF-α. Oxidative response was greatest in non-winter months.	Monn et al. (2003)
Human PMN	Aqueous and organic extracts of TSP (from Dusseldorf and Duisburg, Germany)	1×10^6 cells/mL	0.51 and 0.78 mg/mL (aqueous extracts) 0.42 – 0.65 mg/mL (organic extracts)	Collected by high volume sampler, 90% < 5 µm, 50% < 1µm, max at 0.3-0.45 µm Water and dichloromethane used to yield aqueous and organic extracts	Up to 35 min	PM aqueous extract significantly stimulated the production and release of ROS at 0.42 mg/mL in resting but not in zymosan-stimulated PMN. The effects of the PM extracts were inhibited by SOD, catalase and sodium azide (NaN_3); Zymosan-induced LCL is inhibited by both types of extracts, but aqueous extracts have a stronger inhibitory effect. Phagocytosis not affected.	Hitzfeld et al. (1997)
RLE-6TN cells (type II like cell line)	$PM_{2.5}$ (Burlington, VT); Fine/ultrafine TiO_2	1×10^6 cells/mL	α-quartz, [0-200 µg/mL] 1, 2.5, 5, 10 µg/mL $PM_{2.5}$, or up to 5 µg/mL TiO_2	$PM_{2.5}$: 39 nm Fine TiO_2: 159 nm UF TiO_2: 37 nm	24 and 48 h exposure	PM increases in c-Jun kinase activity at ≥ 10 µg/mL, levels of phosphorylated c-Jun immunoreactive protein at ≥ 5 µg/mL; and transcriptional activation of activator protein-1-dependent gene expression; elevation in number of cells incorporating 5'-bromodeoxyuridine at ≥ 1 µg/mL.. UF TiO_2 increased c-Jun kinase activity compared to fine TiO_2.	Timblin et al. (1998)
Human AM	Chapel Hill PM extract; both H_20 soluble(s) and insoluble(is)	2×10^6 cells/mL	100 µg/mL	$PM_{2.5}$ $PM_{10\text{-}2.5}$	24 h	Increased cytokine production (IL-6, TNF-α, MCP-1); $isPM_{10} > sPM_{10} > isPM_{2.5}$; $sPM_{2.5}$ was inactive; endotoxin was partially responsible.	Soukup and Becker (2001)
Human AM from healthy males and females, age 20-35 years CHO expressing CD14 and TLR2 or TLR4	EHC-93 (Ott) MSH Vol. Ash ROFA (Niagra, NY) silica PM bacteria from Chapel Hill, NC ambient air	$2\text{-}3 \times 10^5$ cells/mL	PM - 30 µg/mL; bacteria - 10^3 - 2×10^6/tube	2.5-10 µm	overnight	Three times more gram+ bacteria were required to elicit the same level of cytokine induction as gram- bacteria. This induction was inhibited by anti-CD14 and required serum. TLR4 was involved in $PM_{10\text{-}2.5}$ and gram- induced activation. TLR2 activation was induced by both gram + and - bacteria and by PM.	Becker et al. (2002)

TABLE 7-10 (cont'd). IN VITRO EFFECTS OF AMBIENT PARTICULATE MATTER AND PARTICULATE MATTER CONSTITUENTS

Species, Cell Type, etc.[a]	Particle or Constituent[b]	Cell Count	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
Human AM	Urban PM (Netherlands)	3×10^5 cells/mL	770 pg/mL 1781 pg/mL 20411 pg/mL	< 0.1 µm 0.1-2.5 µm 2.5-10 µm	18-20 h	IL-6 levels induced by $PM_{2.5-10}$ were 10x higher than $PM_{0.1-2.5}$. Levels induced by $PM_{0.1-2.5}$ were 2-3× higher than $PM_{<0.1}$. Induction was inhibited by antibody to CD14Phagaocytosis of osonized yeast and yeast-induced oxidative burst inhibited by larger PM. Larger PM decreased CD11b expression more.	Becker et al. (2003)
Mouse monocytes and mouse mesenchymal cells	PM from Northern and Southeastern Mexico City		20, 40 or 80 µg/cm^2	10 or 2.5 µm	24 h	S.E. Mexico City PM_{10} had most endotoxins and induced the most TNF-α and IL-6 at all doses. Cytokine release was reduced 50-75% by rENPNorthern PMs most cytotoxic.	Osornio-Vargas, et al. (2003)
Mouse monocyte-macrophage cell line RAW 264.7	PM from Taiwan		40 µg/mL	< 2.5 µm 2.5-10 µm	16 h	$PM_{2.5-10}$ had greater endotoxin content and TNF-α production, which was inhibited by polymyxinB.	Huang et al. (2002)

[a] Cell types: RTE = Rat tracheal epithelial cells; GPTE = Guinea pig tracheal epithelial cells; NHBE = Normal human bronchial epithelial cells; A549 = Human lung epithelial cell line; BEAS - 2B = human airway epithelial cell line; AM = Alveolar macrophage.

[b] CAP = Concentrated ambient particles
UAP = Urban ambient PM
DOFA = Domestic oil fly ash
ROFA = Residual oil fly ash
TSP = Total suspended particles
VO = Vanadate oxide
PFA = Pulverized fuel ash
CFA = Coal fly ash
DPM = Diesel particulate matter
TiO_2 = Titanium oxide
MSH = Mt. Saint Helen volcanic ash

DEF = Deferoxamine

TABLE 7-11. IN VITRO EFFECTS OF ROFA AND OTHER COMBUSTION-SOURCE PARTICULATE MATTER CONSTITUENTS

Species, Cell Type, etc. [a]	Particle or Constituent [b]	Cell Count	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
Rat AM	ROFA (Florida), iron sulfate, nickel sulfate, vanadyl sulfate Latex particles with metal complexed on the surface	0.5 – 1.0 × 10^6 cells/mL	0.01–1.0 mg/mL	3.6 µm MMAD (dust) 0.945 µm (latex beads)	Up to 400 min	At all concentrations, increased chemiluminescence, inhibited by DEF and hydroxyl radical scavengers; solutions of metal sulfates and metal-complexed latex particles similarly elevated chemiluminescence. Effects were generally dose-dependent, with largest dose creating effects over the shortest period of exposure.	Ghio et al. (1997a)
NHBE BEAS-2B	ROFA (Florida)		5, 50, 200 µg/mL	3.6 µm	2 and 24 h	mRNA for ferritin did not change; ferritin protein increase at ≥ 50 µg/mL; mRNA for transferrin receptor decreased at ≥50 µg/mL; mRNA for lactoferrin increased; transferrin decreased at ≥ 50 µg/mL, whereas lactoferrin increased at ≥ 50; deferoxamine alone increased lactoferrin mRNA; effects significant for two highest exposure following 24 h exposure.	Ghio et al. (1998c)
BEAS-2B respiratory epithelial cells	ROFA (Florida)		100 µg/mL	3.6 µm	5 min – 1 h	Lactoferrin binding with PM metal occurred within 5 min and $Fe^{(III)}$, but not Ni, increased the concentration of lactoferrin receptor.	Ghio et al. (1999b)
NHBE cells	ROFA (Florida)		0, 5, 50, or 200 µg/mL (actual dose delivered 1.6-60 µg/cm^2)	< 10 µm	2 or 24 h	Increase in expression of the cytokines IL-6 and IL-8 at all exposure concentrations; TNF-α increased at ≥ 50 µg/mL; inhibition by DMTU or deferoxamine.	Carter et al. (1997)
Primary cultures of RTE	ROFA; (Florida) metal solutions		5, 10, or 20 µg/cm^2	1.95 µm MMAD	Analysis at 24 h	ROFA, V, or Ni + V (at ≥10 µg/cm^2), but not Fe or Ni, increased epithelial permeability, decreased cellular glutathione, cell detachment, and lytic cell injury; treatment with DMTU inhibited expression of MIP-2 and IL-6 genes.	Dye et al. (1999)
Hamster AM	ROFA or CAPs (Boston)	0.5 × 10^6 cells/mL	ROFA: 0, 25, 50, 100, or 200 µg/mL CAPs: 1:5, 1:10, 1:20 (described as 4, 10, 20 µg/mL)	CAPs: 0.1–2.5 µm (from Harvard concentrator) TiO_2: 1 µm	30 min incubation, analysis immediately following	Dose-dependent increase in AM oxidant stress with both ROFA and CAPs (at 4 µg/mL). Increase in particle uptake; Mac-type SR mediate a substantial proportion of AM binding; particle-associated components (e.g., transition metals) are likely to mediate intracellular oxidant stress and proinflammatory activation.	Goldsmith et al. (1997)

TABLE 7-11 (cont'd). IN VITRO EFFECTS OF ROFA AND OTHER COMBUSTION-SOURCE PARTICULATE MATTER CONSTITUENTS

Species, Cell type, etc. [a]	Particle or Constituent[b]	Cell Count	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
Hamster AM Mouse AM	ROFA, CAPs, and their water-soluble and particulate fractions (Boston)	0.5×10^6 cells/mL	ROFA: 25, 50, 100, 200 µg/mL, 50 and 250 µg/mL, and 100, 200, 400 µg/mL CAPs: 38-180 µg/mL	CAPs = 0.1-2.5 µm ROFA = 1.0 µm	30 min	ROFA (particles ‑50, 100, and 200 µg/mL and water soluble components ‑200 µg/mL only dose tested) and CAPs (all doses for particulate fraction and 150-180 µg/mL for soluble fraction - only dose tested) caused increases in DCFH oxidation; CAPs samples and components showed substantial day-to-day variability in their oxidant effects; ROFA increased MIP-2 in hamster AMs exposed to 50 or 250 µg/mL and TNF-α production in mouse AM exposed to 100, 200, 400 µg/mL. Effects inhibited by NAC.	Goldsmith et al. (1998)
Human AM	ROFA (Florida) UAP (#1648, 1649) MSH Vol. Ash	1×10^6 cells/mL	0, 25, 100, or 200 µg/mL	Volume median diameter: ROFA: 1.1 µm #1648: 1.4 µm #1649: 1.1 µm MSH: 2.3 µm	24 h	ROFA highly toxic; urban PM toxic at 200 µg/mL; ROFA produced significant apoptosis as low as 25 µg/mL; UAP produced apoptosis at 100 µg/mL; ROFA and UAP also affect AM phenotype: increased immune stimulatory, whereas decreased immune suppressor phenotype.	Holian et al. (1998)
BEAS-2B	ROFA (Florida, #6 LoS)		0, 6, 12, 25, or 50 µg/mL	1.96 µm	1 to 24 h	Transient activation at 50 µg/mL of IL-6 gene by NF-κB activation and binding to specific sequences in promoter of IL-6 gene at all dose levels; inhibition of NF-κB activation by DEF and NAC; activation NF-B may be a critical first step in the inflammatory cascade following exposure to ROFA particles.	Quay et al. (1998)
BEAS-2B	ROFA (Florida)	5×10^6 cells/mL	0, 0.5, or 2.0 mg in 10 mL	1.95 µm	1 h	ROFA induced production of acetaldehyde in dose-dependent fashion. No effects on cell viability.	Madden et al. (1999)
Primary GPTE cells	ROFA (Florida) DOFA (Durham) STL (St. Louis) WDC (Wash., DC) OT (Ottawa) MSH Vol. Ash	$2 – 5 \times 10^5$ cells/cm^2	6.25, 12.5, 25, and 50 µg/cm^2	N/A	4, 8, and 24 h	ROFA the most toxic (effects seen at 12.5 µg/cm^2), enhancing mucin secretion at 50 µg/cm^2 and causing toxicity, assessed by LDH release at ≥ 25 µg/cm^2. DOFA produced significant effect at 25 µg/cm^2. Several other particles toxic at 50 µg/cm^2 for 24 h.	Jiang et al. (2000)
Human blood monocytes and neutrophils (PMN)	ROFA (Florida); CFA (Linden, NJ; Niagra, NY; Western U.S.). SRM 1649 (Dusseldorf, Eliz. City, NJ; Charlottesville); MSH Vol. Ash	2×10^5 cells/ 0.2 mL	100 µg 25, 50, 100, 150, 200 µg	N/A	40 min	ROS generation, measured by LCL increase in PMN and monocytes; PMN effects were correlated with Si, Fe, Mn, Ti, and Co content but not V, Cr, Ni, and Cu. Deferoxamine, a metal ion-chelator, did not affect LCL in PMN, suggesting that metal ions are not related to induction of LCL. Effects were generally dose-dependent, with effects seen at lowest dose.	Prahalad et al. (1999)

TABLE 7-11 (cont'd). IN VITRO EFFECTS OF ROFA AND OTHER COMBUSTION-SOURCE PARTICULATE MATTER CONSTITUENTS

Species, Cell Type, etc. [a]	Particle or Constituent[b]	Cell Count	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
Human BEAS-2B	ROFA (Florida)		2, 20, or 60 μg/cm^2	1.96 μm	2 or 24-h exposure	Epithelial cells exposed to ROFA at ≥ 20 μg/cm^2 for 24 h secreted substantially increased amounts of the PHS products prostaglandins E_2 and $F_{2\alpha}$; ROFA-induced increase in prostaglandin synthesis was correlated with a marked increase in PHS activity.	Samet et al. (1996)
Human BEAS-2B	ROFA (Florida) Synthetic ROFA (soluble Ni, Fe, and V)		ROFA: 0-200 μg/mL Synthetic ROFA (100 μg/mL): Ni, 64 μM Fe, 63 μM V, 370 mM	ROFA: 1.96 μm Synthetic ROFA: N/A (soluble)	5 min to 24 h	Tyrosine phosphatase activity, which was known to be inhibited by vanadium ions, was markedly diminished after ROFA treatment at ≥ 50 μg/mL; effects were dose- and time-dependent; ROFA exposure induces vanadium ion-mediated inhibition of tyrosine phosphatase activity, leading to accumulation of protein phosphotyrosines in cells.	Samet et al. (1997)
Human airway epithelium-derived cell lines BEAS-2B	Particle components As, Cr, Cu, Fe, Ni, V, and Zn		500 μM of As, F, Cr (III), Cu, V, Zn	N/A (soluble)	20 min; analyses conducted 6 and 24 h following exposure	Noncytotoxic concentrations of As, V, and Zn induced a rapid phosphorylation of MAPK in cells; activity assays confirmed marked activation of ERK, JNK, and P38 in cells exposed to As, V, and Zn. Cr and Cu exposure resulted in a relatively small activation of MAPK, whereas Fe and Ni did not activate MAPK under these conditions; the transcription factors c-Jun and ATF-2, substrates of JNK and P38, respectively, were markedly phosphorylated in cells treated with As, Cr, Cu, V, and Zn; acute exposure to As, V, or Zn that activated MAPK was sufficient to induce a subsequent increase in IL-8 protein expression in cells. Most effects seen by 6 h postexposure.	Samet et al. (1998)
Human lung mucoepidermoid carcinoma cell line, NCI-H292	ROFA (Florida)	1×10^6 cells/mL	10, 30, 100 μg/mL	N/A	6 and 24 h	Epithelial cells secreted increased mucin at ≥ 10 μg/mL and lysozyme ≥ 30 μg/mL; effect was time- and concentration-dependent; effects significant for mucin at the lowest exposure dose for both exposure periods; effects on lysozyme only significant at highest dose for 6 h exposure and two highest doses for 24 h exposure; caused by V-rich fraction (18.8%).	Longphere et al. (2000)
Rat, Long Evans epithelial cells	CFA PFA α-quartz.	1×10^4 cells/ 100 μL		1.5-3.0 μm 17.7 μm 2.5 μm	3 h	CFA produced highest level of hydroxyl radicals; no relationship between hydroxy/radical generation and CFA particle size, surface area, quartz, or iron content, but positive correlation noted with iron mobilization.	Van Maanen et al. (1999)
BEAS-2B	ROFA (Birmingham, AL) 188 mg/g of VO		100 μg/mL	N/A	2-6 h	ROFA caused increased intracellular Ca^{2+}, IL-6, IL-and TNF-α through activation of capsicin- and pH-sensitive receptors; effects seen at the lowest dose tested.	Veronesi et al. (1999a)

TABLE 7-11 (cont'd). IN VITRO EFFECTS OF ROFA AND OTHER COMBUSTION-SOURCE PARTICULATE MATTER CONSTITUENTS

Species, Cell Type, etc. [a]	Particle or Constituent [b]	Cell Count	Concentration	Particle Size	Exposure Duration	Effect of Particles	Reference
Human lung epithelial (A549) cells	ROFA (Boston), α-quartz, TiO_2	2.5×10^5 cells/mL	25-200 µg/mL	N/A	60 min	Exposure of A549 cells to ROFA at ≥ 50 µg/mL, α-quartz at ≥ 25 µg/mL, but not TiO_2, caused increased IL-8 production in TNF-α primed cells.	Stringer and Kobzik (1998)
Male (Wistar) rat lung macrophages	Urban dust SRM 1649, TiO_2, quartz	2×10^5 cells/mL	0-100 µg/mL	0.3 – 0.6 µm	18 h	Cytotoxicity ranking was quartz > SRM 1649 > TiO_2, based on cellular ATP decrease and LDH, acid phosphatase, and β-glucuronidase release. Effects were noted at the lowest exposure dose.	Nadeau et al. (1996)
Human lung epithelial (A549) cells	TiO_2, Fe_2O_3, CAP (Boston), and the fibrogenic particle α-quartz	3×10^5 cells/mL	TiO_3: 40 µg/mL; Fe_2O_3: 100 µg/mL, α-quartz: 200 µg/mL; CAP: 40 µg/mL	N/A	24 h	TiO_2 > Fe_2O_3 > α-quartz > CAP in particle binding; binding of particle was found to be calcium-dependent for TiO_2 and Fe_2O_3, while α-quartz binding was calcium-independent; scavenger receptor, mediate particulate binding; α-quartz caused a dose-dependent production of IL-8 (≥ 26.6 µg/cm^2). Il-8 was not present in TiO_2 and CAPs treated cells.	Stringer et al. (1996)
Rat (Wistar) AM RAM cells (a rat AM cell line)	TiO_2	1×10^6 cells/mL	20, 50, or 80 µg/mL	N/A	4 h	Opsonization of TiO_2 with surfactant components resulted in a modest dose-dependent increase in AM uptake compared with that of unopsonized TiO_2 at ≥ 50 µg/mL; surfactant components increase AM phagocytosis of particles.	Stringer and Kobzik (1996)
Human bronchial epithelial cells, asthmatic (ASTH) nonasthmatic (NONA)	DPM		10-100 µg/mL	0.4 µm	2, 4, 6, 24 h	DPM caused no gross cellular damage. Ciliary beat frequency was attentuated at all doses. DPM caused IL-8 release at 10 µg/mL in ASTH and at 50 µg/mL in NONA. Higher concentrations (50 and 100 µg/mL) DPM suppressed IL-8 and GM-CSF, in ASTH cells.	Bayram et al. (1998a)
Human bronchial epithelial cells (smokers)	DPM		10-100 µg/mL in culture medium 50 µg/mL filtered solution	0.4 µm	24 h	DPM attenuated ciliary beating. Release of IL-8 protein increased by exposure to ≥ 50 µg/mL DPM in culture medium, but 10-fold higher increase by DPM filtered solution. GM-CSF and CAM-1 increased after 50-100 µg/mL.	Bayram et al. (1998b)

[a] Cell types: RTE = Rat tracheal epithelial cells; GPTE = Guinea pig tracheal epithelial cells; NHBE = Normal human bronchial epithelial cells; A549 = Human lung epithelial cell line; BEAS-2B = human airway epithelial cell line; AM = Alveolar macrophage.

[b] CAP = Concentrated ambient particles; UAP = Urban ambient PM; CFA = Coal fly ash; ROFA = Residual oil fly ash; DOFA = Domestic oil fly ash; PFA = Pulverized fuel ash; DPM = Diesel particulate matter; VO = Vanadate oxide; TiO_2 = Titanium oxide; TSP = Total suspended particles; MSH = Mt. Saint Helen volcanic ash; DEF = Deferoxamine

very high on a cellular basis, thus requiring much caution in attempting to extrapolate in vitro findings to in vivo exposure conditions. It would be useful if in vitro studies included, in addition to the high doses, lower doses more comparable to environmental doses predicted to occur at the cellular level under in vivo conditions. Even with these limitations, however, in vitro studies do provide a useful approach by which to explore potential cellular and molecular mechanisms by which PM mediates health effects, allowing mechanisms identified in vitro to be evaluated later in vivo or possibly helping to confirm mechanisms suggested by the results of in vivo studies.

The following subsection discusses the more recently published studies that provide an in vitro approach toward identifying potential mechanisms by which PM mediates cardiovascular and respiratory health effects. Based on these available data the ensuing subsection then discusses the potential mechanisms in relation to PM size or chemical characteristics.

7.4.2 Ambient Particle Effects

Newly available in vitro studies since the 1996 PM AQCD include many that exposed airway epithelial cells, alveolar macrophages, or blood monocytes and erythrocytes to aqueous extracts of ambient PM to investigate cellular processes, e.g., oxidant generation and cytokine production, that may contribute to respiratory and/or cardiovascular pathophysiological responses seen in vivo. The ambient PM evaluated includes samples collected from: Boston, MA (Goldsmith et al., 1998); North Provo, UT (Ghio et al., 1999a,b); St. Louis, MO (SRM 1648, Dong et al., 1996; Becker and Soukup, 1998); Washington, DC (SRM 1649, Becker and Soukup, 1998); Ottawa, Canada (EHC-93, Becker and Soukup, 1998); Dusseldorf and Duisburg, Germany (Hitzfeld et al., 1997), Mexico City (Bonner et al., 1998), Terni, Italy (Fabiani et al., 1997); and Rome, Italy (Diociaiuti et al., 2001).

Because soluble metals from ROFA-like particles have been shown to be associated with pathophysiologic/toxic effects, several new studies have investigated whether the soluble components of ambient PM may exert similar effects. For example, extracts of ambient PM samples collected from North Provo, UT, (during 1981 and 1982) were used to test whether the soluble components or ionizable metals, which accounted for only ~0.1% of the mass, are responsible for the biological activity of the extracted PM components. These North Provo

extracts stimulated IL-6 and IL-8 production, as well as increased IL-8 mRNA and enhanced expression of intercellular adhesion molecule-1 (ICAM-1) in human airway epithelial (BEAS-2B) cells (Kennedy et al., 1998). Cytokine secretion was preceded by activation of nuclear factor kappa B (NF-κB) and was reduced by treatment with superoxide dismutase (SOD), Deferoxamine (DEF), or N-acetylcysteine (NAC). The addition of similar quantities of Cu^{2+} as found in the Provo extract replicated the biological effects observed with particles alone. When normal constituents of airway lining fluid (mucin or ceruloplasmin) were added to BEAS cells, particulate-induced secretion of IL-8 was modified. Mucin reduced IL-8 secretion; whereas ceruloplasmin significantly increased IL-8 secretion and activation of NF-κB. The authors suggest that copper ions may cause some of the biologic effects of inhaled PM in the Provo region and may provide an explanation for the sensitivity of asthmatics to Provo PM seen in epidemiologic studies. Also, release of IL-8 from BEAS-2B cells, oxidant generation (thiobarbituric acid reactive products), and PMN influx in rats exposed to these samples correlated with sulfate content and the ionizable concentrations of metals in such Provo-PM extracts (Ghio et al., 1999a,b).

Frampton et al. (1999) examined the effects of the same ambient PM samples collected from Utah Valley in the late 1980s (see Section 7.2.1). Aqueous extracts of the filters were analyzed for metal and oxidant production and added to BEAS-2B cultures for 2 or 24 h. Particles collected in 1987, when the steel mill was closed had the lowest concentrations of soluble Fe, Cu, and Zn and showed the least oxidant generation. Ambient PM collected before and after plant closing induced expression of IL-6 and IL-8 in a dose-response relationship (125, 250, and 500 μg/mL) with effects seen at all doses. Ambient PM collected after reopening of the steel mill also caused cytotoxicity, as demonstrated by microscopy and LDH release at the highest concentration used (500 μg/mL).

Molinelli et al. (2002) also exposed BEAS-2B cultures for 24 h to an aqueous extract of PM collected in the Utah Valley. A portion of the extract was treated with Chelex, an agent that removes transition metals from solution. Cells incubated with the untreated extract showed a significant concentration-dependent increase at the lowest concentration of 62.5 μg/mL in the inflammatory mediator IL-8 when compared to the control cells. However, cells incubated with Chelex-treated extract produced no change (relative to control) in IL-8. They exposed rats in vivo for 24 h to the same treatments as the in vitro cells and found significant increases in

lactate dehydrogenase (LDH) and total protein in the rats exposed to the untreated extract and to the Chelex-treated extract with metals added back to achieve original concentrations. There was an attenuation of the observed LDH and total protein increases in the rats instilled with the Chelex-treated extract. The authors concluded that removal of metal cations attenuates cellular responses to the aqueous extract and suggest a role for transition metal involvement in PM-associated increases in morbidity and mortality.

Soukup et al. (2000), using similar ambient PM extracts as did Frampton et al. (1999), examined effects on human alveolar macrophages (AM). The phagocytic activity and oxidative response of AMs were measured after segmental instillation of aqueous extracts from the Utah Valley or after overnight in vitro cell culture exposure to such ambient PM at 500 μg/mL. Ambient PM collected before closure of the steel mill inhibited AM phagocytosis of (FITC)-labeled *Saccharomyces cerevisiae* by 30%; but no significant effect on phagocytosis was seen with the other two extracts. Furthermore, although extracts of ambient PM collected before and after plant closure inhibited oxidant activity of AMs when incubated overnight in cell culture, only the former particles caused an immediate oxidative response in AMs. Host defense effects were attributed to apoptosis, which was most evident for exposures to particles collected before plant closure. Interpretation of loss of these effects by chelation removal of the metals was complicated by the observed differences in apoptosis despite similar metal contents of ambient PM collected during the steel mill operation.

Wu et al. (2001) investigated intracellular signaling mechanisms related to pulmonary responses to Utah Valley PM extracts. Human primary airway epithelial cells were exposed to aqueous extracts of PM at doses of 50, 100, or 200 μg/mL collected from the year before, during, and after the steel mill closure in Utah Valley. Transfection with kinase-deficient extracellular signal-regulated kinase (ERK) constructs partially blocked the PM-induced IL-8 promoter reporter activity that was present at all doses. The mitogen-activated protein kinase/ERK kinase (MEK) activity inhibitor PD-98059 significantly abolished IL-8 released in response to the PM, as did the epidermal growth factor (EGF) receptor kinase inhibitor AG-1478. Western blotting showed that the PM-induced phosphorylation of EGF receptor tyrosine, MEK1/2, and ERK1/2 could be ablated with AG-1478 or PD-98059. The results indicate that the potency of Utah Valley PM collected during plant closure was lower than that collected while the steel mill was

was in operation and imply that Utah Valley PM can induce IL-8 expression at concentrations ≥ 50 μg/mL partially through the activation of the EGF receptor signaling.

There are regional as well as daily variations in the composition of ambient PM and, hence, its biological activities. For example, concentrated ambient PM (CAP), from Boston urban air has substantial day-to-day variability in its composition and oxidant effects (Goldsmith et al., 1998). Similar to Utah PM, the water-soluble component of Boston CAPs significantly increased AM oxidant production and inflammatory cytokine (MIP2 and TNF-α) production over negative control values. These effects could be blocked by metal chelators or antioxidants, suggesting important roles for metals in contributing to the observed Boston particle effects on AM function.

In another study, the effects of water soluble as well as organic components (extracted in dichloromethane) of ambient PM were investigated by exposing human PMN to PM extracts (Hitzfeld et al., 1997). PM was collected with high-volume samplers in two German cities, Dusseldorf and Duisburg, sites having high traffic and high industrial emissions, respectively. Organic, but not aqueous, extracts of PM at concentrations of 0.03 μg/mL alone significantly stimulated production and release of ROS in resting human PMN. The effects of the PM extracts were inhibited by SOD, catalase, and sodium azide (NaN_3). Similarly, the organic fraction (extractable by acetone) of ambient PM from Terni, Italy, was shown to produce cytotoxicity, superoxide release in response to PMA, and zymosan in peripheral monocytes (Fabiani et al., 1997).

Becker and Soukup (1998) found interesting differences between biological activity of PM materials from urban air particle (UAP) sources (baghouse collection in St. Louis and Ottawa), ROFA samples from a power plant, and Mt. St. Helen volcanic ash stored since 1980. Exposure of human AMs and blood-derived monocytes (MO) to 100 μg/mL of UAP (0.2 to 0.7 μm MMAD originally) both from Boston and St. Louis reduced expression of certain receptors (important for recognition of microbial entities), the phagocytosis of bioparticles (yeast cell walls), and oxidant generation (an important bactericidal mechanism) in both AM and MO. All of these were little affected at 33 μg/mL of UAP. Exposure to 100 μg/mL of ROFA (0.5 μm MMAD originally) also significantly decreased AM (but not MO) phagocytosis (likely due to ROFA cytotoxic effects on AM), but the volcanic ash had little effect on phagocytosis. The oxidative burst response was significantly decreased by ROFA in both AM and MO, but only in

the AM by the volcanic ash. Administration of 10 mg/mL of lipopolysaccaride (LPS), the active endotoxin component, reduced AM receptor expression similar to UAP, but did not reduce all the same receptor expression as UAP in MO. The authors noted that their results indicated (a) differences in biological activity between urban air-related particles (both baghouse collected and ROFA) and the more inert Mt. St. Helens volcanic ash particles (that had little effect on any of the receptors or phagocytosis functions studied); and (b) that UAP endotoxin content may be an important effector in UAP-modulation of some, but certainly not all, macrophage functions.

The findings of Dong et al. (1996) also suggest that biological activity of some ambient PM materials may result from the presence of endotoxin on the particles. Using the same urban particles (SRM 1648), cytokine production (TNF-α, IL-1, IL-6, CINC, and MIP-2) was increased in macrophages following treatment with 50 to 200 μg/mL of urban PM (Dong et al., 1996). The urban particle-induced TNF-α secretion was abrogated completely by treatment with polymyxin B (an antibiotic that blocks LPS-associated activities), but not by antioxidants.

The potential involvement of endotoxin, at least partially, in some PM-induced biological effects has been explored further by Bonner et al. (1998) and Soukup and Becker (2001). Bonner et al. (1998) used urban PM_{10} at a concentration of 10 $\mu g/cm^2$ collected from north, south, and central regions of Mexico City with SD rat AM to examine PM effects on platelet-derived growth factor (PDGF) receptors on lung myofibroblasts. Mexico City PM_{10} (but not volcanic ash) stimulated secretion of upregulatory factors for the PDGF α receptor, possibly via IL-1β. In the presence of an endotoxin-neutralizing protein, the Mexico City PM_{10} effect on PDGF was blocked partially, suggesting that LPS was partly responsible for the PM_{10} effect. In addition, both LPS and V (both present in the PM_{10}) acted directly on lung myofibroblasts, even though the ambient V levels in Mexico City PM_{10} were probably not high enough to exert an independent effect. The authors concluded that PM_{10} exposure could lead to airway remodeling by enhancing myofibroblast replication and chemotaxis.

Soukup and Becker (2001) used a dichotomous sampler to collect fresh $PM_{2.5}$ and $PM_{10-2.5}$ from the ambient air of Chapel Hill, NC and compared the activity of these two particle size fractions. Both water soluble and insoluble components at concentrations of 100 μg/mL were assessed for cytokine production, inhibition of phagocytosis, and induction of apoptosis. The insoluble $PM_{10-2.5}$ fraction was the most potent in terms of inducing cytokines and increasing oxidant generation, thus suggesting the importance of the coarse fraction in contributing to

ambient PM health effects. Endotoxin appeared to be responsible for much of the cytokine production, whereas inhibition of phagocytosis was induced by other moieties in the coarse material. None of the activities were inhibited by the metal chelator deferoxamine.

Diociaiuti et al. (2001) compared the in vitro toxicity of fine ($PM_{2.5}$) and thoracic coarse ($PM_{10-2.5}$) fraction particulate materials extracted from sampling filters collected in an urban area of Rome (average 24-h levels of 31 and 19 $\mu g/m^3$, respectively). Cell cultures were exposed to the extracted PM materials suspended in saline at doses ranging from 0 to 80 μg/mL. The in vitro toxicity assays included evaluation of human red blood cell hemolysis, cell viability, and nitric oxide (NO) release in the RAW 264.7 macrophage cell line. There was a dose-dependent hemolysis in human erythrocytes when they were incubated with either fine or coarse particles, but the hemolytic potential was greater for the fine than for the coarse particles in equal mass concentration, the fine particles being linearly related from 0 to 80 μg/mL, but the coarse ones not showing any effect below 50μg/mL. However, when data were expressed in terms of PM surface area per volume of suspension, the hemolytic activity of the fine fraction was not markedly different from that of the coarse fraction, thus suggesting that oxidative stress induced by PM on the blood cell membranes could be due mainly to the interaction between the particle surfaces and the cell membranes. Although RAW 264.7 cells challenged with fine and coarse particles showed decreased viability and an increased release of NO (a key inflammatory mediator) both effects were not dose-dependent in the tested concentration range. The fine particles were the most effective in inducing these effects either when the data were expressed as mass concentration or as surface area per unit volume. The authors concluded that these differences in biological activity were due to differences in the physicochemical nature of the particles, their noting that the possible causative agent in the fine fraction could be carbon-rich particles with an associated sulfur-containing acidic component.

7.4.3 Comparison of Ambient and Combustion Source-Related Particles

In vitro toxicology studies using AMs as target cells (Imrich et al., 2000; Long et al., 2001; Ning et al., 2000; Mukae et al., 2000, 2001; Van Eeden et al., 2001) have found that urban ambient air particles are much more potent for inducing cellular responses than individual combustion particles such as diesel or ROFA. Metals, on the other hand, do not seem to affect cytokine production, consistent with studies showing that ROFA does not induce macrophage

cytokine production. However, in some studies (Long et al., 2001), cytokine responses in AMs appeared to be correlated with LPS content of the PM samples tested. These results may be important because LPS is an important component associated with both ambient coarse and fine particles (Menetrez et al., 2001).

Van Eeden et al. (2001) compared effects of EHC-93 atmospheric PM sample materials from Ottawa, ROFA, and different size latex particles on cytokine induction by human AMs. The EHC-93 particles produced greater than 8-fold induction of various cytokines (including IL-1, TNF, GMCSF) at concentrations as low as 0.01 mg/mL. The other particles at concentrations of 0.1 mg/mL only induced these cytokines by ~2-fold. Using the same EHC-93 particles, Mukae et al. (2000, 2001) found that inhalation exposure of 0.1 mg/mL also stimulated bone marrow band cell-granulocyte precursor production and that the magnitude of the response was correlated with the amount of phagocytosis of the particles by AMs. These results may indicate that macrophages produce factors which stimulate bone marrow, including IL-6 and GMCSF. In fact, AMs exposed in vitro to these particles released cytokines; and when the supernatant of PM-stimulated macrophages was instilled into rabbits, the bone marrow was stimulated.

In a series of studies using the same ROFA samples collected from an oil-burning power plant in Florida, several in vitro experiments have investigated the biochemical and molecular mechanisms involved in ROFA-induced cellular injury. Prostaglandin metabolism in cultured human airway epithelial cells (BEAS-2B and NHBE) exposed to ROFA was investigated by Samet et al. (1996). Epithelial cells exposed to 20 $\mu g/cm^2$ ROFA for 24 h secreted substantially increased amounts of prostaglandins E2 and F2α. The ROFA-induced increase in prostaglandin synthesis was correlated with a marked increase in activity of the prostaglandin H synthase-2 (PHS-2) as well as mRNA coded for this enzyme. In contrast, expression of the PHS1 form of the enzyme was not affected by ROFA treatment of airway epithelial cells. These investigators further demonstrated that the ROFA induced a significant dose- and time-dependent increase in protein tyrosine phosphate, an important index of signal transduction activation leading to a broad spectrum of cellular responses. Concentrations used were 5 to 200 $\mu g/mL$, with effects seen at $\geq$ 50 mg/mL ROFA. ROFA-induced increases in protein phosphotyrosines were associated with its soluble fraction and were mimicked by V-containing solutions but not Fe or Ni solutions (Samet et al., 1997).

ROFA also stimulates respiratory cells to secrete inflammatory cytokines such as IL-6, IL-8, and TNF. Normal human bronchial epithelial cells exposed to Florida ROFA produced significant amounts of IL-8, IL-6, and TNF, as well as mRNAs coding for these cytokines (Carter et al., 1997). Increases in cytokine production were dose-dependent. The cytokine production was inhibited by the addition of metal chelator, DEF, or the free radical scavenger dimethylthiourea (DMTU). Similar to the data of Samet et al. (1997), V but not Fe or Ni compounds were responsible for these effects. Cytotoxicity and decreased cellular glutathione levels in primary cultures of rat tracheal epithelial (RTE) cells exposed to suspensions of ROFA indicated that respiratory cells exposed to ROFA were under oxidative stress. Treatment with buthionine sulfoxamine (an inhibitor of γ-glutamyl cysteine synthetase) augmented ROFA-induced cytotoxicity; whereas treatment with DMTU that inhibited ROFA-induced cytoxicity further suggested that ROFA-induced cell injury may be mediated by hydroxyl-radical-like reactive oxygen species (ROS; Dye et al., 1997). Using BEAS-2B cells, a time- and dose-dependent increase in IL-6 mRNA induced by ROFA was shown to be preceded by the activation of nuclear proteins, for example, NF-κB (Quay et al., 1998). Taken together, these studies indicate that exposure to ROFA in high doses increases oxidative stress, perturbs protein tyrosine phosphate homeostasis, activates NF-κB, and up-regulates inflammatory cytokine and prostaglandin synthesis and secretion to produce lung injury.

Stringer and Kobzik (1998) observed that "primed" lung epithelial cells exhibited enhanced cytokine responses to certain particulate materials. Compared to normal cells, exposure of tumor necrosis factor (TNF)-α-primed A549 cells to ROFA (Boston area) or α-quartz caused increased IL-8 production in a concentration-dependent manner for particle concentrations ranging from 0 to 200 μg/mL. Addition of the antioxidant NAC (1.0 mM) decreased ROFA and α -quartz-mediated IL-8 production by about 50% in both normal and TNF-α-primed A549 cells. Exposure of A549 cells to ROFA caused an increase in oxidant levels that could be inhibited by NAC. These data suggest that (1) lung epithelial cells primed by inflammatory mediators show increased cytokine production after exposure to PM and (2) oxidant stress is an important mechanism for this response.

Imrich et al. (2000) found that, when mouse AMs were stimulated with CAPs ($PM_{2.5}$) at a concentration of 100 μg/mL, the resulting TNF responses could be inhibited by an endotoxin neutralizing agent [e.g., polymyxin-B (PB)]. Because the MIP-2 response (IL-8) was only partly

inhibited by PB, however, the authors concluded that endotoxin primed AM cells to respond to other particle components. In a related study (Ning et al., 2000), the use of PB showed that particle-absorbed endotoxin in CAPs suspensions caused activation of normal (control) AMs, while other (nonendotoxin) components were predominantly responsible for the enhanced cytokine release observed for primed AMs incubated with CAPs. The non-LPS component was not identified in this study; however, the AM biological response did not correlate with any of several elements quantified within the insoluble CAPs samples (e.g., Al, Cd, Cr, Cu, Fe, Mg, Mn, Ni, S, Ti, V).

Osornio-Vargas et al. (2003) compared exposures of mouse monocytes to $PM_{2.5}$ or to PM_{10} collected in either southeastern or northern Mexico City, and characterized as to metal and endotoxin content. Tumor necrosis factor-α and IL-6 were measured from exposures both with and without recombinant endotoxin-neutralizing protein (rENP). The southeastern PM_{10} samples had the highest endotoxin levels, which correlated with greater cytokine secretion. rENP reduced cytokine secretion by 50-75%, suggesting to the authors that the endotoxin-independent, transition metal-dependent mechanism for fine PM contributed to cytotoxicity effects, whereas an endotoxin-dependent mechanism was responsible for the proinflammatory response to PM_{10}.

Rat AM exposed to PM_{10} collected from both rural and urban sites in Switzerland during all four seasons demonstrated increased cytotoxicity from all PM samples (Monn et al., 2003). TNF-α and oxidative radical release were highest with PM collected during non-winter months. ENP inhibited cytotoxic effects and oxidative radical release, suggesting that endotoxin in some ambient PM_{10} samples during warm months may affect some types of macrophage activity.

In central Taiwan, Huang et al. (2002) collected $PM_{2.5}$ and PM_{10} samples, to which RAW 264.7 cells, a mouse monocyte-macrophage cell line, were then exposed at 40 µg/mL. After 6 h exposure, either with or without polymyxin B, TNF-α levels were assayed. Higher TNF-α secretion was stimulated by PM_{10}-exposed cells; and PB-inhibited TNF-α by 42% and 32% in PM_{10} and $PM_{2.5}$ exposures, respectively, suggesting that endotoxin may contribute more to TNF-α stimulation by coarse than fine fraction particles.

Becker et al. (2002) hypothesized that PM activates receptors involved in recognition of microbial cell structures. They coated model pollution particles with either gram-negative (*Pseudomonas*) or gram-positive (*Staphloccocus* or *Streptococcus*) bacteria. Three times more gram-positive bacteria were required to elicit the same level of cytokine induction as gram-

negative bacteria. This inhibition was inhibited by anti-CD14 and required serum. This study further found a suggested role of Toll-like receptors (TLR) in PM recognition, thus implicating likely bacterial components as a factor contributing to PM-induced AM inflammatory responses. Becker et al. (2003) exposed human AM to ultrafine (< 0.1 μm), fine ($PM_{0.1-2.5}$) or coarse ($PM_{2.5-10}$) particles collected in two urban sites in the Netherlands. IL-6 induction levels and reductions in CD11b phagocyte receptor expression were positively correlated with particle size. Induction of IL-6 was inhibited by an antibody to CD14. Yeast-induced oxidative burst and inhibition of phagocytosis of opsonized yeast was also correlated with size, with the ultrafine particles having no effect. The authors concluded that human AM recognize microbial cell structures, which are more prevalent in larger particles, and that exposure to PM is associated with inflammatory events and decreased pulmonary defenses.

In summary, exposure of lung epithelial cells to ambient PM or ROFA leads to increased production of cytokines and the effects may be mediated, at least in part, through production of ROS. Day-to-day variations in the components of PM (such as soluble transition metals) which may be critical to eliciting the response are suggested. The involvement of organic components (e.g., endotoxins) in ambient PM was also suggested by some studies as contributing to ambient PM (especially coarse thoracic $PM_{10-2.5}$) effects on some types of AM functions.

7.4.4 Potential Cellular and Molecular Mechanisms

The numerous studies assessed in the foregoing sections provide evidence for various types of PM effects on cardiopulmonary system components and functions. Considerable interest and research attention has been accorded to effects aimed at characterizing specific cellular and molecular mechanisms underlying PM effects. The ensuing sections highlight information derived in part from in vivo, but more so, from in vitro, studies that supports identification of several general types of mechanisms as mediating various PM-induced pathophysiological responses likely underlying PM effects on cardiopulmonary and other functions. This includes, in particular, evidence for important involvement in mediating PM effects of (a) reactive oxygen species; (b) intracellular signaling mechanisms; and (c) other types of mechanisms, e.g., impacts on sensory nerve receptors.

7.4.4.1 Reactive Oxygen Species

Transition metals are capable of catalyzing the production of reactive free radicals such as the hydroxyl (·OH) radical through the following reaction:

$$Fe^{+2} + H_2O_2 \rightarrow Fe^{3+} \ ^{\bullet}OH + HO^{-} \quad (7\text{-}1)$$

It should be noted that the actual reaction is more complex than given above and is commonly referred to as the iron-catalyzed Haber-Weiss Reaction or Fenton's Reaction. Fe^{3+} produced in the above reaction can be reduced to Fe^{2+} by reactions such as:

$$Fe^{3+} + O_2^{\bullet -} \rightarrow Fe^{2+} + O_2 \quad (7\text{-}2)$$

where $O_2^{\bullet -}$ is the superoxide radical. Hydrogen peroxide is formed by

$$2\ O_2^{\bullet -} + 2\ H^{+} \rightarrow H_2O_2 + O_2 \quad (7\text{-}3)$$

This reaction is catalyzed by superoxide dismutase (SOD). SODs are present as Cu-Zn SOD in cytoplasm, Mn-SOD in mitochondria and extra-cellularly as Cu SOD. Iron will participate in the above reactions and hydroxyl radicals will continue to be generated so long as there are sufficient reductants and H_2O_2 present. In addition to hydroxyl radicals, electronically excited O_2 produced in the reactions given above may also be involved in promoting cellular damage.

Soluble metals from inhaled PM dissolved into the fluid lining of the airway lumen can react directly with biological molecules (acting as a reductant in the above reactions) to produce ROS. For example, ascorbic acid in the human lung epithelial lining fluid can react with Fe(III) from inhaled PM to cause single strand breaks in supercoiled plasmid DNA, ϕX174 RFI (Smith and Aust, 1997). The DNA damage caused by some PM_{10} samples can be inhibited by mannitol, an hydroxyl radical scavenger, further confirming the involvement of free radicals in these

reactions (Gilmour et al., 1996; Donaldson et al., 1997; Li et al., 1997). Because the clear supernatant of the centrifuged PM_{10} suspension contained all of the suspension activity, the free radical activity is derived either from a fraction that is not centrifugable (10 min at 13,000 rpm on a bench centrifuge) or the radical generating system is released into solution (Gilmour et al., 1996; Donaldson et al., 1997; Li et al., 1997).

In addition to measuring the interactions of ROS and biomolecules directly, the role of ROS in PM-induced lung injury also can be assessed by measuring the electron spin resonance (ESR) spectrum of radical adducts or fluorescent intensity of dichlorofluorescin (DCFH), an intracellular dye that fluoresces on oxidation by ROS. Alternatively, ROS can be inhibited using free radical scavengers, such as DMTU; antioxidants, such as glutathione or NAC; or antioxidant enzymes, such as SOD. The diminished response to PM after treatment with these antioxidants may indicate the involvement of ROS; but, some antioxidants (e.g., thiol-containing) can interact with metal ions directly.

As described earlier, Kadiiska et al. (1997) used the ESR spectra of 4-POBN [α-(4-pyridyl-1-oxide)-N-tert-butylnitrone] adducts to measure ROS in rats instilled with ROFA and demonstrated the association between ROS production within the lung and soluble metals in ROFA. Using DMTU to inhibit ROS production, Dye et al. (1997) had shown that systemic administration of DMTU impeded development of the cellular inflammatory response to ROFA, but did not ameliorate biochemical alterations in BAL fluid. Goldsmith et al. (1998), as described earlier, showed that ROFA and CAPs caused increases in ROS production in AMs. The water-soluble component of both CAPs and ROFA significantly increased AM oxidant production over negative control values. In addition, increased PM-induced cytokine production was inhibited by NAC. Li et al. (1996, 1997) instilled rats with PM_{10} particles (collected on filters from an Edinburgh, Scotland monitoring station). Six hours after intratracheal instillation of PM_{10}, they observed a decrease in glutathione (GSH) levels in the BAL fluid. Although this study does not describe the composition of the PM_{10}, the authors suggest that changes in GSH, an important lung antioxidant, support the contention that the free radical activity of PM10 is responsible for its biological activity in vivo.

In addition to ROS generated directly by PM, resident or newly recruited AMs or PMNs also are capable of producing these reactive species on stimulation. The ROS produced during the oxidative burst can be measured using a chemiluminescence (CL) assay. With this assay,

AM CL signals in vitro have been shown to be greatest with ROFA containing primarily soluble V and were less with ROFA containing Ni plus V (Kodavanti et al., 1998a). As described earlier, exposures to Dusseldorf and Duisburg PM increased the resting ROS production in PMNs, which could be inhibited by SOD, catalase, and sodium azide (Hitzfeld et al., 1997). Stringer and Kobzik (1998) showed that addition of NAC (1.0 mM) decreased ROFA-mediated IL-8 production by approximately 50% in normal and TNF-α-primed A549 cells. In addition, exposures of A549 cells to ROFA caused a substantial (and NAC inhibitable) increase in oxidant levels as measured by DCFH oxidation. In human AMs, Becker et al. (1996) found a CL response for ROFA, but not urban air particles (Ottawa and Dusseldorf) or volcanic ash.

Metal compounds of PM are the most probable species capable of catalyzing ROS generation on exposure to airborne PM. To determine elemental content and solubility in relation to their ability to generate ROS, PMN or monocytes were exposed to a wide range of air particles from divergent sources (one natural dust, two types of oil fly ash, two types of coal fly ash, five different ambient air samples, and one carbon black sample), and CL production was measured over a 20-min period postexposure (Prahalad et al., 1999). Percent of sample mass accounted for by X-ray fluorescence (XRF) detectable elements was 1.2% (carbon black); 22 to 29% (natural dust and ambient air particles); 13 to 22% (oil fly ash particles); and 28 to 49% (coal fly ash particles). The major proportion of elements in most of these particles were aluminosilicates and insoluble Fe, except oil derived fly ash particles in which soluble V, and Ni were in highest concentration, consistent with particle acidity as measured in the supernatants. All particles induced CL response in cells, except carbon black. The CL response of PMNs in general increased with all washed particles, with oil fly ash and one urban air particle showing statistical differences between deionized water washed and unwashed particles. These CL activities were significantly correlated with the insoluble Si, Fe, Mn, Ti, and Co content of the particles. No relationship was found between CL and soluble transition metals such as V, Cr, Ni, and Cu. Pretreatment of the particles with a metal ion chelator, DEF, did not affect CL activities. Particle sulfate content and acidity of the particle suspension did not correlate with CL activity.

Soluble metals can be mobilized into the epithelial cells or AMs to produce ROS intracellularly. Size-fractionated coal fly ash particles (2.5, 2.5 to 10, and < 10 μm) of bituminous b (Utah coal), bituminous c (Illinois coal), and lignite (Dakota coal) were used to

compare the amount of iron mobilization in A549 cells and by citrate (1 mM) in cell-free suspensions (Smith et al., 1998). Iron was mobilized by citrate from all three size fractions of all three coal types. More iron, in Fe(III) form, was mobilized by citrate from the < 2.5-μm fraction than from the > 2.5-μm fractions. In addition, the amount of iron mobilized was dependent on the type of coal used to generate the fly ash (Utah coal > Illinois coal = Dakota coal) but was not related to the total amount of Fe present in the particles. Ferritin (an iron storage protein) levels in A549 cells increased by as much as 12-fold in cells treated with coal fly ash (Utah coal > Illinois coal > Dakota coal). More ferritin was induced in cells treated with the < 2.5-μm fraction than with the > 2.5-μm fractions. Mossbauer spectroscopy of a fly ash sample showed that the bioavailable Fe was assocated with the glassy aluminosilicate fraction of the particles (Ball et al., 2000). As with the bioavailability of Fe, there was an inverse correlation between the production of IL-8 and fly ash particle size, with the Utah coal fly ash being the most potent.

Using ROFA and colloidal iron oxide, Ghio et al. (1997b; 1998a,b,c; 1999c; 2000b) have shown that exposures to these particles disrupted Fe homeostasis and induced the production of ROS in vivo and in vitro. Treatment of animals or cells with metal-chelating agents such as DEF with an associated decrease in response has been used to infer the involvement of metal in PM-induced lung injury. Metal chelation by DEF (1 mM) caused significant inhibition of particulate-induced AM oxidant production, as measured using DCFH (Goldsmith et al., 1998). DEF treatment also reduced NF-κB activation and cytokine secretion in BEAS-2B cells exposed to Provo PM (Kennedy et al., 1998). However, treatment of ROFA suspension with DEF was not effective in blocking leachable metal induced acute lung injury (Dreher et al., 1997). Dreher et al. (1997) indicated that DEF could chelate Fe(III) and V(II), but not Ni(II), suggesting that metal interactions played a significant role in ROFA-induced lung injury.

Other than Fe, several V compounds have been shown to increase mRNA levels for selected cytokines in BAL cells and to induce pulmonary inflammation (Pierce et al., 1996). $NaVO_3$ and $VOSO_4$, highly soluble forms of V, tended to induce pulmonary inflammation and inflammatory cytokine mRNA expression more rapidly and intensely than the less soluble form, V_2O_5, in rats. Neutrophil influx was greatest following exposure to $VOSO_4$ and lowest after exposure to V_2O_5. However, metal components of fly ash have not been shown to consistently increase ROS production from bovine AM treated with combustion particles (Schlüter et al., 1995). As(III), Ni(II), and Ce(III), major components of fly ash, did inhibit the secretion of

superoxide anions (O_2^-) and hydrogen peroxide, but in the same study, O_2^- were lowered by Mn(II) and Fe(II), whereas V(IV) increased O_2^- and H_2O_2. In contrast, Fe(III) increased O_2^- production, showing that the oxidation state of a metal may influence its oxidant-generating properties. Other fly ash components, e.g., Cd(II), Cr(III), and V(V), had no effects on ROS.

It is likely that a combination of several metals rather than a single metal in ambient PM is responsible for PM-induced cellular responses. For example, V and Ni+V but not Fe or Ni alone (in saline with the final pH at 3.0) resulted in increased epithelial permeability, decreased cellular glutathione, cell detachment, and lytic cell injury in rat tracheal epithelial cells exposed to soluble salts of these metals at equivalent concentrations found in ROFA (Dye et al., 1999). Treatment of V-exposed cells with buthionine sulfoximine further increased cytotoxicity. Conversely, treatment with radical scavenger DMTU inhibited the effects in a dose-dependent manner. These results suggest that soluble metal or combinations of several metals in ROFA may be responsible for these effects.

Similar to combustion particles such as ROFA, the biological response to exposure to ambient PM also may be influenced by the metal content of the particles. Human subjects were instilled with 500 μg (in 20 mL sterile saline) of Utah Valley dust (UVD1, 2, 3, collected during 3 successive years) in the left segmental bronchus and on the right side with sterile saline as control, followed by phagocytic cells being obtained from the segmental bronchi at 24 h postinstillation. Alveolar macrophage from subjects instilled with UVD, obtained by BAL 24 h postinstillation, were incubated with fluoresceinated yeast (Saccharomyces cerevisiae) to assess their phagocytic ability. Although the same proportion of AMs that were exposed to UVD phagocytized yeast, AMs exposed to UVD1, (which was collected while a local steel mill was open), took up significantly less particles than AMs exposed to other extracts (UVD2 when the steel mill was closed and UVD3 when the plant reopened). AMs exposed to UVD1 also exhibited a small decrease in oxidant activity (using dihydrorhodamine-123, DHR). AMs from healthy volunteers were incubated in vitro with the various UVD extracts to assess whether effects on human AMs could be observed similar to those seen following in vivo exposure. The percentage of AMs that engulfed yeast particles was significantly decreased by exposure to UVD1 at 100 μg/mL, but not at 25 μg/mL. However, the amount of particles engulfed was the same following exposure to all three UVD extracts. AMs also demonstrated increased oxidant stress (using CL) after in vitro exposure to UVD1, and this effect was not abolished with

pretreatment of the extract with the metal chelator DEF. As with the AMs exposed to UVD in vivo, AM exposed to UVD in vitro had a decreased oxidant activity (DHR assay). UVD1 contains 61 times and 2 times the amount of Zn compared to UVD 2 and UVD3, respectively; whereas UVD3 contained 5 times more Fe than UVD1. Ni and V were present only in trace amounts. Using similarly extracted samples, Frampton et al. (1999) exposed BEAS-2B cells for 2 and 24 h. Similar results were observed for oxidant generation in these cells (i.e., UVD 2, which contains the lowest concentrations of soluble Fe, Cu, and Zn, produced the least response). Only UVD 3 produced cytotoxicity at a dose of 500 μg/mL. UVD 1 and 3, but not 2, induced expression of IL-6 and IL-8 in a dose-dependent fashion. Taken together, the above results showed that the biological response to ambient particle extracts is heavily dependent on the source and the chemical composition of PM.

7.4.4.2 Intracellular Signaling Mechanisms

In has been shown that the intracellular redox state of the cell modulates the activity of several transcription factors, including NF-κB, a critical step in the induction of a variety of proinflammatory cytokine and adhesion-molecule genes. NF-κB is a heterodimeric protein complex that in most cells resides in an inactive state in the cell cytoplasm by binding to inhibitory kappa B alpha (IκBα). On appropriate stimulation by cytokines or ROS, IκBα is phosphorylated and subsequently degraded by proteolysis. The dissociation of IκBα from NF-κB allows the latter to translocate into the nucleus and bind to appropriate sites in the DNA to initiate transcription of various genes. Two in vitro studies (Quay et al., 1998; Kennedy et al., 1998) have shown the involvement of NF-κB in particulate-induced cytokine and ICAM-1 production in BEAS-2B cells. Cytokine secretion was preceded by activation of NF-κB and was reduced by treatment with antioxidants or metal chelators. These results suggest that metal-induced oxidative stress may contribute to the initiation phase of the inflammatory cascade following some PM exposures.

A second well-characterized human transcription factor, AP-1, also responds to the intracellular ROS concentration. AP-1 exists in two forms, either in a homodimer of c-Jun protein or a heterodimer consisting of c-Jun and c-Fos. Small amounts of AP-1 already exist in the cytoplasm in an inactive form, mainly as phosphorylated c-Jun homodimer. Many different oxidative stress-inducing stimuli, such as UV light and IL-1, can activate AP-1. Exposure of rat

lung epithelial cells to ambient PM in vitro resulted in increases in c-Jun kinase activity, levels of phosphorylated c-Jun immunoreactive protein, and transcriptional activation of AP-1-dependent gene expression (Timblin et al., 1998). This study showed that interaction of ambient particles with lung epithelial cells initiates a cell signaling cascade related to aberrant cell proliferation.

Early response gene transactivation has been linked to the development of apoptosis, a potential mechanism to account for PM-induced changes in cellular response. Apoptosis of human AMs exposed to urban PM or ROFA (25 μg/mL) was observed by Holian et al. (1998). In addition, both urban PM and ROFA upregulated the expression of the $RFD1^+$ (immune stimulating macrophages) AM phenotype; whereas only ROFA decreased the $RFD1^+7^+$ (suppressor macrophages) phenotype. It has been suggested that an increase in the AM phenotype ratio of $RFD1^+/RFD1^+7^+$ may be related to disease progression in patients with inflammatory diseases. These data showed that urban PM and ROFA can induce apoptosis of human AMs and increase the ratio of AM phenotypes toward a higher immune active state and may contribute to or exacerbate lung inflammation.

Inhaled fine and coarse particles are deposited in the epithelial lining of the nasal and tracheal airways. Somatosensory neurons located in the dorsal root ganglia (DRG) innervate the upper thoracic region of the airways and extend their terminals over and between the epithelial lining of the lumen. Given this anatomical proximity, the sensory fibers and the tracheal epithelial cells that they innervate encounter inhaled pollutants, such as PM, early during inhalation. The differential responses of these cell types to PM derived from various sources (i.e., industrial, residential, volcanic) were examined with biophysical and immunological endpoints (Veronesi et al., 2002a). Although the majority of PM tested stimulated IL-6 release in both BEAS-2B epithelial cells and DRG neurons in a receptor-mediated fashion, the degree of these responses was markedly higher in the sensory neurons. Epithelial cells are damaged or denuded in many common health disorders (e.g., asthma, viral infections), allowing PM particles to directly encounter the sensory terminals and their acid-sensitive receptors.

Another intracellular signaling pathway that could lead to diverse cellular responses such as cell growth, differentiation, proliferation, apoptosis, and stress responses to environmental stimuli, is the phosphorylation-dependent, mitogen-activated protein kinase (MAPK). Significant dose- and time-dependent increases in protein tyrosine phosphate levels have been

seen in BEAS cells exposed to 100 μg/mL ROFA for periods ranging from 5 min to 24 h (Samet et al., 1997). In a subsequent study, the effects of As, Cr, Cu, Fe, Ni, V, and Zn on the MAPK, extracellular receptor kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 in BEAS cells were investigated (Samet et al., 1998). Arsenic, V, and Zn induced a rapid phosphorylation of MAPK in BEAS cells. Activity assays confirmed marked activation of ERK, JNK, and P38 in BEAS cells exposed to As, V, and Zn; Cr and Cu exposure resulted in a relatively small activation of MAPK; whereas Fe and Ni did not activate MAPK. Similarly, the transcription factors c-Jun and ATF-2, substrates of JNK and p38, respectively, were markedly phosphorylated in BEAS cells treated with As, Cr, Cu, V, and Zn. The same acute exposure to As, V, or Zn that activated MAPK was sufficient to induce a subsequent increase in IL-8 protein expression in BEAS cells. All exposures were noncytotoxic based on measurement of LDH release and microscopic examination of trypan blue or propidium iodide exclusion (Samet et al., 1996). These data suggest that MAPK may mediate metal-induced expression of inflammatory proteins in human bronchial epithelial cells. The ability of ROFA to induce activation of MAPKs in vivo was demonstrated by Silbajoris et al. (2000; see Table 7-6). In addition, Gercken et al. (1996) showed that the ROS production induced by PM was markedly decreased by the inhibition of protein kinase C as well as phospholipase A_2. Comparisons of in vitro and in vivo exposures of ROFA to airway epithelial cells requires consideration of in vivo dosimetry and ambient concentrations. Therefore, such extrapolations must be made with caution.

The major cellular response downstream of ROS and the cell signaling pathways described above is the production of inflammatory cytokines or other reactive mediators. In an effort to determine the contribution of cyclooxygenase to the pulmonary responses to ROFA exposure in vivo, Samet et al. (2000) intratracheally instilled Sprague-Dawley rats with ROFA (200 or 500 μg in 0.5 mL saline). These animals were pretreated ip with 1 mg/kg NS398, a specific prostaglandin H synthase 2 (COX2) inhibitor, 30 min prior to intratracheal exposure. At 12 h after intratracheal instillations, ip injections (1 mL of NS398 in 20% ethanol in saline) were repeated. ROFA treatment induced a marked increase in the level of PGE_2 recovered in the BAL fluid, which was effectively decreased by pretreating the animals with the COX2 inhibitor. Immunohistochemical analyses of rat airway showed concomitant expression of COX2 in the proximal airway epithelium of rats treated with soluble fraction of ROFA. This study further showed that, although COX2 products participated in ROFA-induced lung inflammation, the

COX metabolites are not involved in IL-6 expression nor the influx of PMN into the airway. However, the rationale for the use of intraperitoneal challenge was not elaborated.

The production of cytokines and mediators also has been shown to depend on the type of PM used in the experiments. A549 cells (a human airway epithelial cell line) were exposed in vitro to several particulate materials: carbon black (CB, Elftex-12, Cabot Corp.), diesel soot from two sources (ND from NIST, LD produced from General Motors LH 6.2 V8 engine at light duty cycle), ROFA (from the heat exchange section of the Boston Edison), OAA (Ottawa ambient air PM, EHC-93), SiO_2, and Ni_3S_2 at 0.01, 0.03, 0.1, 0.3, 1.0, 3.0, 100, 300, 1000 μg/cm^2 for 18 h (Seagrave and Nikula, 2000). Endpoints included loss of adherence to tissue culture substratum as evaluated by crystal violet staining, cell death measured by LDH release, mitotic fraction and apoptosis, release of IL-8 measured by enzyme-linked immunosorbent assay, and release of alkaline phosphatase measured by enzymatic activity using paranitrophenol phosphate. Results indicated that (a) SiO_2 and Ni_3S_2 caused dose dependent acute toxicity and apototic changes; (b) ROFA and ND were acutely toxic only at the highest concentrations; (c) SiO_2 (30, 100, 300 μg/cm^2) and Ni_3S_2 (10, 30, 100, 300 μg/cm^2) increased IL-8 (three and eight times over the control, respectively) but suppressed IL-8 release at the highest concentration; (d) OAA and ROFA also induced IL-8 but to a lesser degree; and (e) both diesel soots suppressed IL-8 production. The authors speculated that the suppression of IL-8 release may contribute to increased respiratory disease as a result of decreased response to infectious agents. Silicon dioxide and Ni_3S_2 increased the release of alkaline phosphatase, a marker of toxic responses, only slightly. The less acutely toxic compounds caused significant release of alkaline phosphatase. The order of potency in alkaline phosphatase production was OAA > LD = ND > ROFA >> SiO_2 = Ni_3S_2. These results indicate that the type of particle used has a strong influence on the biological response.

Dye et al. (1999) carried out reverse transcriptase-polymerase chain reactions on RNA from rat tracheal epithelial cells to evaluate changes in steady-state gene expression of IL-6, MIP-2, and inducible NOS (iNOS) in cells exposed for 6 h to ROFA (5 μg/cm^2) and Ni, V, or Ni and V (water-soluble equivalent metal solution [pH 3.0]). Expression of MIP-2 and IL-6 genes was significantly upregulated as early as 6 h post-ROFA-exposure in rat tracheal epithelial cells; whereas gene expression of iNOS was maximally increased 24 h postexposure. Vanadium but not Ni appeared to be mediating the effects of ROFA on gene expression. Treatment with

DMTU (4 and 40 mm) inhibited both ROFA and V induced gene expression in a dose-dependent manner.

It appears that many biological responses are produced by PM whether it is composed of a single component or a complex mixture. The newly developed gene DNA microarrays monitors the expressions of many mediator genes that regulate complex and coordinated cellular events involved in tissue injury and repair. Using an array consisting of 27 rat genes representing inflammatory and anti-inflammatory cytokines, growth factors, adhesion molecules, stress proteins, metalloproteinases, vascular tone regulatory molecules, transcription factors, surfactant proteins and antioxidant enzymes, Nadadur et al. (2000) measured pulmonary effects in rats 3 and 24 h following intratracheal instillation of ROFA (3.3 mg/kg), $NiSO_4$ (1.3 μmol/kg), and VSO_4 (2.2 μmol/kg). Their data revealed a 2- to 3-fold increase in the expression of IL-6 and TIMP-1 at 24 h post-Ni exposure. The expression of cellular fibronectin (cFn-EIIIA) and iNOS increased 24 h following ROFA exposure. Cellular fibronectin, interferon, iNOS and ICAM-1 was increased 24 h following Ni exposure and IL-6 was increased 24 h postexposure in V-exposed animals. There was a modest increase in the expression of surfactant protein A (SP-A) and β-actin genes. There was a 2-fold increase in the expression of IL-6 24 h following exposure to ROFA, Ni, and V using the Northern blot analysis. A densitometric scan of an autoradiograph of blots stripped and reprobed with SP-A cDNA insert indicated a minimal increase in the expression of SP-A, both 3 and 24 h postexposure in all test groups. The findings in this study suggest that DNA microarray may provide a tool for screening the expression profile of tissue specific markers following exposure to PM. However, care should be taken in reviewing such findings because of the variations in dose, instillation versus inhalation, and the time-course for gene expression.

To investigate the interaction between respiratory cells and PM, Kobzik (1995) showed that scavenger receptors are responsible for AM binding of unopsonized PM and that different mechanisms mediate binding of carbonaceous dusts such as DPM. In addition, surfactant components can increase AM phagocytosis of environmental particles in vitro, but only slightly relative to the already avid AM uptake of unopsonized particles (Stringer and Kobzik, 1996). Respiratory tract epithelial cells are also capable of binding with PM to secrete cytokine IL-8. Using a cell line A549, Stringer et al. (1996) found that binding of particles to epithelial cells was Ca-dependent for TiO_2 and Fe_2O_3, while α-quartz binding was not Ca-dependent.

In addition, as observed in AMs, PM binding by A549 cells also was mediated by scavenger receptors, albeit those distinct from the heparin-insensitive acetylated-LDL receptor. Furthermore, α-quartz, but not TiO_2 or CAPs, caused a dose-dependent production of IL-8 (range 1 to 6 ng/mL), demonstrating a particle-specific spectrum of epithelial cell cytokine (IL-8) response.

7.4.4.3 Particle Charge and Stimulation of Sensory Nerve Receptors

Colloidal particles carry an inherently negative surface charge (i.e., zeta potential) that attracts protons from their vaporous milieu. These protons form a neutralizing, positive ionic cloud around the individual particle (Hunter, 1981). Several early studies in the 1980s demonstrated the influence of surface charge on toxicity of particulates. Work by Heck and Costa (1983), for example, found crystalline NiS, Ni_3S_2, and NiO, all particulates with strong zeta potentials (i.e., electronegativity) to be more rapidly phagocytosed than amorphous positively-charged NiS. Additionally, they found that freshly suspended amorphous NiS particles were phagocytosed to a greater degree than particles aged for 1 to 7 days in water or culture medium. These data suggested to the authors that a loss of negative charge during aging is responsible for decreased phagocytosis, and correspondingly, decreased carcinogenicity. The significance of particulate aging was also shown by Vallyathan et al. (1988), who compared the effects of freshly-ground and aged silica in isolated rat AM. Freshly ground silica produced greater respiratory burst, hydrogen peroxide release, superoxide anion secretion, and cytotoxicity in AM than the aged dust. The authors suggested that this freshly fractured silica dust is responsible for the pathogenesis of acute silicosis. A similar relationship between fresh and aged particles was also observed with coal dust (Dalal et al., 1989). Both bituminous (72% carbon) and anthracite (95% carbon) coal were ground and assayed for free radical concentration by electron spin resonance spectroscopy. The freshly-ground anthracite coal had both greater concentrations of free radicals and greater free radical activity than the bituminous coal. This free radical activity correlated with toxicity of the coal dust. After several hours of being ground, the coal dust lost significant free radical activity. Further, Dalal et al. examined lung tissue from coal miners at autopsy and found free radicals, which they suggested may be available for biological effects years after deposition.

New insights with regard to the potential importance of particle charge have begun to emerge in connection with the delineation of the important role of sensory nerve receptors in the initiation of PM inflammation, as demonstrated in a series of newly available studies. Neuropeptide and acid-sensitive sensory irritant (i.e., capsaicin, VR1) receptors were first identified on BEAS-2B cells. To address whether PM could initiate airway inflammation through these acid sensitive sensory receptors, BEAS-2B cells were exposed to ROFA from Birmingham, AL. The BEAS-2B cells responded with an immediate increase in $[Ca^{2+}]_i$ at 100 μg/mL ROFA, followed by a concentration-dependent release of inflammatory cytokines (i.e., IL-6, IL-8, TNF-α) and their transcripts at doses of 12 to 200 μg/mL (significance levels not given; Veronesi et al., 1999a). To test the relevance of neuropeptide or capsaicin VR1 receptors to these changes, BEAS-2B cells were pretreated with neuropeptide receptor antagonists or capsazepine (CPZ), the antagonist for the capsaicin (i.e., VR1) receptor. The neuropeptide receptor antagonists reduced ROFA-stimulated cytokine release by 25 to 50%. However, pretreatment of cells with CPZ inhibited the immediate increases in $[Ca^{2+}]_i$, diminished transcript (i.e., IL-6, IL-8, TNF-α) levels and reduced IL-6 cytokine release to control levels (Veronesi et al., 1999a). The above studies suggested that ROFA inflammation was mediated by acid sensitive VR1 receptors located on the sensory nerve fibers that innervate the airway and on epithelial target cells.

Since VR1 irritant receptors were found to respond to acidity (i.e., protonic charge), experiments have been conducted to see if the surface charge carried by ROFA or other PM particles could biologically activate cells and stimulate inflammatory cytokine release. Oortgiesen et al. (2000) measured the mobility of ROFA particles in an electrically charged field (i.e., micro-electrophoresis) microscopically and calculated their zeta potential. Next, synthetic polymer microspheres (SPM) i.e., polymethacrylic acid nitrophenylacrylate microspheres were prepared with attached carboxyl groups to yield SPM particles with a geometric diameter of 2 ± 0.1 and 6 ± 0.3 μm and with negative zeta potentials (−29 mV) similar to ROFA particles. These SPM acted as ROFA surrogates with respect to their size and surface charge, but lacked all contaminants thought to be responsible for its toxicity (e.g., transition metals, sulfates, volatile organics and biologicals). Concentrations of SPM at 18.8 μg/mL and ROFA particles from Birmingham, AL at 50 μg/mL were used to test BEAS-2B cells and mouse DRG sensory neurons, both targets of inhaled PM. Equivalent degrees of biological activation (i.e., increase in

intracellular calcium, $[Ca^{2+}]_i$, IL-6 release) occurred in both cell types in response to either ROFA or SPM, and both responses could be reduced by antagonists to VR1 receptors or acid-sensitive pathways. Neutrally charged SPM (i.e., zeta potential of 0 mV), however, failed to stimulate increases in $[Ca^{2+}]_i$ or IL-6 release (Oortgiesen et al., 2000).

To expand on these findings (Veronesi et al., 2002b), a larger set of PM was obtained from urban (St. Louis, Ottawa), residential (wood stove), volcanic (Mt. St. Helens), and industrial (oil fly ash, coal fly ash) sources. Each PM sample was described physicochemically (i.e., size and number of particles, acidity, zeta potential) and used to test BEAS-2B epithelial cells at a concentration of 10 μg/mL. The resulting biological effect (i.e., increases in $[Ca^{2+}]_i$, IL-6 release) was related to their physicochemical characteristics. When examined by linear regression analysis, the only measured physicochemical property that correlated with increases in $[Ca^{2+}]_i$ and IL-6 release was the zeta potential of the visible particles ($r^2 > 0.97$).

A recent study (Agopyan et al., 2003) has evaluated the hypothesis that the mechanism by which negatively-charged PM acts on bronchial epithelial cells and sensory neurons is by activation of capsaicin-sensitive vanilloid or acid-sensing receptors. They used BEAS-2B cells, HEK293 cells expressing vanilloid receptors, and rat trigeminal ganglion neurons to which they exposed negatively charged 2 and 10 μm polystyrene carboxylate-modified particles. They found that the negatively-charged particles can activate capsazepine- and amiloride-sensitive proton-gated receptors. This activation leads to increases in intracellular Ca^{2+}, cyclic AMP, and IL-6 release. Corroborating this study, Veronesi et al. (2003) conducted similar experiments using positively- or negatively-charged synthetic polystyrene micells exposures to BEAS-2B cells. They reported increases in intracellular Ca^{2+} and IL-6, which they attributed to the negative charge on the particles. This negative charge, they hypothesize, acquires a cloud of protons which then activates the proton-sensitive vanilloid and acid-sensitive receptors.

Thus, both older and newer studies have provided evidence that both the charge and the age of the PM are important factors in its toxicity. Also, several newer in vitro studies demonstrate a plausible neurogenic basis for PM inflammation by which the positively-charged proton cloud associated with negatively-charged colloidal PM particles can activate acid-sensitive VR1 receptors found on human airway epithelial cells and sensory terminals. This activation is thought to result in an immediate influx of calcium and release of inflammatory

cytokines and neuropeptides, which then initiate and sustain inflammatory events in the airways via neurogenic inflammation (Veronesi and Oortgiesen, 2001).

7.4.4.4 Other Potential Cellular and Molecular Mechanisms

A potential mechanism involved in the alteration of surface tension may be related to changes in the expression of matrix metalloproteinases (MMPs), such as pulmonary matrilysin and gelatinase A and B, and tissue inhibitor of metalloproteinase (TIMP; Su et al., 2000a,b). Sprague-Dawley rats exposed to ROFA by intratracheal injection (2.5 mg/rat) had increased mRNA levels of matrilysin, gelatinase A, and TIMP-1. Gelatinase B, not expressed in control animals, was increased significantly from 6 to 24 h following ROFA exposure. Alveolar macrophages, epithelial cells, and inflammatory cells were major cellular sources for the pulmonary MMP expression. The expression of Gelatinase B in rats exposed to the same dose of ambient PM (< 1.7 μm and 1.7 to 3.7 μm) collected from Washington, DC, was significantly increased as compared to saline control; whereas the expression of TIMP-2 was suppressed. Ambient PM between 3.7 and 20 μm also increased the Gelatinase B expression. Increases in MMPs, which degrade most of the extracellular matrix, suggest that ROFA and ambient PM can similarly increase the total pool of proteolytic activity to the lung and contribute in the pathogenesis of PM-induced lung injury. Since no control particles were used in this study, the results must be interpreted with caution because it is possible that any particle administered in high doses could have a similar effect.

7.4.5 Specific Particle Size and Surface Area Effects

Most particles used in laboratory animal toxicology studies are greater than 0.1 μm in size. However, the enormous number and huge surface area of ultrafine particles highlight the likely importance of considering the size of the particle in assessing response. Ultrafine particles with a diameter of 20 nm, when inhaled at the same mass concentration, have a number concentration that is approximately 6 orders of magnitude higher than for a 2.5-μm diameter particle; particle surface area is also greatly increased (Table 7-12).

Many studies assessed in 1996 PM AQCD, as well as here, suggest that the surface of particles or substances released from the surface (e.g., transition metals, organics) interact with biological substrates, and that surface-associated free radicals or free radical-generating systems

TABLE 7-12. NUMBERS AND SURFACE AREAS OF MONODISPERSE PARTICLES OF UNIT DENSITY OF DIFFERENT SIZES AT A MASS CONCENTRATION OF 10 μg/m^3

Particle Diameter (μm)	Particle Number (per cm^3 air)	Particle Surface Area (μm^2 per cm^3 air)
0.02	2400000	3016
0.1	19100	600
0.5	153	120
1	19	60
2.5	1.2	24

Source: Oberdörster (1996a).

may be responsible for toxicity. Thus, if ultrafine particles were to cause toxicity by a transition metal-mediated mechanism, for example, then the relatively large surface area for a given mass of ultrafine particles would imply high concentrations of transition metals being available to cause oxidative stress to cells.

Two groups have examined toxicity differences between fine and ultrafine particles, with the general finding that ultrafine particles show a significantly greater response at similar mass doses (Oberdörster et al., 1992; Li et al., 1996, 1997, 1999). However, only a few studies have investigated the ability of ultrafine particles to generate a greater oxidative stress when compared to fine particles of the same material. Osier and Oberdörster (1997) compared the response of rats (F344) exposed by intratracheal inhalation to "fine" (~250 nm) and "ultrafine" (~21 nm) TiO_2 particles and found the ultra fine particles to be more effective in producing lung inflammatory responses as indexed by several markers.

Consistent with these in vivo studies, Finkelstein et al. (1997) has shown that exposing primary cultures of rat Type II cells to 10 μg/mL ultrafine TiO_2 (20 nm) causes increased TNF and IL-1 release throughout the entire 48-h incubation period. In contrast, fine TiO_2 (200 nm) had no effect. In addition, ultrafine polystyrene carboxylate-modified microspheres (UFP, fluorospheres, Molecular Probes, 44 ± 5 nm) have been shown to induce a significant enhancement of both substance P(SP) and histamine release after administration of capsaicin

(10^{-4} M), to stimulate C-fiber, and carbachol (10^{-4} M), a cholinergic agonist in rabbit intratracheally instilled with UFP (Nemmar et al., 1999). A significant increase in histamine release also was recorded in the UFP-instilled group following the administration of both SP (10^{-6} M) plus thiorpan (10^{-5} M) and compound 48/80 (C48/80, 10^{-3} M) to stimulate mast cells. Bronchoalveolar lavage analysis showed an influx of PMN, an increase in total protein concentration, and an increase in lung wet weight/dry weight ratio. Electron microscopy showed that both epithelial and endothelial injuries were observed. The pretreatment of rabbits in vivo with a mixture of either SR 140333 and SR 48368, a tachykinin NK_1 and NK_2 receptor antagonist, or a mixture of terfenadine and cimetidine, a histamine H_1 and H_2 receptor antagonist, prevented UFP-induced PMN influx and increased protein and lung WW/DW ratio.

It is believed that ultrafine particles cause greater cellular injury because of the relatively large surface area for a given mass. In addition, the fate of ultrafines after deposition is also different in that they interact more rapidly with epithelial target cells rather than to be phagocytized by AMs. However, in a study that compared the response to CB particles of two different sizes, Li et al. (1999) demonstrated that in the instillation model, a localized dose of particle over a certain level causes the particle mass to dominate the response, rather than the surface area. Ultrafine CB (ufCB, Printex 90), 14 nm in diameter, and fine CB (CB, Huber 990), 260 nm in diameter, were instilled intratracheally in rats, and BAL profile at 6 h was assessed. At mass of 125 μg or below, ufCB generated a greater response (increase LDH, epithelial permeability, decrease in GSH, TNF, and NO production) than fine CB at various times postexposure. However, higher doses of CB caused more PMN influx than the ufCB. In contrast to the effect of CB, which showed dose-related increasing inflammatory response, ufCB at the highest dose caused less of a neutrophil influx than at the lower dose, confirming earlier work by Oberdörster et al. (1992). Moreover, when the PMN influx was expressed as a function of surface area, CB produced greater response than ufCB at all doses used in this study. Although particle interstitialization with a consequent change in the chemotatic gradient for PMN was offered as an explanation, these results need further scrutiny. Moreover, these findings imply that mass is relatively less important than surface area and that the latter metric may be more useful for assessing PM toxicity. However, it is unclear if this finding is restricted to the particular endpoints addressed and/or CB, the PM compound studied.

Oberdörster et al. (2000) reported on a series of studies in rats and mice using ultrafine particles of various chemical composition. In rats sensitized with endotoxin (70 EU) and exposed to ozone (1 ppm) plus ultrafine carbon particles (~100 $\mu g/m^3$), they found a 9-fold greater release of ROS in old rats (20 months) than in similarly treated young rats (10 weeks). Exposure to ultrafine PM alone in sensitized old rats also caused an inflammatory response.

Although the potential mechanisms of ultrafine-induced lung injury remain unclear, it is likely that ultrafine particles, because of their small size, are not effectively phagocytized by AMs and can easily penetrate the airway epithelium, gaining access to the interstitium. Using electron microscopy, Churg et al. (1998) examined particle uptake in rat tracheal explants. Explants were exposed to either fine (0.12 μm) or ultrafine (0.021 μm) TiO_2 particles and examined after 3 or 7 days. They found both size particles in the epithelium at both time points; but, in the subepithelial tissues, only at day 7. The volume proportion (the volume of TiO_2 over the entire volume of epithelium or subepithelium area) of both fine and ultrafine particles in the epithelium increased from 3 to 7 days. It was greater for ultrafine at 3 days but was greater for fine at 7 days. The volume proportion of particles in the subepithelium at day 7 was equal for both particles, but the ratio of epithelial to subepithelial volume proportion was 2:1 for fine and 1:1 for ultrafine. Ultrafine particles persisted in the tissue as relatively large aggregates; whereas the size of fine particle aggregates became smaller over time. Ultrafine particles appeared to enter the epithelium faster and, once in the epithelium, a greater proportion of them were translocated to the subepithelial space compared to fine particles. However, the authors assumed that the volume proportion is representative of particle number and the number of particles reaching the interstitial space is directly proportional to the number applied (i.e., there is no preferential transport from lumen to interstitium by size). These data are in contrast to the results of instillation or inhalation of fine and ultrafine TiO_2 particles reported earlier (Ferin et al., 1990, 1992). However, the explant and intratracheal instillation test systems differ in many aspects, making direct comparisons difficult. Limitations of the explant test system include traumatizing the explanted tissue, introducing potential artifacts through the use of liquid suspension for exposure, the absence of inflammatory cells, and possible overloading of the explants with dust.

Two studies examined the influence of specific surface area on biological activity (Lison et al., 1997; Oettinger et al., 1999). The biological responses to various MnO_2 dusts with different specific surface area (0.16, 0.5, 17, and 62 m^2/g) were compared in vitro and in vivo (Lison et al., 1997). In both systems, the results show that the amplitude of the response is dependent on the total surface area that is in contact with the biological system, indicating that surface chemistry phenomena are involved in the biological reactivity. Freshly ground particles with a specific surface area of 5 m^2/g also were examined in vitro. These particles exhibited an enhanced cytotoxic activity that was almost equivalent to that of particles with a specific surface area of 62 m^2/g, indicating that undefined reactive sites produced at the particle surface by mechanical cleavage also may contribute to the toxicity of insoluble particles.

In another study (Oettinger et al., 1999), two types of CB particles were used: (1) Printex 90 or P90 (formed by controlled combustion and consisting of defined granules with specific surface area of 300 m^2/g and particle size of 14 nm) is predominantly loaded with metallic components (< 100 ppm Fe; < 50 ppm Pb; < 10 ppm Se; < 10 ppm As; < 10 ppm Zn); and (2) soot FR 101 (with specific surface area of 20 m^2/g, particle size of < 95 nm) has the ability to adsorb polycyclic and other carbons. Exposure of AMs to 100 $\mu g/10^6$ cells of FR 101 and P90 resulted in a 1.4- and 2.1-fold increase in ROS release, respectively. These exposures also caused a 4-fold up-regulation of NF-κB gene expression. This suggests that carbon particles with larger surface area produce greater biological response than carbon particles with smaller surface area. Another study by Schlüter et al. (1995), showed that by exposing bovine AMs to metal oxide coated 5 μm silica particles, most of the metal coatings (As, Ce, Fe, Mn, Ni, Pb, and V) had no effect on ROS production by these cells. However, coating with CuO markedly lowered the O_2^- and H_2O_2, whereas V(IV) increased both reactive oxygen intermediates (ROI). This study suggests that, in addition to specific surface area, chemical composition of the particle surface also influences its cellular response.

Thus, ultrafine particles apparently have the potential to significantly contribute to the adverse effects of PM. These studies, however, have not considered the portion of ambient ultrafine particles not solid in form. Droplets (e.g., sulfuric acid droplets) and organic-based ultrafine particles exist in the ambient environment; and they can spread, disperse, or dissolve after contact with liquid surface layers and may thereby contribute further to PM-related effects.

7.5 FACTORS AFFECTING SUSCEPTIBILITY TO PARTICULATE MATTER EXPOSURE EFFECTS

Susceptibility of an individual to adverse health effects of PM can vary depending on a variety of host factors such as age, physiological activity profile, genetic predisposition, or preexistent disease. The potential for preexistent disease to alter pathophysiological responses to toxicant exposure is widely acknowledged but poorly understood due, in part, to the statistical limitations of toxicological studies noted earlier. Epidemiologic studies have demonstrated that the effects of PM exposure tend to be more evident in populations with preexisting disease; and it is logical that important mechanistic differences may exist among these populations. However, because of inherent variability (necessitating large numbers of subjects) and ethical concerns associated with using diseased subjects in clinical research studies, a solid database on human susceptibilities is lacking. For more control over both environmental and host variables, animal models are often used. Many laboratory studies have shown alterations in a variety of endpoints in experimental animals following exposure to laboratory-generated particles. These findings (e.g., increased pulmonary inflammation, increased airway resistance, and decrements in pulmonary host defenses) may be of limited value because of inherent differences between the laboratory-generated particles and actual ambient air particle mixes. Thus, care must be taken in extrapolation from animal models of human disease to humans. Rodent models of human disease, their use in toxicology, and the criteria for judging their appropriateness as well as their limitations must be considered (Kodavanti et al., 1998b; Kodavanti and Costa, 1999; Costa, 2000; Conn et al., 2000; Bice et al., 2000; Mauderly et al., 2000; Muggenburg et al., 2000b).

7.5.1 Pulmonary Effects of Particulate Matter in Compromised Hosts

Epidemiologic studies suggest that there may be subsegments of human populations that are especially susceptible to effects from inhaled particles (see Chapter 8). The elderly with chronic cardiopulmonary disease, those with pneumonia and possibly other lung infections, and those with asthma (at any age) appear to be at higher risk than healthy people of similar age. Apropos to this, although many of the newly available toxicology studies used healthy adult animals, a growing number of other newer studies examined effects of ambient or surrogate particles in compromised host models. For example, Costa and Dreher (1997) used a rat model of cardiopulmonary disease to explore the question of susceptibility and possible mechanisms by

which PM effects are potentiated. Rats with advanced monocrotaline (MCT)-induced pulmonary vasculitis/hypertension were given intratracheal instillations of ROFA (0, 0.25, 1.0, and 2.5 mg/rat). The MCT animals had a marked neutrophilic inflammation. In the context of this inflammation, ROFA induced a 4- to 5-fold increase in BAL PMNs. There was also a ROFA dose-dependent increased mortality at 96 h postexposure.

As discussed previously, Kodavanti et al. (1999) also studied PM effects in the MCT rat model of pulmonary disease. Rats treated with 60 mg/kg MCT were exposed to 0, 0.83 or 3.3 mg/kg ROFA by intratracheal instillation and to 15 mg/m^3 ROFA by inhalation. Both methods of exposure caused inflammatory lung responses; and ROFA exacerbated the lung lesions, as shown by increased lung edema, inflammatory cells, and alveolar thickening.

The manner in which MCT can alter the response of rats to inhaled particles was examined by Madl and colleagues (1998). Rats were exposed to fluorescent colored microspheres (1 μm) 2 weeks after treatment with MCT. In vivo phagocytosis of the microspheres was altered in the MCT rats in comparison with control animals. Fewer microspheres were phagocytized in vivo by AMs, and there was a concomitant increase in free microspheres overlaying the epithelium at airway bifurcations. The decrease in in vivo phagocytosis was not accompanied by a similar decrease in vitro. Macrophage chemotaxis, however, was impaired significantly in MCT rats compared with control rats. Thus, MCT appeared to impair particle clearance from the lungs via inhibition of macrophage chemotaxis.

Respiratory infections are common in all individuals. The infections are generally cleared quickly, depending on the virulence of the organism; however, in individuals with immunologic impairment or lung diseases such a COPD, the residence time in the lung is extended. A variety of viral and bacterial agents have been used to develop infection models in animals. Viral infection models primarily use mice and rats. The models focus on the proliferation and clearance of the microorganisms and the associated pulmonary effect. The models range from highly virulent and lethal (influenza A/Hong Kong/8/68, H3N2) to nonlethal (rat-adapted influenza virus model [RAIV]). The lethal model terminates in extensive pneumonia and lung consolidation. Less virulent models (A/Port Chalmers/1/73 and H3N2) exhibit airway epithelial damage and immune responses. The nonlethal model exhibits airway reactivity that subsides, with recovery being complete in about 2 weeks (Kodavanti et al., 1998b). Bacterial infection models mimic the chronic bacterial infections experienced by humans with other underlying

disease conditions. The animal models develop signs similar to those in humans but to a milder degree. To mimic the chronic infections, the bacteria are encased in agar beads to prevent rapid clearance. Generally, the models involve preexposure to the irritant followed by the bacterial challenge. More recently, bacterial infection models have involved pre-exposure by the bacteria followed by exposure to the irritant (Kodavanti et al., 1998b).

Elder et al. (2000a,b) exposed 8-week to 22-months old Fischer 344 rats and 14- to 17-months old T_{sk} mice to 100 μg/m^3 of ultrafine carbon (UF) and/or 1.0 ppm O_3 for 6 h after a 12-min exposure to a low dose (70 EU) of endotoxin (lipopolysaccharide, LPS). The ultrafine carbon had a small effect on lung inflammation and inflammatory cell activation. The effects were enhanced in the compromised lung and in older animals. The greatest effect was in the compromised lung exposed to both ultrafine carbon and ozone.

Chronic bronchitis is the most prevalent of the COPD-related illnesses. In humans, chronic bronchitis is characterized by pathologic airway inflammation and epithelial damage, mucus cell hyperplasia and hypersecretion, airway obstruction and in advance cases, airway fibrosis. The most widely used animal models of bronchitis (rat and dog) are those produced by subchronic exposure to high sulfur dioxide (SO_2) concentrations (150 to 600 ppm) for 4 to 6 weeks. Exposure to SO_2 produces changes in the airways similar to those of chronic bronchitis in humans. There is an anatomical difference between the rat and the human in the absence of submucosal glands in the rat. However, like humans, rats exhibit increased airway responsiveness to inhaled bronchoconstricting agonists. Sulfur dioxide-induced lesions include increased numbers of epithelial mucus-producing cell, loss of cilia, airway inflammation, increased pro-inflammatory cytokine expression, and thickening of the airway epithelium. When the cause of the chronic bronchitis is removed, the pathology slowly reverses. The time course and the extent of reversal differs between the human and rodent. Consequently, care should be exercised when applying this model (Kodavanti et al., 1998b).

The SO_2-induced model of chronic bronchitis has been used to examine the potential interaction of PM with preexisting lung injury. Clarke and colleagues pretreated SD rats for 6 weeks with air or 170 ppm SO_2 for 5 h/day and 5 days/week (Clarke et al., 1999; Saldiva et al., 2002). Exposure to CAPs for 5 h/day for 3 days to PM concentrations ranging from 73.5 to 733 μg/m^3 produced significant changes in both cellular and biochemical markers in lavage fluid. In comparison to control animal values, protein was increased ~3-fold in SO_2-pretreated

animals exposed to concentrated ambient PM. Lavage fluid neutrophils and lymphocytes were increased significantly in both groups of rats exposed to concentrated ambient PM, with greater increases in both cell types in the SO_2-pretreated rats. Thus, exposure to concentrated ambient PM produced adverse changes in the respiratory system, but no deaths, in both normal rats and in a rat model of chronic bronchitis.

Clarke et al. (2000b) next examined the effect of CAPs from Boston, MA, in normal rats of different ages. Unlike the earlier study that used Sprague-Dawley rats, 4- and 20-mo-old Fischer 344 rats were examined after exposure to concentrated ambient PM for 5 h/day for 3 consecutive days. They found that exposure to the daily mean concentrations of 80, 170, and 50 $\mu g/m^3$ PM, respectively, produced statistically significant increases in total neutrophil counts (over 10-fold) in lavage fluid of the young, but not the old, rats. Thus, repeated exposure to relatively low concentrations of ambient PM produced an inflammatory response, although the actual percent neutrophils in the concentrated ambient PM-exposed young adult rats was low (~3%). On the other hand, Gordon et al. (2000) found no evidence of neutrophil influx in the lungs of normal and MCT-treated Fischer 344 rats exposed in nine separate experiments to concentrated ambient PM from New York, NY at concentrations as high as 400 $\mu g/m^3$ for a 6-h exposure or 192 $\mu g/m^3$ for three daily 6-h exposures. Similarly, normal and cardiomyopathic hamsters showed no evidence of pulmonary inflammation or injury after a single exposure to the same levels of concentrated ambient PM. Gordon and colleagues did report a statistically significant doubling in protein concentration in lavage fluid in MCT-treated rats exposed for 6 h to 400 $\mu g/m^3$ New York City CAPs.

Kodavanti and colleagues (1998b) also have examined the effect of CAPs in normal rats and rats with SO_2 chronic bronchitis. Among the four separate exposures to PM, there was a significant increase in lavage fluid protein in bronchitic rats from only one exposure protocol in which the rats were exposed to 444 and 843 $\mu g/m^3$ PM on 2 consecutive days (6 h/day). Neutrophil counts were increased in bronchitic rats exposed to concentrated ambient PM in three of the four exposure protocols, but was decreased in the fourth protocol. No other changes in normal or bronchitic rats were observed, even in the exposure protocols with higher PM concentrations. Thus, rodent studies have demonstrated that inflammatory changes can be produced in normal and compromised animals exposed to CAPs. These findings are important

because only a limited number of studies have used real-time inhalation exposures to actual ambient urban PM.

Pulmonary function measurements are often less invasive than other means to assess the effects of inhaled air pollutants on the mammalian lung. After publication of the 1996 PM AQCD, a number of investigators examined the response of rodents and dogs to inhaled ambient particles. In general, these investigators have demonstrated that ambient PM has minimal effects on pulmonary function. Gordon et al. (2000) exposed normal and MCT-treated rats to filtered air or 181 $\mu g/m^3$ concentrated ambient PM for 3 h. For both normal and MCT-treated rats, no differences in lung volumes or CO diffusing capacities monoxide were observed between the air- or PM-exposed animals at 3 or 24 h after exposure. Similarly, in cardiomyopathic hamsters, concentrated ambient PM had no effect on these same pulmonary function measurements.

Other pulmonary function endpoints have been studied in animals exposed to CAPs. Clarke et al. (1999) observed that tidal volume was increased slightly in both control rats and rats with SO_2-induced chronic bronchitis exposed to 206 to 733 $\mu g/m^3$ PM on 3 consecutive days. No changes in peak expiratory flow, respiratory frequency, or minute volume were observed after exposure to CAPs. In the series of dog studies by Godleski et al. (2000; also see Section 7.3), no signficant changes in pulmonary function were observed in normal mongrel dogs exposed to CAPs, although a 20% decrease in respiratory frequency was observed in dogs that underwent coronary artery occlusion and were exposed to PM. Thus, studies using normal and compromised animal models exposed to CAPs have found minimal biological effects of ambient PM on pulmonary function.

Kodavanti et al. (2000b; 2001) used genetically predisposed spontaneously hypertensive (SH) rats as a model of cardiovascular disease to study PM-related susceptibility. The SH rats were more susceptible to acute pulmonary injury from intratracheal ROFA exposure than normotensive control Wistar Kyoto (WKY) rats (Kodavanti et al., 2001). The primary metal constituents of ROFA, V and Ni, caused differential species-specific effects. Vanadium, which was less toxic than Ni in both strains, caused inflammatory responses only in WKY rats, but Ni was injurious to both WKY and SH rats (SH > WKY). This differential responsiveness of V and Ni was correlated with their specificity for airway and parenchymal injury, discussed in another study (Kodavanti et al., 1998b). When exposed to the same ROFA by inhalation (15 mg/m^3, 6 h/day, 3 days), protein levels in BAL of both the WKY and SH rats increased significantly, but

the increase in SH rats was greater than that of the WKY rats (Kodavanti et al., 2000b). The SH rats exhibited a hemorrhagic response to ROFA. Oxidative stress was much higher in ROFA-exposed SH rats than matching WKY rats. Also, SH rats, unlike WKY rats, showed a compromised ability to increase BAL glutathione in response to ROFA, suggesting a potential link to increased susceptibility. However, LDH and NAG activities were higher in WKY rats. Lactate dehydrogenase was slightly higher in SH rats instilled with ROFA (Kodavanti et al., 2001). Cardiovascular effects were characterized by ST-segment area depression of the ECG in ROFA-exposed SH but not WKY rats. When the same rats were exposed to ROFA by inhalation to 15 mg/m^3, 6 h/day, 3 days/week for 1, 2, or 4 weeks compared to intratracheal exposure to 0, 1.0, 5.0 mg/kg in saline (Kodavanti et al., 2002a), differences in effects were dependent on the length of exposure. After acute exposure, increased plasma fibrinogen was associated with lung injury; longer-term, episodic ROFA exposure resulted in progressive protein leakage and inflammation that was significantly worse in SH rats versus WKY rats. These studies demonstrate the potential utility of cardiovascular disease models for the study of PM health effects and show that genetic predisposition to oxidative stress and cardiovascular disease may play a role in increased sensitivity to PM-related cardiopulmonary injury.

On the basis of in vitro studies, Sun et al. (2001) predicted that the antioxidant and lipid levels in the lung lining fluid may determine susceptibility to inhaled PM. In a subsequent study from the same laboratory, Norwood et al. (2001) conducted inhalation studies on guinea pigs to test this hypothesis. On the basis of dietary supplementation or depletion of ascorbic acid and glutathione (GSH) the guinea pigs were divided into four groups: (+C + GSH), (+C – GSH), (–C + GSH), and (–C – GSH). All groups were exposed (nose-only) for 2 h to clean air or ROFA (< 2.5 μm) at 19-25 mg/m^3. Nasal lavage and BAL fluid and cells were examined at 0 h and 24 h postexposure. Exposure to ROFA increased lung injury in the (-C-GSH) group only (as shown by increased BAL fluid protein, LDH, and PMNs and decreased BAL macrophages) and resulted in lower antioxidant concentrations in BAL fluid than were found with single deficiencies.

In summary, although more of these studies are just beginning to emerge and are only now being replicated or followed more thoroughly to investigate underlying mechanisms, they do provide evidence suggestive of enhanced susceptibility to inhaled PM in “compromised” hosts.

7.5.2 Genetic Susceptibility to Inhaled Particles and Their Constituents

A key issue in understanding adverse health effects of inhaled ambient PM is identification of which classes of individuals are susceptible to PM. Although factors such as age and health status have been studied in both epidemiology and toxicology studies, some investigators have begun to examine the importance of genetic susceptibility in the response to inhaled particles because of evidence that genetic factors play a role in the response to inhaled pollutant gases. To accomplish this goal, investigators typically have studied the interstrain response to particles in rodents. The response to ROFA instillation in different strains of rats has been investigated by Kodavanti et al. (1996, 1997a). In the first study, male SD and F-344 rats were instilled intratracheally with saline or ROFA particles (8.3 mg/kg). ROFA instillation produced an increase in lavage fluid neutrophils in both SD and F-344 rats; whereas a time-dependent increase in eosinophils occurred only in SD rats. In the subsequent study (Kodavanti et al., 1997a), SD, Wistar (WIS), and F-344 rats (60 days old) were exposed to saline or ROFA (8.3 mg/kg) by intratracheal instillation and examined for up to 12 weeks. Histology indicated focal areas of lung damage showing inflammatory cell infiltration as well as alveolar, airway, and interstitial thickening in all three rat strains during the week following exposure. Trichrome staining for fibrotic changes indicated a sporadic incidence of focal alveolar fibrosis at 1, 3, and 12 weeks in SD rats; whereas WIS and F-344 rats showed only a modest increase in trichrome staining in the septal areas. One of the isoforms of fibronectin mRNA was upregulated in ROFA-exposed SD and WIS rats, but not in F-344 rats. Thus, in rats there appears to be a genetic based difference in susceptibility to lung injury induced by instilled ROFA.

Differences in the degree of pulmonary inflammation have been described in rodent strains exposed to airborne pollutants. To understand the underlying causes, signs of airway inflammation (i.e., airway hyper-responsiveness, inflammatory cell influx) were established in responsive (BABL/c) and non-responsive (C57BL/6) mouse strains exposed to ROFA (Veronesi et al., 2000). Neurons taken from the ganglia (i.e., DRG) that innervate the nasal and upper airways were cultured from each mouse strain and exposed to 25 or 50 μg/mL ROFA for 4 h. The difference in inflammatory response noted in these mouse strains in vivo was retained in culture, with C57BL/6 neurons showing significantly lower signs of biological activation (i.e., increased intracellular calcium levels) and cytokine (i.e., IL-6, IL-8) release relative to BALB/c mice. RT-PCR and immunocytochemistry indicated that the BALB/c mouse strain had a

significantly higher number of neuropeptide and acid-sensitive (i.e., NK1, VR1) sensory receptors on their sensory ganglia relative to the C57BL/6 mice. Such data indicate that genetically-determined differences in sensory inflammatory receptors can influence the degree of PM-induced airway inflammation.

Kleeberger and colleagues have examined the role that genetic susceptibility plays in the effect of inhaled acid-coated particles on macrophage function. Nine inbred strains of mice were exposed nose-only to very high doses of carbon particles coated with acid (10 mg/m^3 carbon with 285 μg/m^3 sulfate) for 4 h (Ohtsuka et al., 2000a). Significant inter-strain differences in Fc-receptor-mediated macrophage phagocytosis were seen with C57BL/6J mice being the most sensitive. Although neutrophil counts were increased more in C3H/HeOuJ and C3H/HeJ strains of mice than in the other strains, the overall magnitude of change was small and not correlated with the changes in macrophage phagocytosis. In follow-up studies using the same type particle, Ohtsuka et al. (2000a,b) performed a genome-wide scan with an intercross cohort derived from C57BL/6J and C3H/HeJ mice. Analyses of phenotypes of segregant and nonsegregant populations derived from these two strains indicate that two unlinked genes control susceptibility. They identified a 3-centiMorgan segment on mouse chromosome 17 which contains an acid-coated particle susceptibility locus. Interestingly, this quantitative trait locus (a) overlaps with those described for ozone-induced inflammation (Kleeberger et al., 1997) and acute lung injury (Prows et al., 1997) and (b) contains several promising candidate genes that may be responsible for the observed genetic susceptibility for macrophage dysfunction in mice exposed to acid-coated particles.

Leikauf and colleagues (Leikauf et al., 2000; Wesselkamper et al., 2000; McDowell et al., 2000; Prows and Leikauf, 2001; Leikauf et al., 2001) have identified a genetic susceptibility in mice that is associated with mortality following exposures to high concentrations (from 15 to 150 μg/m^3) of a "$NiSO_4$" aerosol (0.22 μm MMAD) for up to 96 h. These studies also have preliminarily identified the chromosomal locations of a few genes that may be responsible for this genetic susceptibility. Though death is a somewhat crude endpoint in genetic studies, this finding is significant in light of the toxicology studies demonstrating that bioavailable, first-row transition metals participate in acute lung injury following exposure to emission and ambient air particles. Similar genes may be involved in human responses to particle-associated metals; but

additional studies are needed to determine whether the identified metal susceptibility genes are involved in human responses to ambient levels of particulate-associated metals.

One study has examined the interstrain susceptibility to ambient particles. C57BL/6J and C3H/HeJ mice were exposed to 250 $\mu g/m^3$ concentrated ambient $PM_{2.5}$ for 6 h and examined at 0 and 24 h after exposure for changes in lavage fluid parameters and cytokine mRNA expression in lung tissue (Shukla et al., 2000). No interstrain differences in response were observed. Surprisingly, although no indices of pulmonary inflammation or injury were increased over control values in the lavage fluid, increases in cytokine mRNA expression were observed in both murine strains exposed to $PM_{2.5}$. Although the increase in cytokine mRNA expression was generally small (approximately 2-fold), the effects on IL-6, TNF-α, TGF-β2, and γ-interferon were consistent.

Thus, a few studies have begun to demonstrate that genetic susceptibility can play a role in the response to inhaled particles. However, the doses of PM administered in these studies, whether by inhalation or instillation, were extremely high in comparison to ambient PM levels. Similar strain differences in response to inhaled metal particles have been observed by other investigators (McKenna et al., 1998; Wesselkamper et al., 2000), although the concentration of metals used in these studies were also more relevant to occupational rather than environmental exposure levels. The extent to which genetic susceptibility plays as significant a role in the adverse effects of ambient PM as does age or health status remains to be determined.

7.5.3 Particulate Matter Effects on Allergic Hosts

Relatively little is known about the effects of inhaled particles on humoral (antibody) or cell-mediated immunity. Alterations in the response to a specific antigenic challenge have been observed in animal models at high concentrations of acid sulfate aerosols (above 1000 $\mu g/m^3$; Pinto et al., 1979; Kitabatake et al., 1979; Fujimaki et al., 1992). Several studies have reported an enhanced response to nonspecific bronchoprovocation agents, such as acetylcholine and histamine, after exposure to inhaled particles. This nonspecific airway hyperresponsiveness, a central feature of asthma, occurs in animals and human subjects exposed to sulfuric acid under controlled conditions (Utell et al., 1983; Gearhart and Schlesinger, 1986). Although, its relevance to specific allergic responses in the airways of atopic individuals is unclear, it demonstrates that the airways of asthmatics may become sensitized to either specific or

nonspecific triggers that could result in increases in asthma severity and asthma-related hospital admissions (Peters et al., 1997; Jacobs et al., 1997; Lipsett et al., 1997). Combustion particles also may serve as carrier particles for allergens (Knox et al., 1997).

A number of in vivo and in vitro studies have demonstrated that particles (PM) can alter the immune response to challenge with specific antigens and suggest that PM may act as an adjuvant. For example, studies have shown that treatment with diesel particulate matter (DPM) enhances the secretion of antigen-specific IgE in mice (Takano et al., 1997) and in the nasal cavity of human subjects (Diaz-Sanchez et al., 1996, 1997; Ohtoshi et al., 1998; Nel et al., 2001). Because IgE levels play a major role in allergic asthma (Wheatley and Platts-Mills, 1996), upregulation of its production could lead to an increased response to inhaled antigen in particle-exposed individuals.

Van Zijverden et al. (2000) and Van Zijverdan and Granum (2000) used mouse models to assess the potency of particles (diesel, CB, silica) to adjuvate an immune response to a protein antigen. All types of particles exerted an adjuvant effect on the immune response to coadministered antigen, apparently stimulated by the particle core rather than the attached chemical factors. Different particles, however, stimulated distinct types of immune responses. In one model (Van Zijverden et al., 2001), BALB/c mice were intranasally treated with a mixture of antigen (model antigen TNP-Ovalbumin, TNP-OVA) and particles on three consecutive days. On day 10 after sensitization, mice were challenged with the antigen TNP-OVA alone, and five days later the immune response was assessed. Diesel particulate matter, as well as CB, were capable of adjuvating the immune response to TNP-OVA as evidenced by an increase of TNP-specific antibody (IgG1 and IgE) secreting B cells antibodies in the lung-draining lymph nodes. Increased antigen-specific IgG1, IgG2a, and IgE isotypes were measured in the serum, indicating that the response resulted in systemic sensitization. Importantly, an increase of eosinophils in the BAL was observed with CB. Companion studies with the intranasal exposure model showed that the adjuvant effect of CB particles was even more pronounced when the particles were given during both the sensitization and challenge phases; whereas administration during the challenge phase caused only marginal changes in the immune response. These data show that PM can increase both the sensitization and challenge responses to a protein antigen, and the immune stimulating activity of particles appears to be a time-dependent process, suggesting that an

inflammatory microenvironment (such as may be created by the particles) is crucial for enhancing sensitization by particles.

Only a small number of studies have examined mechanisms underlying the enhancement of allergic asthma by ambient urban particles. Ohtoshi et al. (1998) reported that a coarse-size fraction of resuspended ambient PM, collected in Tokyo, induced the production of granulocyte macrophage colony stimulating factor (GMCSF), an upregulator of dendritic cell maturation and lymphocyte function, in human airway epithelial cells in vitro. In addition to increased GMCSF, epithelial cell supernatants contained increased IL-8 levels when incubated with DPM, a principal component of ambient particles collected in Tokyo. Although the sizes of the two types of particles used in this study were not comparable, the results suggest that ambient PM, or at least the DPM component of ambient PM, may be able to upregulate the immune response to inhaled antigen through GMCSF production. Similarly, Takano et al. (1998) has reported airway inflammation, airway hyperresponsiveness, and increased GMGSF and IL-5 in mice exposed to diesel exhaust.

In a study by Walters et al. (2001), PM_{10} was found to induce airway hyperresponsiveness, suggesting that PM exposure may be an important factor contributing to increases in asthma prevalence. Naive mice were exposed to a single dose (0.5 mg/mouse) of ambient PM, coal fly ash, or diesel PM. Exposure to PM_{10} induced increases in airway responsiveness and BAL cellularity; whereas diesel PM induced significant increases in BAL cellularity, but not airway responsiveness. On the other hand, coal fly ash exposure did not elicit significant changes in either of these parameters. Ambient PM-induced airway hyperresponsiveness was sustained over 7 days. The increase in airway responsiveness was preceded by increases in BAL eosinophils; whereas a decline in airway responsiveness was associated with increases in macrophages. Thus, ambient PM can induce asthma-like parameters in naive mice.

Several other studies have examined in greater detail the contribution of the particle component and the organic fraction of DPM to allergic asthma. Tsien et al. (1997) treated transformed IgE-producing human B lymphocytes in vitro with the organic extract of DPM. The organic phase extraction had no effect on cytokine production but did increase IgE production. In these in vitro experiments, DPM appeared to be acting on cells already committed to IgE production, thus suggesting a mechanism by which the organic fraction of combustion particles can directly affect B cells and influence human allergic asthma.

Cultured epithelial cells from atopic asthmatics show a greater response to DPM exposure when compared with cells from nonatopic nonasthmatics. IL-8, GM-CSF, and soluble ICAM-1 increased in response to DPM at a concentration of 10 μg/mL DPM (Bayram et al., 1998a,b). This study suggests that particles could modulate airway disease through their actions on airway epithelial cells. This study also suggests that bronchial epithelial cells from asthmatics are different from those of nonasthmatics in regard to their mediator release in response to DPM.

Sagai and colleagues (1996) repeatedly instilled mice with DPM for up to 16 weeks and found increased numbers of eosinophils, goblet cell hyperplasia, and nonspecific airway hyperresponsiveness, changes which are central features of chronic asthma (National Institutes of Health, 1997). Takano et al. (1997) extended this line of research and examined the effect of repeated instillation of DPM on the antibody response to antigen OVA in mice. They observed that antigen-specific IgE and IgG levels were significantly greater in mice repeatedly instilled with both DPM and OVA. Because this upregulation in antigen-specific immunoglobulin production was not accompanied by an increase in inflammatory cells or cytokines in lavage fluid, it would suggest that, in vivo, DPM may act directly on immune system cells, as described in the work by Tsien et al. (1997). Animal studies have confirmed that the adjuvant activity of DPM also applies to the sensitization of Brown-Norway rats to timothy grass pollen (Steerenberg et al., 1999).

Steerenberg et al. (2003) expanded on these findings using a range of PM collected for the EU study, "Respiratory Allergy and Inflammation Due to Ambient Particles." The Brown Norway rat (BN) was utilized as a pollen allergy model and the BALB/c mouse was used as an OVA allergy model. PM included were two DEP samples (DEP_I from Lovelace Respiratory Research Institute, DEP_{II} from NIST, SRM 2975), ROFA (collected in Niagra, NY), Ottawa dust (EHC-93), and road tunnel dust (RTD, collected in Noord tunnel near Hendrik-Ido Ambacht, NL). Endotoxins in the PM were below detection levels except for EHC-93 (50 ng endotoxin/mL) and RTD (1 ng endotoxin/mL). The animals were exposed to either just allergen or allergen and PM combined during the sensitization and/or challenge phases. In the BN pollen model only DEP_1 stimulated IgE and IgG response to pollen allergens. The pollen + PM rats had fewer eosinophilic granulocytes than rats exposed to pollen alone. In the BALB/c OVA model all of the PM samples when coexposed with OVA during the sensitization phase (but not the challenge phase), created increases in IgE serum responses. Both histopathological examination

of the lung and BAL analysis showed inflammatory response in the lung, predominantly due to an influx of eosinophilic granulocytes. Increases were also seen in BAL levels of IL-4. The authors ranked the adjuvant capacity of the particles tested based on the OVA model results as: RTD > ROFA > EHC-93 > DEP_I > DEP_{II}.

Diaz-Sanchez and colleagues (1996) have continued to study the mechanism of DPM-induced upregulation of allergic response in the nasal cavity of human subjects. In one study, a 200-μL aerosol bolus containing 0.15 mg of DPM was delivered into each nostril of subjects with or without seasonal allergies. In addition to increases in IgE in nasal lavage fluid (NAL), they found an enhanced production of IL-4, IL-6, and IL-13, cytokines known to be B cell proliferation factors. The levels of several other cytokines also were increased, suggesting a general inflammatory response to a nasal challenge with DPM. In a following study, these investigators delivered ragweed antigen, alone or in combination with DPM, on two occasions, to human subjects with both allergic rhinitis and positive skin tests to ragweed (Diaz-Sanchez et al., 1997). They found that the combined challenge with ragweed antigen and DPM produced significantly greater antigen-specific IgE and IgG4 in NAL. A peak response was seen at 96 h postexposure. The combined treatment also induced expression of IL-4, IL-5, IL-10, and IL-13, with a concomitant decrease in expression of Th1-type cytokines. Although the treatments were not randomized (antigen alone was given first to each subject), the investigators reported that pilot work showed no interactive effect of repeated antigen challenge on cellular and biochemical markers in NAL. Diesel PM also resulted in the nasal influx of eosinophils, granulocytes, monocytes, and lymphocytes, as well as the production of various inflammatory mediators. The combined DPM plus ragweed exposure did not increase the rhinitis symptoms beyond those of ragweed alone. Thus, DPM can produce an enhanced response to antigenic material in the nasal cavity.

Extrapolation of these findings of enhanced allergic response in the nose to extremely high concentrations of DPM to the human lung would suggest that ambient combustion particles containing any ambient PM may have significant effects on allergic asthma. A study by Nordenhall et al. (2001) has addressed the effects of diesel PM on airway hyperresponsiveness, lung function and airway inflammation in a group of atopic asthmatics with stable disease. All were hyperresponsive to methacholine. Each subject was exposed to DE (DPM = 300 $\mu g/m^3$) and air for 1 h on two separate occasions. Lung function was measured before and immediately

after the exposures. Sputum induction was performed 6 h, and methacholine inhalation test 24 h, after each exposure. Exposure to DE was associated with a significant increase in the degree of hyperresponsiveness, as compared to after air, a significant increase in airway resistance and in sputum levels of interleukin (IL)-6 ($p = 0.048$). No changes were detected in sputum levels of methyl-histamine, eosinophil cationic protein, myeloperoxidase, and IL-8.

These studies provide biological plausibility support for the exacerbation of allergic asthma likely being associated with episodic exposure to PM. Although DPM may make up only a fraction of the mass of urban PM, because of their small size, DPM may represent a significant fraction of the ultrafine particle mode in urban air, especially in cities and countries that rely heavily on diesel-powered vehicles.

In an examination of the effect of concentrated ambient PM on airway responsiveness in mice, Goldsmith et al. (1999) exposed control and OVA-sensitized mice to an average concentration of 787 $\mu g/m^3$ PM for 6 h/day for 3 days. Although OVA sensitization itself produced an increase in the nonspecific airway responsiveness to inhaled methylcholine (MCh), concentrated ambient PM did not change the response to MCh in OVA-sensitized or control mice. For comparison, these investigators examined the effect of inhalation of an aerosol of the active soluble fraction of ROFA on control and OVA-sensitized mice and found that ROFA could produce nonspecific airway hyperresponsiveness to MCh in both control and OVA-sensitized mice. Similar increases in airway responsiveness have been observed after exposure to ROFA in normal and OVA-sensitized rodents (Gavett et al., 1997, 1999; Hamada et al., 1999, 2000).

Gavett et al. (1999) have investigated the effects of ROFA (intratracheal instillation) in OVA sensitized and challenged mice. Instillation of 3 mg/kg (~ 60 µg) ROFA induced inflammatory and physiological responses in the OVA mice that were related to increases in Th2 cytokines (IL-4, IL-5). Compared to OVA sensitization alone, ROFA induced greater than additive increases in eosinophil numbers and in airway responsiveness to MCh.

Hamada et al. (1999, 2000) have examined the effect of a ROFA leachate aerosol in a neonatal mouse model of allergic asthma. In the first study, neonatal mice sensitized by intraperitoneal (ip) injection with OVA developed airway hyperresponsiveness, eosinophilia, and elevated serum anti-OVA IgE after a challenge with inhaled OVA. Exposure to the ROFA

leachate aerosol had no marked effect on the airway responsiveness to inhaled MCh in nonsensitized mice, but did enhance the airway hyperresponsiveness to MCh produced in OVA-sensitized mice. No other interactive effects of ROFA exposure with OVA were observed. In a subsequent study, Hamada et al. clearly demonstrated that, whereas inhaled OVA alone was not sufficient to sensitize mice to a subsequent inhaled OVA challenge, pretreatment with a ROFA leachate aerosol prior to the initial exposure to aerosolized OVA resulted in an allergic response to the inhaled OVA challenge. Thus, exposure to a ROFA leachate aerosol can alter the immune response to inhaled OVA both at the sensitization stage at an early age and at the challenge stage.

Lambert et al. (1999) and Gilmour et al. (2001) also examined the effect of ROFA on a rodent model of pulmonary allergy. Rats were instilled intratracheally with 200 or 1000 μg ROFA 3 days prior to sensitization with house dust mite (HDM) antigen. HDM sensitization after 1000 μg ROFA produced increased eosinophils, LDH, BAL protein, and IL-10 relative to HDM alone. Although ROFA treatment did not affect antibody levels, it did enhance pulmonary eosinophil numbers. The immediate bronchoconstrictive and associated antigen-specific IgE response to a subsequent antigen challenge was increased in the ROFA-treated group in comparison with the control group. Together, these studies suggest that components of ROFA can augment the immune response to antigen.

Evidence that metals are responsible for augmentation of an allergic sensitization by ROFA was demonstrated by Lambert et al. (2000). In this follow-up study, BN rats were instilled with 1 mg ROFA or the three main metal components of ROFA (Fe, V, or Ni) prior to sensitization with instilled HDM. The three individual metals augmented different aspects of the immune response to HDM: Ni and V produced an enhanced immune response to the antigen as seen by higher HDM-specific IgE serum levels after an antigen challenge at 14 days after sensitization, Ni and V also produced an increase in the lymphocyte proliferative response to antigen in vitro; and the antigen-induced bronchoconstrictive response was greater only in Ni-treated rats. Thus, instillation of metals at concentrations equivalent to those present in the ROFA leachate mimicked the response to ROFA, suggesting that the metal components of ROFA may be responsible for increased allergic sensitization observed in ROFA-treated animals.

Although these studies demonstrate that inhalation or instillation of ROFA augments the immune response in allergic hosts, the applicability of these findings to ambient PM is an important consideration. Goldsmith et al. (1999) compared the effects of inhalation of CAPs for 6 h/day for 3 days versus the effect of a single exposure to a ROFA leachate aerosol on the airway responsiveness to MCh in OVA-sensitized mice. Exposure to ROFA leachate aerosols at a concentration of 50 ng/mL significantly enhanced the airway hyperresponsiveness in OVA-sensitized mice; whereas exposure to CAPs (average concentration of 787 $\mu g/m^3$) had no effect on airway responsiveness in six separate experiments. Thus, the effect of the ROFA leachate aerosols on the induction of airway hyperresponsiveness in allergic mice was significantly different than that of high concentrations of ambient PM. Although airway responsiveness was examined at only one postexposure time point, these findings do suggest that a great deal of caution should be used in interpreting the results of studies using ROFA particles or leachates in efforts to investigate the biologic plausibility of the adverse health effects of ambient PM.

7.5.4 Resistance to Infectious Disease

Development of an infectious disease requires both the presence of an appropriate pathogen and host susceptibility to the pathogen. There are numerous specific and nonspecific host defenses against microbes, and the ability of inhaled particles to modify resistance to bacterial infection could result from a decreased ability either to clear or to kill microbes. Rodent infectivity models have frequently been used to examine effects of inhaled particles on host defense and infectivity. Mice or rats are challenged with a bacterial or viral load either before or after exposure to the particles (or gas) of interest; mortality rate, survival time, or bacterial clearance are then examined. Numerous studies that used the infectivity model to assess inhaled PM effects were assessed previously (U.S. Environmental Protection Agency, 1982, 1989, 1996a). In general, acute exposure to sulfuric acid aerosols at concentrations up to 5,000 $\mu g/m^3$ were not very effective in enhancing mortality in a bacterially-mediated murine model. In rabbits, however, sulfuric acid aerosols altered anti-microbial defenses after exposure to 750 $\mu g/m^3$ for 2 h/day for 4 days (Zelikoff et al., 1994). Acute or short-term repeated exposures to high concentrations of relatively inert particles have produced conflicting results.

Carbon black (10,000 μg/m^3) was found to have no effect on susceptibility to bacterial infection (Jakab, 1993); whereas TiO_2 (20,000 μg/m^3) decreased the clearance of microbes and the bacterial response of lymphocytes isolated from mediastinal lymph nodes (Gilmour et al., 1989a,b). Also, exposure to DPM (2 mg/m^3, 7 h/day, 5 days/week for 3 and 6 months) has been shown to enhance the susceptibility of mice to the lethal effects of some, but not all, microbial agents (Hahon et al., 1985). Pritchard et al. (1996) observed in CD-1 mice exposed by instillation to particles (0.05 mL of a 1.0 mg/mL suspension) with a high concentration of metals (e.g., ROFA), that the increased mortality rate after streptococcus infection was associated with the amount of metal in the PM. Thus, the pulmonary defense responses to microbial agents has been altered at relatively high particle concentrations in animal models, with observed effects being highly dependent on the microbial challenge and the test animal studied.

There are a few more recent studies that have examined mechanisms potentially responsible for the effect of PM on infectivity. In one study, Cohen and colleagues (1997) examined the effect of inhaled V on immunocompetence. Healthy rats were repeatedly exposed first to 2 mg/m^3 V, as ammonium metavanadate, and then instilled with polyinosinic-polycytidilic acid (poly I:C), a double-stranded polyribonucleotide that acts as a potent immunomodulator. Increases in lavage fluid protein and neutrophils were greater in animals preexposed to V. Similarly, IL-6 and interferon-gamma were increased in V-exposed animals. Alveolar macrophage function, as determined by zymosan-stimulated superoxide anion production and by phagocytosis of latex particles, was also depressed more after poly I:C instillation in V-exposed rats as compared to filtered air-exposed rats. These findings provide evidence that inhaled V, a trace metal found in combustion particles and shown to be toxic in vivo in studies using instilled or inhaled ROFA (Dreher et al., 1997; Kodavanti et al., 1997b, 1999), has the potential to inhibit the pulmonary response to microbial agents. However, it must be remembered that these effects were found at very high exposure concentrations of V, and care must be taken in extrapolating the results to ambient exposures of healthy individuals or those with preexisting cardiopulmonary disease to trace concentrations (~3 orders of magnitude lower concentration) of metals in ambient PM.

7.6 RESPONSES TO PARTICULATE MATTER AND GASEOUS POLLUTANT MIXTURES

Ambient PM itself is comprised of mixtures of particles of varying size and composition which coexist in outdoor and indoor air with a number of ubiquitous co-pollutant gases (e.g., O_3, SO_2, NO_2, CO) and innumerable other non-PM components that are not routinely measured. The following discussion examines effects of mixtures of ambient PM or PM constituents with gaseous pollutants, as evaluated by studies summarized in Table 7-13. Toxicological interactions between PM and gaseous co-pollutants may be antagonistic, additive, or synergistic (Mauderly, 1993). The presence and nature of any interaction likely depends on chemical composition, size, concentration and ratios of pollutants in the mixture, exposure duration, and the endpoint being examined. It is difficult to predict *a priori* from the presence of certain pollutants whether any interaction will occur and, if so, whether it will be synergistic, additive, or antagonistic.

Mechanisms responsible for the various forms of interaction are speculative. In terms of potential health effects, the greatest hazard from pollutant interaction is the possibility of synergy between particles and gases, especially if effects occur at concentrations at which no effects occur when individual constituents are inhaled. Various physical and chemical mechanisms may underlie synergism. For example, physical adsorption or absorption of some other material on a particle could result in transport to more sensitive sites or accumulation at sites where this material would not normally be deposited in toxic amounts. This physical process may explain, for example, interactions found in studies of mixtures of CB and formaldehyde or of CB and acrolein (Jakab, 1992, 1993). However, an earlier study (Rothenberg et al., 1989) has demonstrated that, based on the physical and chemical characteristics of formaldehyde, a 1-h 1-ppm exposure to formaldehyde and dust would result in deposition of ~500 μg of formaldehyde vapor into the upper respiratory tract and deposition of only 2 to 50 ng of formaldehyde adsorbed to dust into the pulmonary compartment. Thus, an important factor in PM/gaseous mixture dose evaluation is the equilibrium that exists between the vapor phase of the gas and the particle-associated gas.

Also, chemical interactions between PM and gases can occur on particle surfaces, thus forming secondary products whose surface layers may be more active toxicologically than the primary materials and that can then be carried to a sensitive site. The hypothesis of such

TABLE 7-13. RESPIRATORY AND CARDIOVASCULAR EFFECTS OF PM AND GASEOUS POLLUTANT MIXTURES

Species, Gender, Strain Age, or Body Weight	Gases and PM	Exposure Technique	Exposure Concentration	Particle Size	Exposure Duration	Cardiopulmonary Effects of Inhaled PM and Gases	Reference
Humans; healthy 15 M, 10 F, 34.9±10 years of age	CAPs + O_3 Filtered air (control)	Inhalation	150 µg/m^3 CAPs 120 ppm O_3 1.6 µg/m^3 $PM_{2.5}$ 8.5 ppb O_3	$PM_{2.5}$ $PM_{2.5}$	2 h 2h	$PM_{2.5}$ CAPs + O_3 exposure increased acute brachial artery vasoconstriction (as determined by vascular ultrasonography performed before and 10 min after exposure), but not endothelial-dependent or -independent nitroglycerine-mediated dilation. Lack of comparison between exposure to PM or O_3 alone precludes attribution of observed effects to PM or O_3 alone or to joint effect.	Brook et al. (2002)
Mice, BALB/c, 3 days old	CAPs (Boston) O_3 CAPs + O_3	Inhalation	0-1500 µg/m^3 0.3 ppm 100-500 µg/m^3 + 0.3 ppm	$PM_{2.5}$	5 h	A small increase in pulmonary resistance and airway responsiveness was found in both normal mice and mice with ovalbumin-induced asthma immediately after exposure to CAPs, but not O_3; no evidence of synergy; activity attributed to the AlSi PM component. For every 100 µg/m^3 CAPs, Penh increased 0.86%.	Kobzik et al. (2001)
Rats	Resuspended Ottawa urban PM and O_3	Inhalation (whole-body)	5,000 or 50,000 µg/m^3 PM and 0.8 ppm O3		Single 4-h exposure	PM alone caused no change in cell proliferation in bronchioles or parenchyma. Coexposure at both dose levels with O_3 greatly potentiated the proliferative changes induced by O_3 alone. These changes were greatest in the epithelium of the terminal bronchioles and alveolar ducts.	Vincent et al. (1997)
Rats	Ottawa urban PM and O_3	Inhalation	40,000 µg/m^3 and 0.8 ppm O_3	4.5 µm MMAD	Single 4-h exposure followed by 20 h clean air	Coexposure to particles potentiated O_3-induced septal cellurity. Enhanced septal thickening associated with elevated production of macrophage inflammatory protein-2 and endothelin 1 by lung lavage cells.	Bouthillier et al. (1998)
Rats, F344: male and female 9 weeks old	Ambient particles and gases	Natural 23 h/day exposure to filtered and unfiltered Mexico City air.	0.018 ppm O_3 3.3 ppb CH_2O 0.068 mg/m^3 TSP 0.032 mg/m^3 PM_{10} 0.016 mg/m^3 $PM_{2.5}$		23 h/day for 7 weeks	Histopathology examination revealed no nasal lesions in exposed or control rats; tracheal and lung tissue from both groups showed similar levels of minor abnormalities.	Moss et al. (2001)

TABLE 7-13 (cont'd). RESPIRATORY AND CARDIOVASCULAR EFFECTS OF PM AND GASEOUS POLLUTANT MIXTURES

Species, Gender, Strain Age, or Body Weight	Gases and PM	Exposure Technique	Exposure Concentration	Particle Size	Exposure Duration	Cardiopulmonary Effects of Inhaled PM and Gases	Reference
Humans, children: healthy (N = 15) asthma (N = 26); Age 9-12 years	H_2SO_4, SO_2, and O_3	Inhalation (chamber)	100 ± 40 µg/m^3 H_2SO_4, 0.1 ppm SO_2, and 0.1 ppm O_3	0.6 µm H_2SO_4	Single 4-h exposure with intermittent exercise	Positive association seen between acid dose and respiratory symptoms, but not spirometry, in asthmatic children. No significant changes in healthy children.	Linn et al. (1997)
Rats	H_2SO_4 and O_3	Inhalation, whole body	20 to 150 µg/m^3 H_2SO_4 and 0.12 or 0.2 ppm O_3	0.4 to 0.8 µm	Intermittent (12 h/day) or continuous exposure for up to 90 days	No interactive effect of H_2SO_4 and O_3 on biochemical and morphometric endpoints.	Last and Pinkerton (1997)
Rats, S-D, male, 250-300 g	H_2SO_4 and O_3	Inhalation, nose-only	500 µg/m^3 H_2SO_4 aerosol (two different particle sizes), with or without 0.6 ppm O_3	Fine (0.3 µm MMD, σ_g = 1.7) and ultrafine (0.06 µm, σ_g = 1.4)	4 h/day for 2 days	The volume percentage of injured alveolar septae was increased only in the combined ultrafine acid/O_3 animals. BrdU labeling in the periacinar region was increased in a synergistic manner in the combined fine acid/O_3 animals.	Kimmel et al. (1997)
Rats, S-D 300 g	H_2SO_4-coated carbon and O_3.	Inhalation, nose-only	0.2 ppm O_3 + 50 µg/m^3 C + 100 µg/m^3 H_2SO_4 0.4 ppm O_3 +250 µg/m^3 C +500 µg/m^3 H_2SO_4	0.26 µm σ_g = 2.2	4 h/day for 1 day or 5 days	No airway inflammation at low dose. Greater inflammatory response at high dose; greater response at 5 days than 1 day. Contrasts with O_3 alone where inflammation was greatest at 0.40 ppm on Day 1.	Kleinman et al. (1999)
Mice, Swiss: female, age 5 weeks	Carbon and SO_2	Inhalation, flow-past, nose-only	10,000 µg/m^3 carbon with or without 5 to 20 ppm SO_2 at 10% or 85% RH	0.3 µm MMAD σ_g = 2.7	Single 4-h exposure	Macrophage phagocytosis was depressed only in animals exposed to the combination of SO_2 and carbon at 85% humidity. This inhibition in macrophage function lasted at least 7 days after exposure.	Jakab et al. (1996) Clarke et al. (2000c)
Rats, Fischer NNia, male, 22 to 24 months old	Carbon, ammonium bisulfate, and O_3	Inhalation	50 µg/m^3 carbon + 70 µg/m^3 ammonium bisulfate + 0.2 ppm O_3 or 100 µg/m^3 carbon +140 µg/m^3 ammonium bisulfate + 0.2 ppm O_3	0.4 µm MMAD σ_g = 2.0	4 h/day, 3 days/week for 4 weeks	No changes in protein concentration in lavage fluid or in prolyl 4-hydroxylase activity in blood. Slight, but statistically significant decreases in plasma fibronectin in animals exposed to the combined atmospheres compared to animals exposed to O_3 alone.	Bolarin et al. (1997)

TABLE 7-13 (cont'd). RESPIRATORY AND CARDIOVASCULAR EFFECTS OF PM AND GASEOUS POLLUTANT MIXTURES

Species, Gender, Strain Age, or Body Weight	Gases and PM	Exposure Technique	Exposure Concentration	Particle Size	Exposure Duration	Cardiopulmonary Effects of Inhaled PM and Gases	Reference
Rats	Elemental carbon + O_3 + ammonium bisulfate	Inhalation	0.2 ppm O_3 + elemental carbon 50 µm/m^3 + ammonium bisulfate 70 µg/m^3	0.46 µm 0.3 µm	4 h/day 3 days/week 4 weeks	Increased macrophage phagocytosis and increased respiratory burst; decreased lung collagen.	Kleinman et al. (2000)
Rats, F344/N male	O_3 + nitric acid NO_2 + carbon particles + ammonium bisulfate	Inhalation	low: 0.16 ppm + 0.11 ppm + 0.05 mg/m^3 + 0.03 mg/m^3 medium: 0.3 ppm + 0.21 ppm + 0.06 mg/m^3 + 0.1 mg/m^3 high: 0.59 ppm + 0.39 ppm + 0.1 mg/m^3 + 0.22 mg/m^3	0.3 µm	4 h/day 3 days/week 4 weeks	Dose-dependent decrease in macrophage Fc-receptor mediated-phagocytosis (only significant in high dose group), nonsignificant increase in epithelial permeability and proliferation, altered breathing pattern in high dose group.	Mautz et al. (2001)
Rats, F344/N male	O_3 HNO_3 O_3 + HNO_3	Inhalation	0.151 ± 0.003 ppm 51.1 ± 5.4 µg/m^3 0.152 ± 0.003 ppm + 49.9 ±7.0 µg/m^3		4 h/day 3 days/week 40 weeks	Increased lung putrescine content in all exposed rats. Synergistic effect.	Sindhu et al. (1998)

chemical interactions has been examined in gas and particle exposure studies by Amdur and colleagues (Amdur and Chen, 1989; Chen et al., 1992) and Jakab and colleagues (Jakab and Hemenway, 1993; Jakab et al., 1996). These investigators have suggested that synergism occurs as secondary chemical species are produced, especially under conditions of increased temperature and relative humidity.

Another potential mechanism of gas-particle interaction may involve a pollutant-induced change in the local microenvironment of the lung, enhancing the effects of the co-pollutant. For example, Last et al. (1984) suggested that the observed synergism between ozone (O_3) and acid sulfates in rats was due to a decrease in the local microenvironmental pH of the lung following deposition of acid, enhancing the effects of O_3 by producing a change in the reactivity or residence time of reactants, such as radicals, involved in O_3-induced tissue injury.

One newly available controlled exposure study evaluated the effects of a combined inhalation exposure to $PM_{2.5}$ CAPs and O_3 in human subjects. In a randomized, double-blind crossover study, Brook et al. (2002) exposed 25 healthy male and female subjects, 34.9 ± 10 (SD) years of age, to filtered ambient air containing 1.6 μg/m^3 $PM_{2.5}$ and 8.5 ppb O_3 (control) or to unfiltered air containing 150 μg/m^3 $PM_{2.5}$ CAPs and 120 ppb O_3 while at rest for 2 h. Blood pressure was measured and high-resolution brachial artery ultrasonography (BAUS) was performed prior to and 10 min after exposure. The BAUS technique was used to measure brachial artery diameter (BAD), endothelium-dependent flow-mediated dilation (FMD), and endothelial-independent nitroglycerine-mediated dilation (NMD). Although no changes in blood pressure or endothelial-dependent or endothelial-independent dilatation were observed, a small (2.6%) but statistically significant ($p = 0.007$) decrease in BAD was observed in CAPs plus O_3 exposures (−0.09 mm) when compared to filtered air exposures (+0.01 mm). Preexposure BAD showed no significant day-to-day variation (± 0.03 mm). This finding suggests that combined exposure to a mixture of $PM_{2.5}$ CAPs plus O_3 produces vasoconstriction, potentially via autonomic reflexes or as the result of an increase in circulating endothelin, as has been described in rats exposed to urban PM (Vincent et al., 2001). It is not known, however, whether this effect is caused by CAPs or O_3 alone. The likelihood that analogous vasoactive responses could be found at ambient $PM_{2.5}$ and O_3 levels typically found in some U.S. urban locations is enhanced by the fact that such responses would likely have been seen at distinctly lower exposure levels

had the PM and O_3 exposures occurred during light, moderate, or heavy exercise (which enhances delivery of both PM and O_3 to lower regions of the respiratory tract).

The interaction of PM and O_3 was further examined in a murine model of OVA-induced asthma. Kobzik et al. (2001) investigated whether coexposure to inhaled, concentrated PM from Boston, MA and to O_3 could exacerbate asthma-like symptoms. On days 7 and 14 of life, half of the BALB/c mice used in this study were sensitized by ip injection of OVA and then exposed to OVA aerosol on three successive days to create the asthma phenotype. The other half received the ip OVA, but were exposed to a phosphate-buffered saline aerosol (controls). The mice were further subdivided ($n \geq 61$/group) and exposed for 5 h to CAPs, ranging from 63 to 1569 $\mu g/m^3$, 0.3 ppm O_3, CAPs + O_3, or to filtered air. Pulmonary resistance and airway responsiveness to an aerosolized MCh challenge were measured after exposures. A small, statistically significant increase in pulmonary resistance and airway responsiveness, respectively, was found in both normal and asthmatic mice immediately after exposure to CAPs alone and to CAPs + O_3, but not to O_3 alone or to filtered air. By 24 h after exposure, the responses returned to baseline levels. No significant increases in airway inflammation were seen after any of the pollutant exposures. In this well-designed study of a small-animal model of asthma, CAPs and O_3 did not appear to be synergistic. In further analysis of the data using specific elemental groupings of the CAPs, the acutely increased pulmonary resistance was found to be associated with the AlSi fraction of PM. Thus, some components of concentrated $PM_{2.5}$ may affect airway caliber in sensitized animals.

Linn and colleagues (1997) examined the effect of a single exposure to 60 to 140 $\mu g/m^3$ H_2SO_4, 0.1 ppm SO_2, and 0.1 ppm O_3 in healthy (N = 15) and asthmatic children (N = 26). The children performed intermittent exercise during the 4-h exposure to increase the inhaled dose of the pollutants. An overall effect on the combined group of healthy and asthmatic children was not observed. The combined pollutant exposure had no effect on spirometry in asthmatic children, and no changes in symptoms or spirometry were observed in healthy children. A positive association between acid concentration and symptoms was seen, however, in the subgroup of asthmatic children. Thus, the effect of combined exposure to PM and gaseous co-pollutants appeared to have less effect on asthmatic children exposed under controlled laboratory conditions in comparison with field studies of children attending summer camp (Thurston et al., 1997). However, prior exposure to H_2SO_4 aerosol may enhance the subsequent

response to O_3 exposure (Linn et al., 1994; Frampton et al., 1995); and the timing and sequence of the exposures may be important.

Vincent et al. (1997) exposed rats to 5 or 50 mg/m^3 of resuspended Ottawa urban ambient particles for 4 h in combination with 0.8 ppm O_3. Although PM alone caused no change in cell proliferation (^{3}H-thymidine labeling), coexposure to either concentration of resuspended PM with O_3 greatly potentiated the proliferative effects of exposure to O_3 alone. These interactive changes occurred in epithelial cells of the terminal bronchioles and the alveolar ducts. These findings using resuspended ambient PM, although at high concentrations, are consistent with studies showing interactions between sulfuric acid (H_2SO_4) aerosols and O_3.

Kimmel and colleagues (1997) examined the effect of acute coexposure to O_3 (0.6 ppm) and fine (MMD = 0.3 μm) or ultrafine (MMD = 0.06 μm) H_2SO_4 aerosols (0.5 mg/m^3) on rat lung morphology. They determined morphometrically that alveolar septal volume was increased in animals coexposed to O_3 and ultrafine, but not fine, H_2SO_4. Interestingly, cell labeling, an index of proliferative cell changes, was increased only in animals coexposed to fine H_2SO_4 and O_3, as compared to animals exposed to O_3 alone. Importantly, Last and Pinkerton (1997), in extending their previous work, found that subchronic exposure to acid aerosols (20 to 150 μg/m^3 H_2SO_4) had no interactive effect on the biochemical and morphometric changes produced by either intermittent or continuous O_3 exposure (0.12 to 0.2 ppm). Thus, the interactive effects of O_3 and acid aerosol coexposure in the lung disappeared during the long-term exposure.

Kleinman et al. (1999) examined the effects of exposure to O_3 (0.2 and 0.4 ppm) plus fine (MMAD = 0.26 μm) H_2SO_4-coated carbon particles (100, 250, and 500 μg/m^3) for 1 or 5 days. They found that the inflammatory response with the O_3-particle mixture was greater after 5 days (4 h/day) than after Day 1. This contrasted with O_3 exposure alone (0.4 ppm), which caused marked inflammation on acute exposure, but no inflammation after 5 consecutive days of exposure.

Kleinman et al. (2000) examined the effects of a mixture of elemental carbon particles (50 μg/m^3), O_3 (0.2 ppm), and ammonium bisulfate (70 μg/m^3) on rat lung collagen content and macrophage activity in senescent rats. Exposures were nose-only, 4 h/day, 3 consecutive days per week for a total of 4 weeks. Decreases in lung collagen, and increases in macrophage respiratory burst and phagocytosis were observed. They found small changes in macrophage function and in injury to cells of the lung parenchyma, with exposures to just carbon and

ammonium bisulfate. With the addition of O_3, changes in those biological responses became significant. These results suggest that (a) O_3 may enhance the toxicity of inhaled particles in terms of the above types of pathophysiologic responses and/or (b) conversely, $PM_{2.5}$ exposure may enhance O_3-induced toxicity in aged rats. Mautz et al. (2001) used a similar mixture (i.e., elemental carbon particles, O_3, ammonium bisulfate, but with NO_2 also) and exposure regimen as Kleinman et al. (2000). There were decreases in pulmonary macrophage Fc-receptor binding and phagocytosis and increases in acid phosphatase staining. Bronchioalveolar epithelial permeability and cell proliferation were increased. Altered breathing patterns were also seen, but with some adaptation evident over the course of repeated O_3 exposure.

Other studies have also examined interactions between carbon particles and gaseous co-pollutants. Jakab et al. (1996) and Clarke et al. (2000c) challenged mice with a single 4-h exposure to a high concentration of carbon particles (10 mg/m^3) in the presence of 10 ppm SO_2 (~140 µg $cpSO_4^{2-}$) at low and high relative humidities. Macrophage phagocytosis was depressed significantly only in mice exposed to the combined pollutants under high relative humidity (85%) conditions. There was no evidence of an inflammatory response based on total cell counts and differential cell counts from BAL; however, macrophage phagocytosis remained depressed for 7 to 14 days. Intrapulmonary bactericidal activity also was suppressed and remained suppressed for 7 days. This study suggests that fine carbon particles can serve as an effective carrier for acidic sulfates where chemical conversion of adsorbed SO_2 to acid sulfate species occurred. Interestingly, the depression in macrophage function was present as late as 7 days postexposure.

Bolarin et al. (1997) exposed rats to 50 or 100 $\mu g/m^3$ carbon particles in combination with ammonium bisulfate (70 or 140 $\mu g/m^3$) and O_3 (0.2 ppm) for 4 h/day, 3 days/week for 4 weeks. Despite 4 weeks of exposure, they observed no changes in protein concentration in lavage fluid or blood prolyl 4-hydroxylase, an enzyme involved in collagen metabolism. Slight decreases in plasma fibronectin were present in animals exposed to the combined pollutants versus O_3 alone. Thus, as previously noted, the potential for adverse effects in the lungs of animals challenged with a combined exposure to particles and gaseous pollutants is dependent on numerous factors, including the gaseous co-pollutant, concentration, and time.

The effects of O_3 modifying the biological potency of PM (diesel PM and CB) were examined by Madden et al. (2000). Reaction of NIST Standard Reference Material # 2975

diesel PM with 0.1 ppm O_3 for 48 h increased the potency (compared to unexposed or air-exposed diesel PM) to induce neutrophil influx, total protein, and LDH in lung lavage fluid in response to intratracheal instillation. Exposure of the diesel PM to high, nonambient O_3 concentration (1.0 ppm) attenuated the increased potency, suggesting destruction of the bioactive reaction products. Unlike the diesel particles, CB particles exposed to 0.1 ppm O_3 did not exhibit an increase in biological potency, which suggested that the reaction of organic components of the diesel PM with O_3 contributed to the increased potency. Reaction of particle components with O_3 was ascertained by chemical determination of specific classes of organic compounds.

In a complex series of exposures, Oberdörster and colleagues examined the interaction of ultrafine carbon particles (100 $\mu g/m^3$) and O_3 (1 ppm) in young and old F-344 rats that were pretreated with aerosolized endotoxin (Elder et al., 2000a,b). In old rats, exposure to singlet ultrafine carbon and O_3 produced an interaction that resulted in a greater influx in neutrophils than that produced by either agent alone. This interaction was not seen in young rats. Oxidant release from lavage fluid cells was also assessed and the combination of endotoxin, carbon particles, and O_3 produced an increase in oxidant release in old rats. This combination produced the opposite response in the cells recovered from the lungs of the young rats, indicating that the lungs of the aged animals underwent greater oxidative stress in response to this complex pollutant mix of particles, O_3, and a biogenic agent.

The effects of gaseous pollutants on PM-mediated responses also have been examined by in vitro studies, though to a limited extent. Churg et al. (1996) demonstrated increased uptake of asbestos or TiO_2 into rat tracheal explant cultures in response to 10 min O_3 (up to 1.0 ppm) preexposure. These data suggest that O_3 may increase the penetration of some types of PM into epithelial cells. Additionally, Madden et al. (2000) demonstrated a greater potency for ozonized diesel PM to induce prostaglandin E_2 production from human epithelial cell cultures, suggesting that O_3 can modify the biological activity of PM derived from diesel exhaust.

In summary, the newly available combined (PM and gaseous co-pollutant) studies provide only relatively limited evidence for additive or interactive joint PM/gaseous pollutant effects on one or the other few health endpoints evaluated. For example, recent studies have demonstrated that coexposures of CAPs and O_3 cause potentiation of proliferative changes in the epithelium of terminal bronchioles (Vincent et al., 1997) and enhanced septal cellularity (Bouthillier et al.,

1998) seen with O_3 exposure alone. Both combined CAPs/O_3 and O_3-alone exposure in a mouse asthma model (Kobzik et al., 2001) showed increases in airway responsiveness and pulmonary resistance, thus indicating a lack of synergism with the combined exposure. Mixtures of elemental carbon particles, O_3, and ammonium bisulfate showed changes in lung collagen, AM respiratory burst, and phagocytosis (Kleinman et al, 2000), the results are ambiguous as to whether PM was enhancing the effects of O_3 or the converse. A short exposure of combined carbon particle/SO_2 caused depressed AM phagocytosis and suppressed intrapulmonary bactericidal activity which lasted for a week (Jakab et al., 1996; Clarke et al., 2000c). On the other hand, other studies using coexposures of PM and gases have demonstrated no changes in histopathological (Moss et al., 2001) or biochemical and morphometric endpoints (Last and Pinkerton, 1997).

The mechanisms by which interactions between PM and gases occur is thought to be by: (1) formation of secondary products by chemical interactions between the gas and the particle, (2) adherence of material to the particle and subsequent transport to sensitive sites, and/or (3) pollutant-induced change in the local microenvironment of the lung (e.g., by decreasing the pH). All of these interactions have the potential to create antagonistic, additive, or synergistic interactions between PM and gases, which can modify their individual effects.

7.7 QUANTITATIVE COMPARISONS OF EXPERIMENTAL PM EFFECTS ON CARDIOVASCULAR/RESPIRATORY ENDPOINTS IN HUMANS AND LABORATORY ANIMALS

7.7.1 Introduction

The extensive literature assessed in the foregoing sections provides considerable new information on experimentally-induced effects of various types of PM on cardiovascular and respiratory endpoints. The ensuing subsections attempt to characterize salient exposure/dose-effect relationships; including comparisons between lowest observed effect levels (LOELs) reported thus far for normal and compromised subjects. In the sections that follow, for both the cardiovascular/systemic and the respiratory effects, the LOELs derived from inhalation studies are first discussed and then those from instillation studies, followed by discussion of in vitro observed effect levels. In addition, efforts are made to delineate key factors important in attempting to extrapolate observed effects across species (rat to human) and/or to human ambient

exposure conditions and to provide illustrative examples of some extrapolation modeling outcomes.

7.7.1.1 Cardiovascular and Systemic Effects of Inhaled Particulate Matter

Newly available studies examining the cardiovascular and systemic effects of inhaled PM have for the most part not carried out dose-response evaluations using multiple exposure levels in the same study. However, various types of effects reported across a wide range of concentrations for various types of PM tested at single exposure levels do allow one to gain some impressions about possible lowest-observed-effect-levels (LOELs).

Concentrated ambient particles were used in a number of studies examining cardiovascular and systemic endpoints, but none were done in a manner so as to allow clear delineation of dose-response relationships for the endpoints evaluated. In fact, as CAPs vary from day to day, any comparisons at different times do not comprise a true dose-response study. Probably the lowest concentrations of U.S. ambient air observed to experimentally induce any cardiovascular effect in humans were those in the study by Ghio et al. (2000a). Healthy adult subjects were divided in three groups plus a fourth group receiving filtered air as control. All three exposure groups (which had $PM_{2.5}$ levels averaging 47.2 ± 5.3, 107.4 ± 9.3, and 206 ± 14.1 $\mu g/m^3$ after concentration) showed increases in plasma fibrinogen which were accompanied by increases in BAL neutrophils. The study did not show a dose response, which would have necessitated exposure of the subjects at differing levels of CAPs. Another very small human exposure study was also reported by Petrovic et al. (2000) to show a trend toward increased blood fibrinogen in two of four human adults exposed for 2 h to Toronto CAPs ranging up to ~125 $\mu g/m^3$. Also, in laboratory animal studies, Godleski et al. (2000) used CAPs from the Boston area and found effects on heart rate and ECG at a CAPs dose of ~100 to 1000 $\mu g/m^3$ in some dogs (though the lowest exposure that produced these effects was not determined). Both normal dogs and dogs compromised by coronary occlusion were reported to be affected. However, a study exposing both F344 rats and hamsters to CAPs collected in Manhattan at concentrations ranging from 132 to 919 $\mu g/m^3$ had contrasting findings (Gordon et al., 2000). That is, in hamsters and in rats, both normal and MCT-treated, there was an increase in HR and peripheral blood cell differential counts, but no other cardiovascular effects were observed. In contrast to these studies, a number of other studies have examined a wide range of cardiovascular endpoints and found no changes

in cardiovascular parameters, e.g., following inhalation exposures of dogs to Boston CAPS at 3 to 360 μg/m^3 (Clarke et al., 2000a), of rats to NYC CAPs at 95 to 341 μg/m^3 (Nadziejko et al., 2002), and of humans to ultrafine carbon particles at 10 μg/m^3 (Frampton, 2001).

A number of other studies have examined cardiovascular and systemic endpoints at much higher concentrations, using UAP and ROFA. For example, two other new studies showed effects of Ottawa UAP on levels of endothelin. Bouthillier et al. (1998) found that 40 mg/m^3 Ottawa UAP in Fischer 344 rats caused an increase in plasma endothelin-1 levels without causing acute lung injury. Also, Vincent et al. (2001) found that 48 mg/m^3 Ottawa UAP caused increases in both endothelin-1 and endothelin-3 in Wistar rats, the endothelins being likely powerful cardiotoxic agents. However, the relevance of these effects of exposures to such extremely high ambient PM concentrations to evaluation of current ambient PM exposures in the U.S. is questionable.

Two studies reported arrhythmias in response to ROFA exposure. Wellenius et al. (2002) exposed healthy SD rats and rats with a model of myocardial infarction to 3 mg/m^3 Boston ROFA and found arrhythmias, ECG abnormalities, and decreases in HRV in the compromised animals. Watkinson et al. (2000b) exposed healthy SD rats and rats with cold stress, O_3 preexposure, or MCT to 15 mg/m^3 ROFA (source not reported). They observed increased arrhythmias, decreased heart rates, and hypothermia in the compromised animals. The same concentration in SH rats caused cardiomyopathy, monocytic cell infiltration, and increased expression of cardiac cytokines IL-6 and TGF-β. The ROFA-exposed SH rats also showed increased ECG abnormalities compared to air-exposed SH rats. In another study, Muggenburg et al. (2000a) exposed beagles to 3 mg/m^3 Boston ROFA and found no effects on ECG and a trend toward decreased heart rate, these overall results not being consistent with the Godleski et al. (2000) findings noted above.

Comparisons were made also between normotensive WKY rats and SH rats following an exposure to 15 mg/m^3 Boston ROFA (Kodavanti et al., 2002a). The SH animals demonstrated increased plasma fibrinogen and small but consistent decreased total white blood cell numbers, the decrease being due mostly to decreased numbers of lymphocytes. Boston ROFA was used in another study by Kodavanti et al. (2003) at a concentration of 2, 5, or 10 mg/m^3 (for 6 h/day for 4 consecutive days) to compare cardiovascular endpoints in normal SD, WKY, and SH rats. In this exposure paradigm, no significant effects were seen for any of the rat strains. However,

with a second exposure paradigm (10 mg/m^3 for 6 h/day for 16 weeks) WKY rats showed cardiac lesions in the form of randomly distributed foci of fibrosis and inflammation in the ventricles and the interventricular septum. Also, normal SD and MCT-treated rats exposed to 0.58 mg/m^3 Boston ROFA showed increased expression of MIP-2, predominantly in heart macrophages, in the MCT-treated animals.

In general, in the studies noted above, lower inhalation doses of CAPs than ROFA have been found to elicit at least some cardiovascular effects. Some $PM_{2.5}$ studies have demonstrated effects (increased blood fibrinogen) at concentrations as low as ~50 to 330 μg/m^3, whereas other studies of CAPs at similar or higher concentrations did not show effects at such levels. Some of the limitations of CAPs studies were discussed earlier in Section 7.1.1 Methodological Considerations, and these must be kept in mind when interpreting CAPs data. Studies of UAP or ROFA at much higher concentrations have also reported effects in healthy animals, but the relevance for evaluation of health effects associated with current ambient PM levels in the United States is unclear. The lack of more data from studies completing dose-response evaluations highlights a need for more rigorous future evaluation of dose-effect relationships.

7.7.1.2 Cardiovascular and Systemic Effects of Instilled Particulate Matter

Recent studies characterizing the cardiovascular and systemic effects of instilled PM show that most effects have been seen in a dose range of 0.7 to 9 mg/kg body weight. To better compare studies here, all reported instillation study doses were converted to mg/kg body weight.

Urban air particles (UAPs) were used in several studies that evaluated changes in heart rate, temperature, and blood parameters. Ottawa UAP at a dose of 7 mg/kg was instilled in aged (15 months old) SH rats (Watkinson et al., 2000a, 2000b). Effects seen at this dose were hypothermia and bradycardia. Mukae et al. (2001) exposed female New Zealand White rabbits to 2 mg/kg Ottawa UAP and found a number of altered cardiovascular endpoints; e.g., increases in circulating PMN band cell numbers and in the size of the bone marrow mitotic pool of PMNs, as well as a shortened transit time of PMN through the postmitotic pool in marrow. Suwa et al. (2002) evaluated similar endpoints with the same UAP, using 1.6 mg/kg in female Watanable heritable hyperlipidemic rabbits. The same increases in PMN parameters were observed in this study, along with progression of atherosclerotic lesions, increases in plaque cell turnover, extracellular lipid pools, and total lipids in aortic lesions.

Dose-response evaluations were carried out in several ROFA studies. Boston or Florida was the origin of ROFA used in many of the IT studies that investigated cardiovascular and systemic effects, (though several research groups neglected to report the source of the ROFA). Arrhythmias were observed with both normal and MCT-treated rats at a dose of 3 mg/kg of Florida ROFA (Watkinson et al., 1998). In another study by the same investigators, a dose of 0.7 mg/kg of ROFA (origin not reported) in SH rats was shown to create significant arrhythmias, whereas 7 mg/kg induced arrhythmias in normal rats (Watkinson et al., 2000a, 2000b). One study demonstrated ECG abnormalities in SD rats compromised by either MCT-pretreatment or cold stress (10 °C) at a dose of 3 mg/kg ROFA (origin not reported). Bradycardia was seen in a number of studies at doses of 0.7 to 7 mg/kg ROFA. Campen et al. (2000) observed a decreased heart rate at 3 mg/kg ROFA (origin not reported) in normal SD rats and at 0.7 mg/kg in rats compromised by cold stress, O_3-pre-exposure, or MCT. Florida ROFA, tested at 7 mg/kg only, caused bradycardia in both normal SD and MCT-treated rats (Costa and Dreher, 1997). Aged SH rats displayed decreased heart rates when exposed to 1.4 mg/kg ROFA (origin not reported; Watkinson et al., 2000a).

The systemic response of hypothermia has been observed in normal SD rats and SD rats compromised by cold stress, O_3-preexposure, or MCT when exposed to 0.7 mg/kg ROFA (origin not reported; Campen et al., 2000). Watkinson et al. (2000b) observed the hypothermic response in compromised rats at 1.4 mg/kg and in normal SD rats at 7 mg/kg. Increases in plasma fibrinogen have been observed in normal SD rats following exposure to 8.3 mg/kg Florida ROFA (Gardner et al., 2000). However, other hemostatic parameters and cardiovascular risk factors, such as activated partial thromboplastin time, prothrombin time, plasma viscosity, and complete blood count, were unaltered by the exposure. Kodavanti et al. (2002a) compared the response to Boston ROFA at doses of 1 and 5 mg/kg in normal WKY and SH rats. Both strains demonstrated increased plasma fibrinogen at the 5 mg/kg dose, while only the WKY rats showed increased hematocrit at that dose. The SH rats demonstrated decreases in blood lymphocytes and increases in blood neutrophils at 5 mg/kg. Lethality was observed in MCT-treated SD rats exposed to 3 or 7 mg/kg Florida ROFA (Costa and Dreher, 1997).

Overall, then, some cardiovascular and systemic effects of instilled ambient PM were observed at instilled doses of ~1.5 to 7 mg/kg body weight. Some effects were also apparent with exposures to ROFA in a dose range of 0.7 to 9 mg/kg body weight. In many cases the

compromised animals in these studies showed effects at lower doses than normal counterparts. Again, instillation studies must be viewed in light of the caveats mentioned earlier regarding possible alteration of the physiochemical characteristics due to collection, storage, and resuspension.

7.7.1.3 Respiratory Effects of Inhaled Particulate Matter

The few available inhalation studies of ambient PM respiratory effects in humans have yielded consistent results in finding little or no indications of pulmonary function decrements or increased respiratory symptoms among healthy adults exposed for 2 h to CAPs from several locations (Toronto, Los Angeles, Chapel Hill, NC) at concentrations across a range of ~25 up to ~300 $\mu g/m^3$ (Ghio et al., 2000a; Petrovic et al., 2000; Gong et al., 2000; Gong et al., 2003). On the other hand, some of these studies did find indications of mild lung inflammatory responses, although some were of unclear health significance.

Relatively few laboratory animal studies have been done to examine the respiratory effects of inhaled PM, versus instillation studies. Mongrel dogs were exposed to Boston CAPs for 6 h/day for 3 days at concentrations varying from ~100 to 1000 $\mu g/m^3$ (Godleski et al., 2000). The only small effects seen were decreased respiratory rate over time and some increases in BAL neutrophils. Also, Clarke et al. (1999) exposed SD rats, both normal and SO_2-pretreated bronchitic rats to Boston CAPs for 5 h/day for 3 days at concentrations of 200, 600, and 730 $\mu g/m^3$ (mean CAPs level for each day). With such CAPs exposures, PEF and TV were increased in the bronchitic rats; and increased levels of BAL protein and percent neutrophils were seen in both normal and bronchitic rats. Comparing this same bronchitic model to normal SD rats, Kodavanti et al. (2000b) observed similar responses to CAPs collected in Research Triangle Park, NC. That is, at a CAPs concentration of 650 $\mu g/m^3$, bronchitic rats had increased levels of BAL protein and neutrophils compared to CAPs-exposed normal SD rats. To test the effects on the respiratory system of combined bacterial infections and CAPs exposures, F-344 rats were exposed for 3 h to NYC CAPs at a mean concentration of 225 $\mu g/m^3$ (Zelikoff et al., 2003). The CAPs exposures had little effect on respiratory parameters when they preceded lung infection with IT-administered *Streptococcus pneumoniae*; but CAPs exposure of previously-infected rats caused reductions in basal superoxide, decreased percentages of neutrophils, and increased bacterial burdens. These CAPs studies most clearly provide indications that exposure

to ambient PM from several locations for 1 to 6 h/day for 1 to 3 days at concentrations across a range of ~200 to 700 $\mu g/m^3$ can cause (a) some lung inflammation in normal and compromised animals and (b) exacerbation of preexisting respiratory infection.

In a study of combustion emission source materials, Killingsworth et al. (1997) exposed by inhalation both normal SD and MCT-treated SD rats to Boston ROFA at a concentration of 580 $\mu g/m^3$. Consequent respiratory effects included increases in neurotrophils in MCT-treated rats and increases in MIP-2 mRNA in normal SD rats. Kodavanti's group (1999, 2000b, 2002a) also completed a number of studies that examined a range of endpoints using a concentration of 15 mg/m^3 of Boston or Florida ROFA. One inhalation study (Kodavanti et al., 2002a) used Boston ROFA inhalation at a concentration of 15 mg/m^3 in both WKY and SH rats to compare normal and cardiovascular compromised animals. Effects seen at this concentration were increases in PMN, AM, BAL protein, LDH, and lung lesions in both rat strains. Only the WKY rats showed increased glutathione in this study. This group also completed two inhalation studies utilizing Florida ROFA, also at a concentration of 15 mg/m^3. Comparisons made of normal SD and MCT-treated rats (Kodavanti et al., 1999) showed that both the normal and MCT-treated rats display lung lesions at this dose; and both groups displayed increases in BAL protein, LDH levels, and IL-6 levels. The healthy SD rats also showed increased MIP-2 expression. A subsequent comparison of WKY and SH rats (Kodavanti et al., 2000a) showed that Florida ROFA had very similar effects on most respiratory parameters in both strains. Airway hyper-reactivity, lung lesions, AM counts, RBCs in BAL, BAL protein, BAL AM, BAL oxidants, and IL-6 all increased with ROFA exposure. As in the previous study, only the normal animals exhibited increased MIP-2 expression. Only one study of combustion source materials (Dormans et al., 1999) reported completing a dose-response evaluation. This laboratory used exposures of 0, 10, 30, and 100 mg/m^3 CFA and only observed a fibrotic reaction at 100 mg/m^3, thus confirming the relatively inert nature of CFA in comparison to ROFA.

Thus, from among the growing number of animal studies in the literature describing the respiratory effects of inhaled PM, dose-response characterizations were generally not reported. So possibilities for reliably estimating LOELs from these data or for attempting extrapolations to human exposures are limited. Probably of most pertinence, for present purposes, are (a) indications from several studies that inhalation exposures to CAPs of several species (rats, hamsters, dogs) for 1 to 6 h/day for 1 to 3 days had little or no effect on pulmonary function, but

induced some signs of lung inflammation in healthy animals and enhanced inflammatory responses in chronic bronchitic rats at CAPs concentrations varying across a range of ~100 to 1000 μg/m^3 (with the inflammatory responses being most clearly shown in a range of ~200 to 700 μg/m^3); and (b) some exacerbation of respiratory infection following acute (3 h) exposure to New York City CAPs at ~225 μg/m^3. On the other hand, analogous but more intensive inflammatory responses were reported for ROFA responses at a concentration of 15 mg/m^3, and CFA was not found to produce any effects until indications of fibrotic changes were seen at 100 mg/m^3.

7.7.1.4 Respiratory Effects of Instilled Particulate Matter

Recent studies characterizing respiratory effects of instilled PM indicate that most effects are observed for endpoints such as PMN, AM, protein, and LDH accumulation in BAL at a dose range of 0.7 to 10 mg/kg body weight in rats, mice and hamsters. Changes in cytokines and oxidant formation have been seen in a similar concentration range in rats. Dose-response evaluations were carried out in about one third of these studies. To better compare studies, all doses from the instillation studies were converted to mg/kg body weight in the instances where researchers reported a dose per animal and an average weight for the animals.

Three studies examined the respiratory effects of instilled ambient PM collected in the Utah Valley near a steel mill that was closed during 1987. Filters were collected before, during, and after the closing and the PM was water-extracted for use in the studies. Ghio and Devlin (2001) intrabronchially instilled the Utah ambient PM in healthy humans at a dose of 0.007 mg/kg and found increases in the cytokines IL-8, TNF, and IL-lβ following exposure to the extracted PM collected while the plant was open. Other parameters increased by this PM exposure were fibrinogen, fibronectin, PMN, and BAL protein, and tissue factor. Dye et al. (2001) found analogous increases with this Utah ambient PM sample in male SD rats at much higher exposure levels. Exposure doses of 3 mg/kg increased BAL LDH, PMN, and total cells counts, whereas doses of 8 mg/kg increased lung lesions and airway reactivity. Sprague-Dawley rats exposed to pre- and post-closure Utah PM demonstrated increased BAL PMN and protein at a concentration of 1.8 mg/kg and increased oxidant formation at a dose of 3.6 mg/kg (Ghio et al., 1999a).

The respiratory effects of UAPs were compared to the effects of ambient PM collected from the Kuwaiti oil fires of 1991 in male Syrian golden hamsters (Brain et al., 1998). Doses of 1.5, 7.5, and 37.5 mg/kg were used; and at the lowest doses, increases in PMNs were observed. At a dose of 7.5 mg/kg, effects seen were increases in BAL AM, protein and LDH.

Instillation of ROFA has been used in many of the newer studies examining the respiratory effects of PM. Residual oil fly ash collected at a temperature of 250-300°C, downstream from the cyclone of a power plant in Florida burning low-sulfur residual oil was the ROFA most commonly used in the following studies. Kodavanti et al. (1997a) found increases in lung lesions, PMN, AM, MIP-2, and IL-6 following instillations of 8.3 mg/kg ROFA in male SD rats. Evaluating possible strain differences, Kodavanti et al. (1997a) found similar inflammatory cell infiltration and alveolar, airway, and interstitial thickening in SD, Wistar, and F-344 rats at the same 8.3 mg/kg ROFA concentration. Another comparison of SD and F-344 rats showed increases in neutrophils in both strains at 8.3 mg/kg (Kodavanti et al., 1996). Florida ROFA at a slightly higher concentration, 9.4 mg/kg, caused increases in airway hyper-reactivity, AM, PMN, LDH, and protein in male SD rats (Gavett et al. (1997). The same laboratory (Gavett et al., 1999) found similar effects in BALB/cJ mice at a dose of 3 mg/kg. Kadiiska et al. (1997) exposed male SD rats to 3.3 mg/kg Florida ROFA and found increases in both PNM and protein. A dose-response study was completed by Kovavanti et al. (2001) that showed that much lower exposures to Florida ROFA could elicit the same effects. At 0.83 mg/kg there were increases in BAL protein, LDH, and PMN in both WKY and SH rats. In the same study, increases in AM were seen at 0.83 mg/kg in SH rats and at 3.3 mg/kg in WKY rats. Another rat strain, BN, was shown to have increased production of LDH at 5.8 mg/kg and increased BAL protein at 1.1 mg/kg Florida ROFA, (Lambert et al., 1999), thus demonstrating some similarity of observed effects across rat strains. In line with these studies, Madden et al. (1999) found increased production of acetaldehyde at a concentration of 3.6 mg/kg Florida ROFA. In another study (Costa and Dreher, 1997), comparing Florida ROFA, domestic oil fly ash (DOFA), CFA, and four UAPs (St. Louis, Washington DC, Dusseldorf, and Ottawa), instillations of 7 mg/kg caused increases in PMNs albumin and LDH.

One study reported on respiratory effects of diesel particles (Ghio et al., 2000c) instilled into SD rats at a concentration of 1.8 mg/kg. Effects seen included increases in BAL protein, LDH, PMN, MIP-2, TNF, and total cells. A decrease in glutathione was also observed.

Overall, the studies of respiratory effects of instilled PM materials have provided limited but interesting information. Perhaps of most importance are the observations of increased levels of inflammatory indicators in BAL samples from adult humans exposed via instillation to as little as 0.007 mg/kg (i.e., 7 μg/kg) of Utah Valley ambient PM_{10} extract obtained during the time the nearby steel mill was operating. Analogously, increased oxidant formation and BAL LDH, PNM and total cell counts were seen in rats instilled with 1.8 or 3.6 mg/kg of the pre-closure Utah ambient PM. As for other laboratory animal studies, effects in animals were observed for the commonly assayed respiratory endpoints, in a PM dose range of 0.7 to 10 mg/kg body weight. ROFA was the most commonly used PM for instillation studies, reflecting a significant data gap for other types of PM and leaving open the question of how relevant many of the results might be for assessing ambient air PM effects at concentrations pertinent to current U.S. conditions.

7.7.1.5 In Vitro Effects of Particulate Matter on ng/Cell Dose Basis

A number of the in vitro studies described previously have reported cell numbers used in the exposures. Based on this information, it is possible to determine the actual dose applied on a per cell basis. This information is important if any comparisons are to be made across studies and, further, so that extrapolations between in vitro studies and in vivo studies may be attempted. In most of these experiments, cells are plated at 1×10^4 to 5×10^6 cells per mL of media, with an average of about a half million cells per experiment. Studies where cell counts were reported, but wherein cells were given additional time to proliferate or possibly grow until confluent, were not used to make PM/cell determinations. Researchers in most cases have carried out dose-response evaluations, so that LOELs can be determined for the endpoints studied. Overall, there is some consistency among studies as to concentrations of PM required to elicit effects, most of which fall within a range across an order of magnitude difference between 0.02 and 0.2 ng/cell.

Urban air particles, ROFA , and CAPS have been most commonly used in these studies. In studies with exposures of both rat and human AM to UAP from St. Louis, Ottawa, Dusseldorf, and Florida, effects on cytokine production were consistently seen at doses as low as 0.02 ng/cell (Becker et al., 1996; Van Eden et al., 2001; Mukae et al., 2000). Washington DC and Boston UAP were both shown to increase TNF-α production in rat AM at doses of 0.1 ng/cell (Imrich et al., 2000). Interestingly, it appears that cytokine production is induced at slightly lower

concentrations in human AM than in rat AM (Becker et al., 1996). Oxidant formation is also induced by UAP exposure in vitro. St. Louis, Ottawa, and Dusseldorf UAP all were shown to induce ROS at doses of 0.05 to 0.5 ng/cell in human AM and blood monocytes (Becker et al., 1996; Becker and Soukup, 1998). Exposure of human AM and blood monocytes to St. Louis and Ottawa UAP inhibited phagocytosis as doses of 0.5 and 0.02 ng/cell, respectively (Becker and Soukup, 1998; Van Eeden et al., 2001). Washington DC UAP has been shown to decrease viability in rat AM at doses of 0.05 ng/cell (Nadeau et al., 1996) and 0.1 ng/cell (Imrich et al., 2000). Washington, DC UAP has also been shown to increase levels of apoptosis at 0.2 ng/cell in human AM (Holian et al., 1998) and to deplete ATP at 0.5 ng/cell in rat AM (Nadeau et al., 1996).

In vitro effects on a wide range of endpoints have been observed with ROFA from Florida and Boston. Tumor necrosis factor-α has been induced with Florida ROFA in human AM at 0.02 ng/cell (Van Eeden et al., 2001) and with Boston ROFA in mouse RAW 264.7 cells at 0.2 ng/cell. Alabama ROFA has been shown to induce IL-6 production in BEAS-2B cells at 0.08 ng/cell (Oortgeisen et al., 2000). Oxidant formation has been induced by Florida ROFA in human AM and human blood monocytes at 0.05 ng/cell (Becker et al., 1996; Becker and Soukup, 1998). A slightly higher concentration of Florida ROFA (0.15 ng/cell)was shown to induce oxidant formation in rat AM (Ghio et al., 1997a; Becker et al., 1996). Boston ROFA was found to induce both oxidant formation and inhibition of phagocytosis at 0.1 ng/cell in hamster AM (Goldsmith et at., 1997; Goldsmith et al., 1998). Florida ROFA in human lung mucoepidermoid carcinoma cells induced mucin secretion at 0.01 ng/cell and lysozyme at 0.03 ng/cell (Longphere et al., 2000). Other observed effects of Florida ROFA include increased apoptosis in human AM at 0.025 ng/cell (Holian et al., 1998), increased acetaldehyde production in BEAS-2B cells at 0.04 ng/cell (Madden et al., 1999), and increased calcium release in BEAS-2B cells at 0.08 ng/cell (Oortgiesen et al., 2000).

Fewer studies have used in vitro exposures to CAPs. Goldsmith et al. (1998) induced oxidant formation in hamster AM with Boston CAPs at 0.08 ng/cell. This group (Goldsmith et al., 1997) also demonstrated oxidant formation and inhibition of phagocytosis in hamster AM with Boston CAPs at doses of 0.01 ng/cell. One PM_{10} study was found that reported cell numbers (Soukup and Becker, 2001). In that study, Chapel Hill PM_{10} (both the soluble and insoluble fractions) caused increased production of IL-6, TNF-α, and MCP-1 at

0.01 ng PM_{10}/cell and inhibition of phagocytosis at 0.05 ng/cell in human AMs. Long et al. (2001) reported that Boston area $PM_{2.5}$ caused increase production of TNF-α at 0.2 ng/cell. Kennedy et al. (1998) exposed BEAS-2B cells to Provo total suspended particulate (TSP) and found increased IL-6 release at 2.5 ng/cell and increased IL-8 release at 1.0 ng/cell. They also exposed human primary tracheal epithelial cells to TSP and saw effects at 0.06 ng/cell, but did not report dose-response information for these effects.

Thus, it appears that the most commonly studied in vitro endpoints have very similar LOELs across many types of PM evaluated, which range from about 0.02 to 0.2 ng/cell. As more in vitro studies are completed with information regarding specific PM exposure parameters and cell numbers used, clearer patterns should begin to emerge with regard to relative toxicities by PM class, cell type, and endpoints affected.

7.7.2 Interspecies Comparisons of Experimental Results

7.7.2.1 Introduction

Much of the new toxicologic data assessed in this chapter has been derived from either (a) in vivo exposures of human subjects or laboratory animals via inhalation exposures or instillation of PM materials or (b) in vitro exposures of various (mostly respiratory tract) cells or tissues to diverse types of PM. The experimental exposure conditions used in these studies are typically different from those experienced through inhalation of airborne PM by human populations in ambient environments. Most notably, the exposure concentrations used in many of the experimental studies are well above ambient PM levels. Therefore, consideration of the relevance of effects demonstrated under experimental conditions compared to the effects observed in humans following ambient PM exposures is useful, especially to the extent that quantitative extrapolation of experimental results across species or to ambient conditions may be feasible based on currently available data.

Appendix 7A provides an analysis of the relationship between rat and human lung doses predicted for various exposure scenarios ranging from ambient PM exposures to PM instillations into the lung. In many studies, both toxicologic and epidemiologic, health endpoints are presented and analyzed as a function of exposure concentration. However, it is generally accepted that the dose to target cells or tissues, rather than exposure concentration per se, is responsible for adverse responses. As discussed in Appendix 7A, establishing a firm linkage

between exposure and dose requires that consideration be given to particle characteristics and biological normalizing factors. Optimally, the dose metrics and normalizing factors should be based on the biological mechanisms mediating an effect. For some effects, the mass of soluble PM depositing in a region of the lung may be an appropriate dose metric. For example, an appropriate normalizing factor for soluble PM could be the surface area of the airways for irritants, whereas body mass might be more suitable when considering systemic effects.

There are two principle applications for the dosimetric assessments presented in Appendix 7A. First, experimental exposure concentrations can be estimated that should result in the same tissue dose in a rat as received by a human exposed to various levels of ambient PM as a function of dose metric, normalizing factor, and level of human exertion. As no single dose metric nor normalizing factor appears to be appropriate for all situations, numerous scenarios were considered in Appendix 7A. The parameters chosen can dramatically affect the rat exposure concentration estimated to be required to provide a normalized dose equivalent to that occurring in a human, as illustrated in Tables 7A-7a through 7A-9b in Appendix 7A. Second, the dose to the lung can be estimated for both animal and human inhalation studies. These analyses make it possible to compare biological responses as a function of dose rather than just exposure. Equal lung doses should not be assumed in comparing studies, even if PM mass concentrations, animal species, and exposure times are identical because of variations in individual breathing patterns, lung anatomy, and particle deposition fractions. Differences in the aerosol size distributions to which animals are exposed also affect dose delivered or retained. For example, in a comparison of several CAPs studies, one study was estimated to have 1.7 times the alveolar dose of another study despite a 10% lower exposure concentration in the first study. Thus, to make accurate estimates of dose, it is essential to have accurate and complete information regarding exposure conditions, i.e., not only concentration and duration of exposure, but also the aerosol size distribution and the level of exertion (and hence breathing rates) for exposed subjects.

It is obviously not feasible, given the complexity involved, to attempt extrapolation modeling for more than a few illustrative health endpoints that were evaluated in the multitude of studies assessed in this Chapter. Nor would such an effort necessarily be particularly useful for present purposes. However, providing some modeling results that estimate comparative exposure concentrations/doses demonstrated experimentally in animal or human studies to be

effective in producing a few important types of health endpoints should be of value in helping to provide a context by which to gauge the potential relevance of experimental results for ambient human exposure conditions.

7.7.2.2 Dosimetric Intercomparison for PMN Influx as a Marker for Lung Inflammation

Various types of particulate materials (both ambient PM and combustion source particles) have been shown to cause inflammation of the lung by migration of PMNs (predominantly neutrophils) into the airways. These cells are initially produced by bone marrow and, along with AM, constitute an important defense mechanism triggered by invasion of PM, bacteria, or some other foreign matter. The PMNs, once in the lung, ingest PM and then may degranulate, forming hydrogen peroxide and superoxide anions. Excessive quantities of PM in the lung can cause the lysosomal enzymes in PMNs to enter the extracellular fluid, creating further inflammatory responses. Additionally, PMNs produce thromboxanes, prostaglandins, and leukotrienes.

Three recent studies provide data on PMN increases following CAPs exposure that allow comparison of rat to human responses. Kodavanti et al. (2000b) exposed both healthy SD rats and rats with SO_2-induced bronchitis to CAPs collected in Research Triangle Park, NC. The particle size distribution in this study averaged 0.98 μm MMAD (σ_g = 1.41), the average concentration was 740 μg/m^3, and exposures consisted of whole-body inhalation of 6 h/day for 2 or 3 days. Inflammation was assessed immediately after exposure or 18 h later. Increases in BAL PMNs were seen only in the CAPs-exposed bronchitic rats compared to healthy CAPs-exposed rats in 2 of 4 separate experiments when rats were lavaged immediately postexposure. The healthy CAPs-exposed rats had no significant differences in PMN counts compared to healthy air-exposed rats. In a similar study, Clarke et al. (1999) exposed healthy and SO_2-induced bronchitic rats to Boston CAPs at an average concentration of 515 μg/m^3. Particle size averaged 0.18 μm MMAD (σ_g = 2.9) and exposures consisted of whole-body inhalation for 5 h/day for 3 consecutive days. PMN levels were assayed 24 h after exposure. Increases in PMNs (both in terms of total PMN counts and as PMN as percent of total cell count) in both the normal and bronchitic rats were seen with CAPs exposure. It is possible to compare these two rat studies to a human study, wherein Ghio et al. (2000a) exposed human subjects to Chapel Hill CAPs. In that study, healthy human volunteers were exposed to ~120 μg/m^3 for 2 h, with 15 minute periods of exercise alternating with 15 minutes of rest. Particle size was 0.65 μm

MMAD (σ_g = 2.35) and BAL analysis was at 18 h PE. Consistent with data from the rat studies, the total numbers of PMNs increased with the human CAPs exposure.

Appendix Section 7A.7.2 compares tissue doses predicted to occur in human and rat CAPs exposures using the Ghio et al. (2000a), Kodavanti et al. (2000b), and Clarke et al. (1999) studies. The Kodavanti et al. (2000a) study consisted of five separate CAPS experiments and the retained CAPs determinations were made from the experiment that utilized the 18 h PE time point. Comparisons of these rat and human studies indicate that in order to obtain the noted similarities in PMN responses observed, rats actually received a far greater alveolar region dose than humans. That is, 60 to 500% increases in PMN numbers were observed in the rat studies with estimated retained alveolar surface area doses of 28 to 47 μg/m^2 of CAPs PM; whereas a 300% increase in PMNs was seen in humans with estimated doses of only 0.7 μg/m^2 of alveolar tissue. This suggests that even healthy humans may be more susceptible to the inflammatory effects of CAPs than are rats. Table 7-14, allows more specific comparisons. Note that the dosimetry model used for these calculations considers only the insoluble component of PM. Consideration of the soluble fraction of the PM would, of course, create a more complete picture of the differences between rats and humans. Interpretation of these data regarding increases in PMN should also be tempered by the caveats that percent increase reported are influenced by basal levels of PMN and that composition, concentrations, and size distributions of CAPs can vary substantially from place to place and from day to day even at the same location.

TABLE 7-14. CAPs: RAT AND HUMAN INHALATION STUDY COMPARISONS

Study	Species	Particle	Exposure Conc. (μg/m^3)	MADD (σ_g)	Exposure duration	Analysis PE	Change in PMN	Estimated alveolar dose per surface area
Kodavanti et al. (2000a)	SD rat SO_2-SD	RTP CAPs	740	0.98 (1.41)	6 h/day for 2-3 days	< 3 h 18 h	255% ↑PMN in 2 of 4 exp (bronchitic rats only) no change in PMN	ND 28 μg/m^2 retained
Clarke et al. (1999)	SD rat SO_2-SD	Boston CAPs	515	0.18 (2.9)	5 h/day for 3 days	24 h	500% ↑PMN 367% ↑PMN	47 μg/m^2 retained
Ghio et al. (2000a)	humans	Chapel Hill CAPs	47	0.65 (2.35)	2 h	18 h	267% ↑PMN	0.7 μg/m^2 retained

7.7.2.3 Inhibition of Phagocytosis by PM Exposure

Phagocytosis is a form of endocytosis wherein bacteria, dead tissue, or other foreign material (e.g., inhaled ambient particles) are engulfed by cells such as AM, MO, or PMN as part of normal lung defense mechanisms. Hence, increases in numbers of AM, MO, or PMN cells in lung tissue represent one indicator of mobilization of lung defenses in response to infection or deposition of inhaled particles. Once ingested by AM, lysosomes act to digest engulfed materials. Inhibition of the phagocytosis by AM would signal interference with lung defense mechanisms by which inhaled bacteria and viruses are killed or other foreign particles are detoxified and/or cleared from the lung. Also, if an AM is overwhelmed by the amount or toxicity of ingested material, that material may be released along with the AM's digestive enzymes onto the alveolar surface and numbers of AM or their phagocytic activities may decrease.

A number of experimental (especially in vitro) studies have demonstrated, that in some instances, one or another type of PM has caused an inhibition of phagocytosis. As with other endpoints affected by PM, this inhibitory effect is determined by the size and composition of the specific particulate materials tested.

For example, Becker and Soukup (1998) exposed human AM to UAP from St. Louis (0.2 to 0.7 μm MMAD) and ROFA from Florida (0.5 μm MMAD). Exposures periods were 18 to 20 h at 100 μg/mL per 2×10^5 cells/mL for a dose per cell of 0.5 ng/cell. AM had a 50% decrease in phagocytosis of *Saccharomyces cerevisiae* with St. Louis UAP and a 30% decrease with ROFA, which the authors attributed to the toxicity of ROFA. The authors noted decreased phagocytosis in cells with both high and low particle burden, and further, that inhibited phagocytosis was more pronounced in the cells with a low burden. They attributed this effect to soluble fine constituents of the UAP more so than to particle-bound insoluble constituents. These researchers (Soukup and Becker, 2001) extended these findings with human AM exposures to Chapel Hill CAPs. They separated the CAPs into $PM_{2.5}$ (soluble and insoluble components) and PM_{10}, (soluble and insoluble) and exposed 2×10^5 cells/mL to 12.5, 25 or 100 μg/mL for 18 h. Phagocytosis was then assayed with fluorescein-tagged, zymosan particles. They observed a dose-dependent decrease in uptake with the insoluble PM_{10} (12% at 12.5 μg/mL, 30% at 25 μg/mL, and 50% at 100 μg/mL). This correlates with doses per cell of 0.06, 0.12, and 0.5 ng/cell, respectively. There was a similar percentage of AM that appeared to

be undergoing apoptosis. They postulated that the decrease in phagocytosis is due to the cells undergoing programmed cell death. In another study by this group, Soukup et al. (2000) found decreased phagocytosis of yeast particles in human AM exposed to Provo PM_{10} (Utah Valley Dust) collected before a steel plant closed. Exposures of 100 μg/mL to 2×10^5 cells/mL (for a dose of 0.5 ng/cell) caused a 30% decrease in phagocytosis. Particles collected during and after the steel mill closure did not cause a similar change in phagocytosis, even though the amount of particles engulfed was the same for all samples of the dust. They suggested that the metal content may not be predictive of decreases in AM phagocytic responses. In another study, Van Eeden et al. (2001) studied human AM exposed to UAP (Ottawa) and ROFA (Florida), both reported to be < 10 μm in diameter, and found an inhibition of phagocytosis at 100 ug/mL, which they attribute to toxicity to the cells. At 24 h PE, phagocytosis was determined by visual inspection of the cells. Cells were plated at a concentration of 0.5×10^6 and phagocytosis was decreased at a dose of 0.2 ng/cell.

These in vitro studies of human AM may be compared to three available studies that investigated animal AM responses to vitro PM exposures. Any conclusions drawn from these comparisons must be tempered with the understanding that the data obtained from differing cell types, culture conditions, and PM species have inherent limitations. Renwick et al. (2001) used a mouse macrophage cell line (J774.2 MΦ) to evaluate inhibition of phagocytosis by both fine and ultrafine particles. They used fine carbon black CB (260.2 nm diameter), ultrafine CB (UCB, 14.3 nm), fine TiO_2 (250.0 nm) and ultrafine TiO_2 ($UTiO_2$, 29.0 nm). The cultured cells at a concentration of 5×10^6 cells/mL were exposed to particles at concentrations of 15.6, 31, 63, or 125 μg/mL for 8h, after which phagocytosis was assessed using 2 μm fluorescent latex beads. Phagocytosis was inhibited by UCB at 63 μg/mL and by all the particles at 125 μg/mL, which corresponds to doses of 0.013 and 0.025 ng/cell, respectively.

Goldsmith et al. (1997) exposed hamster AM to Boston CAPs (1 μm) or Boston ROFA (0.1 to 2.5 μm) for 30 minutes. They measured right angle light scatter to determine cell granularity, as an indicator of phagocytosis. At concentrations of up to 20 μg/mL of CAPs and 200 μg/mL of ROFA, they observed no inhibition of phagocytosis. They listed two limitations of this type of assay to quantify phagocytosis; (1) it provides only a relative measure, not absolute numbers or mass of particles and, (2) it requires cells to be in suspension; whereas in the previously mentioned studies, the AM are adherent and thus capable of functioning in a more

realistic manner. Further, as the exposure was only 30 minutes, it is difficult to compare their results to those of studies using exposures over 18 h.

To make comparisons between rodent and human studies investigating the inhibition of AM phagocytosis by PM, an understanding of the species-specific differences in AM should be noted. Appendix 7A Section 7.3 discusses rat AM function versus volumetric loading. The volume, and presumably the capacity, of AM in rodents are smaller than for human AM. A human AM has an internal volume (not including the cell nucleus) of ~1350 μm^3, compared to the SD rat (1010 μm^3), F344 rat (760 μm^3), hamster (420 μm^3), or mouse (370 μm^3; Miller, 2000). The phagocytic activity of an AM is thought to slowly decrease above a particle loading of ~6% of its interior volume. At about 60% loading, alveolar macrophages become immobile. Considering the phagocytosis of a single particle, a human AM would likely become immobilized following the ingestion of a 11.6 μm diameter particle (0.816 ng assuming unit density), whereas a mouse AM could only ingest a 7.5 μm diameter particle (0.221 ng, unit density). Typically, considerably smaller particles than these (7.5 to 11.6 μm particles) deposit in the alveolar region of the lung and become phagocytosed by AM. In addition to the volume occupied by engulfed particles, another 30% or more of an AM capacity is lost to void spaces between particles packed within an AM . Table 7-15 compares several in vitro studies of human and rodent AM function and makes estimations of the AM loads based on reported PM characteristics.

Only one study was found that used both rat and human AM to compare the effects of PM on AM phagocytosis. Seemayer et al. (1990) exposed AM isolated from BAL to UAP from Duisburg (F.R.G). Both species demonstrated a reduction in phagocytic activity (% cells with > 2 particles) and phagocytic capacity (particles per cell), with little effect on cell viability. Of note, this study indicated a greater inhibition of phagocytosis in human AM compared to rat AM by both criteria, suggesting that human AM are more sensitive to the effects of PM than rat. Unfortunately, given that the study only reported the volume of air from which particles were collected and not particle mass, size, or composition, it is not possible to compare the data with more recent studies. In summary, the above comparisons provide interesting results suggesting that human AM may be at least as sensitive to ambient PM as to ROFA.

Whereas two studies reported no change in AM phagocytosis with exposures of human cells to doses of Ottawa ambient PM or ROFA (Florida) ranging up to 0.4 ng/cell, other studies

TABLE 7-15. INTERSPECIES COMPARISONS OF PARTICLE EFFECTS ON ALVEOLAR MACROPHAGE PHAGOCYTOSIS

Study	Species	PM	Conc	Exposure duration	Particle size	Change in phagocytosis	Estimate dose/cell	Estimated % of cell filled
Becker and Soukup (1998)	human	UAP (St. Louis) ROFA (Florida)	100 µg per 2 $\times 10^5$ cells	18-20 h	0.2-0.7 µm 0.5	↓50% ↓30%	0.5 ng	53
Soukup et al. (2000)	human	CAPs (Chapel Hill - separated into soluble and insoluble components	12.5 25 100 µg per 2 $\times 10^5$ cells	18 h	2.5 or 10 µm	↓12% ↓30% ↓50% with insoluble PM_{10} only	0.06 ng 0.12 0.5	6.3 13 53
Soukup and Becker (2001)	human	PM_{10} (Utah Valley)	100 µg per 2 × 10^6 cells	overnight	10 µm	↓30%	0.05 ng	5.3
Goldsmith et al. (1997)	hamster	CAPs (Boston)	4 µg 10 20	30 min	1 µm	no change	0.008 ng 0.02 0.04	2.7 6.9 14
		ROFA (Boston)	25 50 100 200 per 0.5×10^6 cells		0.1-2.5		0.05 0.1 0.2 0.4	17 34 69 140
VanEeden et al. (2001)	human	UAP (Ottawa) ROFA (Florida)	10 µg 100 per 0.5×10^6 cells	2,4,8,12,24 h (only 24 h data reported)	< 10 µm	no change ↓	0.02 ng 0.2	2.1 21
Renwick et al. (2001)	mouse macrophage cell line J774.2 MΦ	CB UCB TiO2, $UTiO_2$	15, 31,63, or 125 µg per 5×10^6 cells	8h	0.260 µm 0.014 0.250 0.029	↓@125 µg ↓@63 ↓@125 ↓@ 125	0.025 ng 0.013 0.025 0.025	9.7 5.0 9.7 9.7

CB = carbon black
UCB = ultrafine carbon black
TiO_2 = titanium dioxide
$UTiO_2$ = ultrafine titanium dioxide

showed decreased phagocytosis in human AM's exposed to 0.05 to 0.5 ng/cell of Chapel Hill CAPs, Utah Valley PM_{10} extract, St. Louis ambient PM, or Florida ROFA. However, additional more systematic work is necessary to fully characterize the phagocytic dose-response to various species of PM. The efficient removal of inhaled PM by viable, functioning AM cells is a critical respiratory defense mechanism, one thought likely to be impaired by at least some types of ambient PM constituents.

7.8 MUTAGENICITY/GENOTOXICITY EFFECTS

The majority of newly-published PM research since the 1996 PM AQCD have focused on acute cardiovascular or respiratory effects associated with short-term exposure to ambient PM or selected constituents. However, the new epidemiologic analyses by Pope et al. (2002) not only further substantiate associations between long-term exposure to ambient PM and increases in cardiopulmonary mortality but also provide the strongest evidence yet linking such PM exposures to lung cancer. In view of these new ambient PM-carcinogenicity findings (and others from earlier epidemiologic studies), salient results both from some older studies (pre-1996 PM AQCD) and newly available ones are discussed below with regard to evaluations of mutagenic or other genotoxic effects of ambient PM, its constituents, and/or combustion emission source particles thought to be useful as indices of likely carcinogenic potential of such materials. The pertinent studies discussed below are summarized in Tables 7-16, 7-17, and 7-18.

7.8.1 Ambient Particulate Matter Effects

A limited number of new in vitro studies have examined the mutagenic and/or other genotoxic potential of ambient PM from various geographic locations in the U.S. or elsewhere; and, in general, they show some evidence that appears to support the biologic plausibility of lung cancer effects being causally related to long-term exposure to ambient PM, as implied by the epidemiologic findings.

The World Health Organization (1993) has found that the induction of sister chromatid exchanges (SCE) is a sensitive cytogenic endpoint for the demonstration of genotoxic activity of environmental mutagens and carcinogens. In vitro SCE assays using various types of human or laboratory animal cells have been used in new studies, along with other techniques, to evaluate

TABLE 7-16. MUTAGENIC/GENOTOXIC EFFECTS OF AMBIENT PARTICULATE MATTER

Species, gender, strain age, or body weight	Particle or Constituent	Exposure Technique	Concentration Dose (µg/mL)	Particle Characteristics Size (µm); μ_g	Exposure Duration	Effects of Particles on Mammalian Cells or Bacteria	Reference
Human h1A1v2	Ambient PM from Los Angeles, San Nicolas Island, Long Beach, Azusa, and Rubidoux, CA	in vitro	120 µg EOC per 12 mL assay	< 2µm	72h	No seasonal variation in mutagenic potency, leading authors to suggest that mutagenicity is due to ubiquitous emission sources like vehicle traffic or stationary combustion rather than isolated point sources. LA air had 10 times more mutagenicity than background levels (San Nicolas)	Hannigan, et al. (1997)
Human h1A1v2	Composite of ambient PM from Los Angeles, San Nicolas Island, Long Beach, Azusa, and Rubidoux, CA. Fractionated into nonpolar, polar and semipolar components	in vitro	300 - 1200 µg EOC per 12 mL assay	< 2µm	72 h	Most of the mutatenic potency was in the unsubstituted PAC fraction. 2-nitrofluoranthene and 6H-benzo [cd] pyrene were semipolar mutagens.	Hannigan et al. (1998)
Cultured tracheal epithelial cells from Hamster (Syrian golden, young) or rat	Ambient PM: industrial or high traffic areas (Germany)	in vitro	Not given	Dichloromethane extraction of high volume samples.	Dilutions of extracted organic phase of particles incubated with cells for 48 h.	Dose-related increases in sister chromatid exchanges seen in both species. PM from industrial sample had LOEL of 0.11 m^3 air/mL medium. PM from high traffic area had LOEL of 0.16 m^3 air/mL medium.	Hornberg et al. (1996)
Human bronchioepithelial cell line (BEAS-2B)	Urban $PM_{2.5}$ Urban PM_{10} Industrial $PM_{2.5}$ Industrial PM_{10} Rural $PM_{2.5}$ Rural PM_{10} (Germany)	in vitro	6.6 to 26.5 µg/mL 1.7 to 6.9 µg/mL 10.8 to 43.2 µg/mL 5.8 to 23.1 µg/mL 7.8 to 34.1 µg/mL 3.7 to 14.4 µg/mL	Dichloromethane extraction of coarse (PM_{10}) and fine ($PM_{2.5}$) fractions.	Dilutions of extracted organic phase of size-segregated particles incubated with cells for 72 h.	Significant increases in sister chromatid exchanges were greater from all sampling sites at all doses of PM_{10} and $PM_{2.5}$ from urban and industrial regions. Extraction phase of coarse particles produced fewer sister chromatid exchanges than did the fine particles.	Hornberg et al. (1998)

TABLE 7-16 (cont'd). MUTAGENIC/GENOTOXIC EFFECTS OF AMBIENT PARTICULATE MATTER

Species, Gender, Strain Age, or Body Weight	Particle or Constituent	Exposure Technique	Concentration Dose (µg/mL)	Particle Characteristics Size (µm); μ_g	Exposure Duration	Effects of Particles on Mammalian Cells or Bacteria	Reference
Kidney cells from hamster (Syrian golden, 8-10 weeks old)	Ambient PM from urban and industrial areas (Germany)	in vitro	Not given	Dichloromethane (DCM) extraction of high volume samples.	Dilutions of extracted organic phase of particles incubated with cells for 18 h followed by infection with simian virus SV-40.	Significantly greater SV-40-induced transformation of hamster kidney cells pre-treated with organic extractions of urban particles/extracted from 4 m^3 air.	Seemayer and Hornberg (1998)
Cultured hepatoma cells	Ambient PM (Netherlands)	in vitro	Not given	Acetone/DCM extraction of high volume samples.	Dilutions of extracted organic phase of particles incubated with cells for 6 or 48 h.	Extracts of ambient PM both upwind and downwind of highway had genotoxic effects, although PAH content was greater in the downwind samples.	Hamers (2000)
Liver tumor cell line (HEPA1c1c7)	Urban air PM DEP Rubber industries PM Metal industries PM Poultry/swine farm Compost	in vitro	6-12 µg 17-37 µg 36-47 µg 32-175 µg 81-137 µg 42 µg	Aqueous and organic extraction from filters of particles collected with high volume samplers.	4 h	Inhibition of gap-junctional intercellular communication (GJIC) only significant in cells treated with aqueous extract of diesel, compost, or rubber particles.	Alink (1998)

PAC = polyaromatic compounds.

TABLE 7-17. MUTAGENIC/GENOTOXIC EFFECTS OF WOOD AND COAL COMBUSTION-SOURCE PM

Species, gender, strain age, or body weight	Particle or constituent	Exposure Technique	Mass Conc µg/mL or µg/m3	Particle Characteristics Size (µm)	Exposure Duration	Effects of particles on mammalian cells or bacteria	Reference
Salmonella	Emissions from wood (birch, pine, and spruce) combustion	in vitro Ames assay	32 to 100 µg/m^3 of PM and 2.6 to 200 µg organics	PM and organic fractions from wood stoves combustion	48 h	Organic fraction: mutagenic potency of 0.5-21 revertants/µg. The PM fraction demonstrated only very low mutagenicity	Löfroth et al. (1986)
Salmonella: TA98 TA100	Wood, diesel, and coal emissions	in vitro Ames assay (comparing standard plate and spiral assays)	200 µg/plate woodsmoke, 500 µg/plate DE and 200 µg/plate coal		72 h	DE had greatest mutagenicity under all conditions, creating both frameshift and base-pair substitution mutations. Coal just slightly less mutagenic than diesel creating indirect-acting frameshift mutations. Woodsmoke only weakly mutagenic.	Houk et al. (1991)
Salmonella: TA98 Human WBC	Emission from open fireplaces	in vitro Ames assay ^{32}P-post-labelling analysis of DNA adducts		PM extracted with methanol	1 week	Control: 28 revertants/30 m^3 (−S9) and 69 (+S9). Combustion: 153 (−S9) and 369 (+S9). No change in DNA adducts.	Heussen et al. (1994)
Salmonella: TA98 TA100	Wood smoke condensate (Sigma)	in vitro Ames assay	0, 125, 250, 500, 750 and 100 µg/plate		48 h	Not mutagenic at all doses	Putnam et al. (1999)
Salmonella: TA100	Emission PM - collected throughout year from burning fields	in vitro Ames assay	130 units µg/m^3 (winter) to 15 (summer), 170 (winter), 37 (summer)	$PM_{2.5}$ and PM_{10}	48 h	$PM_{2.5}$: 30.6 revertants/m^3 air volume (winter) to 0.1 (summer) with increased mutagenicity with S9 activation. PM_{10}: 28.1 (winter) to 0.7 (summer), revertants/m^3 air volume, S9 activation increasing the mutagenicity.	Vinitketkumnuen et al. (2002)

TABLE 7-17 (cont'd). MUTAGENIC/GENOTOXIC EFFECTS OF WOOD AND COAL COMBUSTION-SOURCE PM

Species, gender, strain age, or body weight	Particle or constituent	Exposure Technique	Mass Conc µg/mL or µg/m3	Particle Characteristics Size (µm)	Exposure Duration	Effects of particles on mammalian cells or bacteria	Reference
Salmonella: TA98 TA100	Wood burning emission PM and gas phase	in vitro Ames assay		Two smoke samples collected, PM and gas phase	48 h	12×10^6 revertants/kg using TA100−S9 and 3.5×10^6 revertants/kg using TA98−S9. Emissions can cause both frameshift and base pair substitution mutations. The gas phase of the wood smoke emission contributed to more than 60% of the direct-acting mutagenicity	Kim Oanh et al. (2002)
Salmonella: TA98 TA100 TA1535 TA1537 TA1538	Coal fly-ash from fluidized-bed (FBC) and conventional combustion (CC) plants	in vitro Ames assay		< 3µm FBC mean diameter 0.54 µm CC mean diameter 1.05 µm	72 h	FBC mutagenic in TA98 (3.32 revertants/mg) and TA 1538 (3.31), both without activation. S9 decreased the mutagenicity of FBC in TA98 and TA 1538. FBC had no mutagenic response in TA1537 and TA1535.	Munford and Lewtas (1982)
Salmonella: TA98 TA100 TA104	Extracts from smoky coal, China	in vitro Ames assay PCR and DNA sequencing				TA98 + S9 mutagenic at ≥ 10 µg/plate; TA98-S9 not mutagenic. Mutation spectrum hotspot. TA100 + S9 mutagenic at ≥ 10 ug/plate; TA100−S9 at ≥ 50 µg/plate. Mutation spectrum: GC → TA or GC → AT transversions. TA104: no mutagenicity	Granville et al. (2003)

TABLE 7-18. MUTAGENIC/GENOTOXIC EFFECTS OF MOBILE COMBUSTION-SOURCE PM

Species, gender, strain age, or body weight	Particle or constituent	Exposure Technique	Mass Conc µg/mL or µg/m3	Particle Characteristics Size (µm)	Exposure Duration	Effects of particles on mammalian cells or bacteria	Reference
Salmonella	PM diesel gasoline	in vitro Ames assay			48 h	DE mutagenic response was 800 (PM fraction) revertants/g fuel used and 210 (condensate fraction). Gasoline 24 (PM fraction) and 39 (condensate).	Löfroth (1981)
Salmonella: TA98 TA100	PM from Diesel, Gasoline, Gasoline + alcohol, liquified petroleum	in vitro Ames assay			48 h	LP cars: 10 rev/L exhaust. Gasoline and gasoline + alcohol: 10-50 rev/L exhaust). Light-duty diesel:50-250 rev/L7	Rannug (1983)
Salmonella: TA98 TA98NR	Fractionate exhaust of gasoline and diesel engines	in vitro Ames assay	Particle emission values for the vehicles were 0.021 g/km and 0.23 g/km		48 h	Most polar subfraction was most mutagenic TA98–S9: 7.8 rev/m^3 (g); 6.1 (d). TA98+S9: 3.3 (g);1.5 (d). TA98NR–S9: 3.7 (g); 4.1 (d). TA98NR response generally lower than TA98 response. Both had similar TA98NR–S9 response, but differed significantly in TA98-S9 response.	Strandell et al. (1994)
Mutagenicity: *S. typhimurium* Microsome assay Cytotoxicity: Mouse fibroblast cell line < 1.292	Diesel exhaust particles (DEP): petroleum DEP vs. rapeseed oil methyl ester (RME) DEP	in vitro Ames assay	Not given	Dichloromethane extraction of particles collected from diesel engine run with diesel fuels with low or high sulfur and plant oil fuel.	48 h incubation with TA98 and TA100 strains.	Revertants were 2- to 10-fold higher with high sulfur diesel fuel particles. Cytotoxicity in fibroblast cells higher for RME.	Bunger (2000)

TABLE 7-18 (cont'd). MUTAGENIC/GENOTOXIC EFFECTS OF MOBILE COMBUSTION-SOURCE PM

Species, Gender, Strain Age, or body weight	Particle or constituent	Exposure Technique	Mass Conc µg/mL or µg/m3	Particle Characteristics Size (µm)	Exposure Duration	Effects of particles on mammalian cells or bacteria	Reference
Salmonella: TA98 TA100	PM and SVOC of exhaust from diesel and gasoline engines	in vitro Ames assay	25-500 µg/plate			Mutagenicity rankings: TA98: current diesel at 30 °F > high emitter diesel > gas emitting white smoke > normal gasoline 72 °F > normal diesel 72 °F > gas emitting black smoke. TA100: current diesel at 30 °F > gas emitting white smoke > high emitter diesel > normal diesel 72 °F > gas emitting black smoke > normal gasoline 30 °F > normal gasoline 72 °F.	Seagrave et al. (2002)
Salmonella: TA98 Calf thymus DNA	PM and SVOC of exhaust from diesel and gasoline engines	in vitro Ames assay Adduct formation	Ames assay: 30-500 µg/PM (−S9) 10-1000 µg/PM (+S9) Adduct:150 µg/PM gasoline extracts. High doses (42-150 µg/PM) and low doses (7.5-18.5 µg/PM) of gasoline and diesel extracts			Gas SVOC fraction less mutagenic than PM fraction, but formed more DNA adducts. Diesel PM and gasoline extracts formed more S9-mediated adducts with increasing doses, but no dose response. Diesel extracts formed higher levels of adducts than gasoline extracts, especially in the presence of XO. Results suggest high nitro-PAH levels in diesel extract.	Pohjola et al. (2003)

the genotoxic potential of ambient PM samples, ambient PM constituents and/or PM emission source constituents. A caveat to interpretation of these data is that there is not a simple linear relationship between mutagenic potential and carcinogenic potential in animals or humans. Additionally, not all Ames assays are equivalent in terms of predicting mutagenicity. These studies, listed in Table 7-18, have focused mainly on the ability of the organic fraction of ambient PM to induce mutagenic effects in mammalian cell lines and bacteria.

Probably of most direct relevance and usefulness for assessing U.S. ambient air carcinogenic potential, Hannigan et al. (1997) examined the mutagenicity of PM from five monitoring sites in southern California. San Nicolas Island in upwind Los Angeles was considered to be a background site with low levels of PM. Central Los Angeles was characterized as a region of high PM resulting from heavy vehicle traffic. Long Beach was another high PM site studied with PM originating from power plants and oil refineries. The two other high PM sites chosen were Azusa and Rubidoux, which were considered receptor sites located downwind from high density primary emission sources. Mutagenic activity of air samples collected in 1993 were assayed using a cultured human cell assay in addition to the standard Ames bacterial mutation assay, which has limitations in terms of relevancy to human mutagenicity. The human cell assay utilizes h1A1v2 cells, which test mutagenic activity at the thymidine kinase locus. The cells contain a plasmid pHSRAA with two copies of human CYP1A1 cDNA, which confers resistance to 1-histidinol. CYP1A1 is a cytochrome P450 capable of activation of PAH. Air samples were collected throughout the year at all sites using a dichotomous sampler. Both seasonal and spatial differences in component elemental and organic carbon were observed. However, both the human cell mutagenicity assay and a *Salmonella* TM677 forward mutation assay showed no systematic seasonal pattern of changes in mutagenicity. These results suggested to the authors that the proportion of mutagenic compounds in the fine organic aerosol mass does not change throughout the year and that perhaps the emission sources that show seasonal variation do not contribute in a major way to the mutagenicity of the PM. They thusly concluded that, in the Los Angeles area, primary particulate emissions from sources that operate on a year-round basis are the important human cell mutagens. Further, since they found very similar mutagenic potencies at all four widely-separated high PM sites, they suggested that the mutagenicity is due most likely to ubiquitous emissions sources rather than to isolated point sources.

To ascertain which components of the Los Angeles area PM were responsible for the observed mutagenicity, Hannigan et al. (1998) extended these findings by combining the four high PM samples and a background site sample described above into a composite sample that was then separated by liquid chromatography into fractions of organic chemicals of similar polarity and functionality. A primary fractionation separated the composite sample into four fractions, designated nonpolar 1, nonpolar 2, semipolar, and polar. To further isolate the mutagens, additional fractionation steps were done by HPLC. The mutagenic potency of the unfractionated sample was 150 induced mutant fraction (IMF) per mass of fine particulate organic carbon or IMF ($\times 10^6$)/mg of EOC. They found that six unsubstituted polyaromatic compounds (PACs) were responsible for much of the mutagenicity. These included benzo[k]fluoranthene, indeno[1,2,3-cd]pyrene, benzo[b]fluoranthene, benzo[g,h,i]perylene, benzo[a]pyrene, and cyclopenta[cd]pyrene. Benzo[k]fluoranthene and benzo[b]fluoranthene sources include vehicle exhaust and natural gas combustion. The source of the other four PACs is mainly gasoline and diesel vehicles. Additionally, two semipolar mutagens were identified: 2-nitrofluoranthene and 6H-benzo[cd]pyren-6-one. The first compound is a product of atmospheric chemical reactions and the other is emitted by noncatalyst gasoline-powered vehicles. The authors estimated that greater than half of the mutagenicity may be attributed to the semipolar and polar fractions of the sample.

Some additional evidence for mutagenetic properties of ambient PM derive from several European studies. For example, Hornberg et al. (1996), evaluated genotoxic effects on cultured rodent (rat; Syrian golden hamster) tracheal epithelium cells exposed in vitro to ambient PM collected on hi-vol (TSP) sampler filters during winter 1991 in a heavily industrialized city (Duisburg) or in another area (Düsseldorf) of Germany dominated by high density vehicular traffic. Exposure to ambient PM extracted (by dichloromethane or DCM) from filters from both types of locations induced highly significant dose-dependent increases in SCE in the tracheal cells of both rodent species. The authors noted that it was remarkable that even quantities of chemical substances equivalent to airborne PM from just 0.11 to 3.5 m^3 air for the samples from the heavy industry area and from 0.16 to 10.2 m^3 for the heavy traffic area induced significant genotoxic effects (i.e., ~2-fold increases in SCE).

Hornberg et al. (1998) also evaluated genotoxic effects on human tracheal epithelial cells of fine ($PM_{2.5}$) and coarse (PM_{10}) fractions of ambient PM collected during winter, 1996 on

dichotomous sampler filters in an urban area (Düsseldorf), an industrial area (Duisburg) and a rural area (Borken) of Germany. Both ambient PM_{10} and especially $PM_{2.5}$ extracted (by DCM) from filters for all three areas significantly increased SCE in the human bronchioepithelial cell line (BEAS-2B) cultured in vitro for a 72 h exposure. The authors noted that the fine fraction ($PM_{2.5}$) exerted stronger genotoxic activity than the PM_{10} from a given area and that, whereas the Düsseldorf and Duisburg ambient PM materials had comparable genotoxic activity, samples from the rural area (Borken) showed lower genotoxicity. The fine fraction $PM_{2.5}$ (equivalent to airborne PM substances from < 0.5 m^3 of air) exerted strong genotoxicity. The $PM_{2.5}$ and PM_{10} extracted PM from the filters were reported to have been drawn from ambient air having concentrations of: 18.4 and 4.8 $\mu g/m^3$ for Düsseldorf; 45 and 24.1 $\mu g/m^3$ for Duisburg, and 21.8 and 10 $\mu g/m^3$ for Borken, respectively (all of which were in 1 mL of medium for exposures).

Based on the above results, Hornberg et al. (1996, 1998) concluded that the increases observed in SCE of tracheal epithelium cells with in vitro exposures to ambient PM materials are indicative of genotoxic activity of such materials and increased risks for humans due to such genotoxicity activity. However, insufficient information was provided by which to estimate the actual exposure doses to the cell cultures in the Hornberg studies. Nevertheless, their results still appear to provide qualitative evidence for mutagenic effects of ambient PM (especially the fine fraction drawn from heavily industrialized or trafficked areas). The authors also noted that the tracheobronchial epithelium is the site of one of the most common cancer in humans, i.e., bronchogenic carcinoma (Tomatis, 1990).

Further evidence for the likely carcinogenic potential of ambient PM, in addition to the above findings, is derived from a study by Seemayer and Hornberg (1998), which employed a bioassay for enhancement of malignment cell transformation in vitro. Exponentially growing cell cultures from the Syrian golden hamster were exposed for 18 h to varying concentrations of PM materials extracted (by DCM) from hi-vol sampler filters that collected ambient PM from Düsseldorf or Duisburg, Germany in winter, 1990. Control and PM-exposed cultures were then infected with the papovivarus simian virus (SV-40). There was a strong dose-dependent enhancement of cell transformation frequency in the kidney cell cultures as a function of varying pretreatment concentrations of ambient PM extracts. Inoculation of transformed cells into syngeneic animals produced a high percentage of malignant tumors, mostly sarcomas. Positive

control cultures pretreated with benzo[a]pyrene (BaP) showed similar dose-dependent enhancement of malignant cell transformations. The authors also noted that the human papovaruses BK and JC are ubiquitous and infect a large proportion of human populations worldwide (Monini et al., 1995); and that interactions of environmental carcinogens and viruses should be considered in human carcinogenesis.

Using a different type of bioassay from Hornberg and colleagues, Hamers et al. (2000) evaluated the genotoxicity of ambient PM collected by hi-vol sampler at several sites in the Netherlands: (1) one site next to a highway traffic point (density of vehicle passages/day = 63×10^3); (2) another next to a higher density (93×10^3 vehicle passages/day) traffic point; and (3) a third in a natural conservation area (with extensive non-manured grasslands and cattle grazing) thought to have background levels of diffuse air pollution. Extracts of PM filter materials, collected from each of these sites in 1997 and/or 1998, were tested for genotoxic activity in the umu-assay (using *S. typhimurium*). Arylhydrocarbon-receptor activation was also assessed by DR-CALUX-assay, using a stably transfected H4IIE hepatoma cell line. Extracts of ambient PM collected downwind from the highway (west-wind) traffic points had increased genotoxicity that appeared to be attributable at least in part to polycyclic aromatic hydrocarbons (PAHs) from traffic exhaust. The extracts of ambient PM collected upwind of the highway (eastern wind) had a different composition of compounds (probably including some transported from nearby Germany), with higher genotoxicity less related to highway-emitted PAH-like compounds. Of interest, even the rural site ambient PM extracts showed some genotoxic activity. The authors concluded that their results showed that the presence of pollutants with genotoxic or PAH-like characteristics pose an undesirable mutagenic risk.

In another study using a less conventional endpoint, Alink, et al. (1998) compared effects on gap-junctional intercellular communications (GJIC) in liver tumor (HEPA1c1c7) cells of in vitro exposures to PM from urban air (geographic area not stated), rubber and metal industries, diesel exhaust, and biological sources (i.e., poultry/pig farming, compost industry). Only diesel and rubber sample filter extract suspensions significantly inhibited GJIC, with up to 83% of the inhibition attributed to the particles per se. More active organics were reported to have been extracted from the rubber industry particles than from the diesel particles by organic solvents. The authors interpreted their results as suggesting that cancer promoting potential (as

indexed by GJIC inhibition) may vary widely depending on particle source and type, possibly due to the particles per se or to surface-bound bio-active material.

Taken together, the results of the above studies provide new evidence indicative of ambient PM (especially the fine fraction) having mutagenic properties, thus supporting the plausibility of epidemiologic evidence linking ambient PM (especially fine PM) to lung cancer. The results further suggest likely contributions to the observed mutagenicity of ambient PM of industrial or motor vehicle combustion sources (which are important emission sources for fine PM). The ensuing subsections discuss studies that evaluated the mutagenic/genotoxic potential of several types of major combustion sources known to contribute to ambient PM (especially fine PM) in many U.S. regions.

7.8.2 Wood and Coal Combustion-Source Effects

Emissions from the combustion of wood and coal, as well as combustion of oil fuels (diesel and gasoline) by mobile source vehicles, all contribute to ambient PM. A number of studies have been done to evaluate the mutagenicity and genotoxicity of these combustion emissions and to compare their relative mutagenic/genotoxic potentials. Table 7-17 summarizes wood/coal combustion studies, discussed first below. These include some earlier studies, conducted prior to the 1996 PM AQCD, given the only very limited more recent evaluation of wood/coal combustion mutagenic/genotoxic effects.

7.8.2.1 Biomass/Wood Burning

Early studies by Löfroth et al. (1986) used the Ames *Salmonella* assay to determine the mutagenicity of emissions from wood (birch, pine, and spruce) burned in conventional wood stoves. Both the PM fraction and the condensable organic fraction were applied in doses of 0.6 to 4.3 liter flue gas per plate (for a range of 32 to 100 mg/m^3 of PM and 2.6 to 200 mg organics). The wide range of doses was due to use of both updraft and downdraft stoves, the latter generating far less combustion emissions. The organic fraction had a mutagenic potency of 0.5 to 21 revertants/ug (rev/µg). The PM fraction demonstrated only very low mutagenicity. The authors compared these results to earlier studies by Löfroth (1981) and Rannug (1983) of gasoline and diesel cars. On a revertant per hour basis, wood stoves produced 6×10^6, gasoline cars 0.5 to 3×10^6, and diesel cars 3 to 20×10^6 rev/µg.

In testing the spiral *Salmonella* assay, Houk et al. (1991) compared the mutagenicity of wood smoke, automotive diesel exhaust and coal combustion emission. This automated bacterial mutagenicity assay dispenses *Salmonella*, the test agent, and the S9 mix in a spiral pattern on an agar plate, creating a uniform density of bacteria and a gradient of test agent. Doses of 200 µg/plate woodsmoke, 500 µg/plate DE and 200 µg/plate coal emission were used on standard Ames assay plates to compare the two assays. Exposures to strains TA98 and TA100, both with and without metabolic activation by S9, showed that DE had the highest mutagenicity. Results from the TA98 and TA100 experiments suggested to the authors that the mutagenic activity is due to both nitrated polynuclear aromatics creating frameshift mutations and nonpolar compounds creating base-pair substitution mutations. Coal was just slightly less mutagenic than diesel; and the data suggested that indirect-acting frameshift mutations were occurring, which is in agreement with Mumford et al. (1987). Woodsmoke was found to be only weakly mutagenic in both strains.

Heussen et al. (1994) collected respirable PM from homes in Wageningen, NL, a region with no significant industrial pollution. For a 1-month control period, the fireplaces were not used in five homes. Wood was then burned in open fireplaces for 4h/day during the evening for 1 week. PM was collected during these same periods in the homes and, also, from some outdoor sampling sites to correct for possible infiltration of ambient mutagens into the homes. Nonsmoking subjects from these homes gave blood samples during the control period, at the beginning of the combustion period, at the end of the combustion period, and 1 week later. Blood was assayed using ^{32}P-postlabeling analysis of DNA adducts from white blood cells. PM samples were assayed by the Ames test (using strain TA98), both with and without S9 activation. The mutagenicity of samples from all 5 homes was increased after the week of fireplace usage. Control values averaged 28 revertants/30 m^3 (−S9) and 69 (+S9), whereas combustion samples averaged 153 (−S9) and 369 (+S9), indicating stronger indirect mutagenicity. However, there was no correlative combustion-related increase in formation of DNA adducts in white blood cells. The authors suggest several reasons for a lack of correlation between the two endpoints: (1) the exposure was too short and/or the dose was too low; (2) white blood cells may not be a suitable cell type for detection of adducts with this type of exposure; and (3) the actual genotoxic damage that occurred my not be detectable by this method of ^{32}P-postlabeling analysis.

The mutagenicity and toxicity of wood smoke condensate was assayed by Putnam et al., (1999) using the Ames assay and neutral red uptake, respectively. The wood smoke condensate was prepared from hardwoods by distillation and filtration, removing 'insoluble tars' and low boiling point substances. The wood smoke condensate was tested for cytoxicity at concentrations of 0, 10, 25, 50, 75, 100, and 150 µg/mL and found to be toxic beginning at 25 µg/mL. Mutagenicity was tested using *S. typhimurium* strains TA98 and TA100, both with and without S9 activation. Concentrations of 0, 125, 250, 500, 750, and 100 µg/plate were used and the wood smoke condensate was found to be nonmutagenic at all the doses.

More recent studies have examined the mutagenicity of biomass combustion in Chaing Mai, Thailand (Vinitketkumnuen et al., 2002). Large open fires created by farmers burning fields and grass in the winter months correlate with increased in PM at that time of year. Twenty-four hour $PM_{2.5}$ and PM_{10} samples were collected on Teflon filters at four outdoor sampling sites over a period of 1 month and then pooled, dissolved in 1 mL DMSO and used for the Ames assay (TS100 strain/0.05 mL sample per assay). Monthly averages of $PM_{2.5}$ ranged from ~130 µg/m^3 (winter) to 15 µg/m^3 (summer) and for PM_{10}, 170 µg/m_3 to 37 µg/m_3, respectively. Mutagencity, expressed as number of revertants/m^3 air volume, for $PM_{2.5}$ ranged from 30.6 (winter) to 0.1 (summer), with the mutagenicity being increased with S9 activation. For PM_{10} the mutagenicity ranged from 28.1 (winter) to 0.7 (summer) revertants/m^3 air volume, again with S9 activation increasing the mutagenicity. One of the collection sites showed a much higher mutagenicity level than the other three, which might be explained by a local source of diesel exhaust. Mobile source emissions contribute to ambient PM levels in Chaing Mai, but as they remain constant throughout the year, the authors suggested that the increased mutagenicity observed in the winter months is due to biomass combustion.

Kim Oanh et al. (2002) examined the mutagenicity and toxicity of emissions from various cooking sources, including wood and kerosene. The wood (Pterocarpus indicus) was burned in a single-stage ceramic cookstove and two samples were collected, a PM phase consisting of the PM collected on the filter and the PM rinsate and a gas phase consisting of XAD-2, the condensate knockout and the rinsate. Toxicity was assayed using a Microtox bioassay and mutagenicity was assayed using the Ames test with TA98 and TA100 strains, both with and without metabolic activation by S9. The highest mutagenicity factor was observed from wood fuel which produced 12×10^6 revertants/kg using TA100−S9 and 3.5×10^6 revertants/kg using

TA98−S9. These results indicate that the wood smoke emissions can cause both frameshift and base pair substitution mutations. The gas phase of the wood smoke emission contributed more than 60% of the direct-acting mutagenicity.

7.8.2.2 Coal Combustion

Coal fly ash samples (< 3 μm) from a southern U.S. conventional combustion (CC) plant and from a Linden, NJ fluidized-bed combustion (FBC) plant (both burning Pennsylvania eastern bituminous coal) were collected by Mumford and Lewtas (1982). They compared the mutagenicity of PM from the two sources using the Ames assay with test trains TA98, TA100, TA1535, TA1537, and TA1538. FBC was mutagenic in TA98 (3.32 revertants/mg) and TA 1538 (3.31), both without S9 metabolic activation. S9 decreased the mutagenicity of FBC in TA98 and TA 1538. FBC had no mutagenic response in TA1537 and TA1535, with or without S9. Thus, FBC fly ash appeared to create direct-acting frameshift mutations. In all of the five strains utilized, the CC fly ash demonstrated no mutagenicity.

Studies characterizing the health effects of coal emissions have focused mainly on the mutagenicity and carcinogenicity of coal smoke exposure in regions of China with a predominance of indoor burning of "smoky" coal (Mumford et al., 1987; Chapman et al., 1988; Mumford et al., 1999). These regions have very high rates of lung cancer mortality that have been linked to exposure to unvented coal smoke.

Mumford et al., (1987) collected indoor air samples from homes burning smoky coal and from homes burning wood and smokeless coal in open hearths in kitchens. The PM levels inside the homes burning smoky coal averaged 23 mg/m^3, compared to 1.8 mg/m^3 for homes burning smokeless coal. The distribution of PM size in the homes burning smoky coal was bimodal, with half the particles < 1 μm and half 1 μm to 10 μm, whereas particle size in wood-burning homes ranged from 1 to 30 μm. Fractionation of the filter extracts created aliphatic, aromatic, moderately polar, and polar components. High concentrations of organic matter were present in the smoky coal (72 to 82%) compared to 27% for the smokeless coal and 55% for the wood sample. Further, the highest PAH levels were found in smoky coal samples. Both neat samples and fractions were tested for mutagenicity by the Ames assay using strain T98, with and without metabolic activation by S9. Most of the samples required S9 activation for mutagenicity, suggesting to the authors the presence of PAH. Smoky coal samples had the highest

mutagenicity (60-17 revertants/m^3 air) compared to wood (11) and smokeless coal (1.3). The fractions that displayed the most mutagenicity were the polar and aromatic, which were shown by GC/MS to consist primarily of nitrogen- and oxygen-containing compounds (polar fraction) and PAH, methylated PAH, and nitrogen heterocyclic compounds (aromatic fraction).

A retrospective epidemiologic study (Lan et al., 2002) evaluated the incidence of lung cancer in a cohort of farmers born in Yunnan Province. The farmers were raised in homes burning smoky coal in unvented firepits and 81% changed to homes utilizing stoves with chimneys that reduced indoor levels of PM_{10} (2.08 mg/m^3 to 0.71 mg/m^3, respectively). After stove improvement, Lan et al. observed a long-term reduction in lung cancer incidence, calculating risk ratios of 0.59 in men and 0.54 in women.

Very recent work (Granville et al., 2003) has focused on the mutation spectra of coal smoke emissions from the Yunnan Province. Smoky coal extracts from the same source as above (Mumford et al., 1987) at doses of 0, 10, 25, 50, and 100 μg/plate were used in the Ames assay with strains TA98, TA100, and TA104, both with and without S9 activation. Molecular analysis of the revertants was then done to identify the mutations. Coal smoke extract was mutagenic in TA98 in the presence of S9 at doses ≥ 10 μg/plate and not mutagenic without S9 activation. The extract was mutagenic in TA100 with S9 at doses ≥ 10 μg/plate and without S9 at doses ≥ 50 μg/plate, but it was not mutagenic in the TA104 strain. The authors interpreted these results to suggest that the coal extract induced mutations primarily at GC sites and that PAHs were probably involved in the mutations because of the greater mutagenicity in TA100+S9 compared to TA98+S9. The mutation spectrum in TA98 showed that the extract induced only the hotspot mutation, which is a 2-base deletion in an 8-base GC repeat. This suggested to the authors that about 70% of the mutations in TA98 were due to standard PAH compounds in the coal smoke. The mutation spectrum in TA100 showed that most of the mutations were GC → TA or GC→AT transversions. The authors then compared these mutation spectra with KRAS and TP53 mutation spectra observed in lung tumors from nonsmoking women exposed to coal smoke emissions. They found similarities in the GC → TA transversions in TA100 with human mutations due to PAH exposures.

Thus, overall, the above findings link exposures to smoky coal in China to human cancer. However, notable differences exist between the high concentrations of combustion products of

smoky coal to which the Chinese populations are exposed versus the much lower exposures to coal combustion emissions products to which U.S. populations are currently exposed.

7.8.3 Mobile Combustion-Source Effects

Numerous studies have linked mutagenic/carcinogenic effects to diesel and gasoline exhaust and/or to particles contained therein, as summarized in Table 7-18 and discussed below.

7.8.3.1 Diesel

Results such as those noted in Table 7-18 add further to an extensive database on diesel-related mutagenicity that was thoroughly reviewed in the 2002 U.S. EPA Diesel Document (U.S. EPA, 2002) alluded to earlier. Important information drawn from that document's evaluation of diesel-related mutagenic properties is recapitulated below (at times verbatim) with particular emphasis on findings bearing on the role of PM components of diesel exhaust.

As noted in the 2002 Diesel Document, use of mutagenicity data as an approach to evaluating potential carcinogenicity of diesel emissions is based on the premise that genetic alterations are found in all cancers and that several of the chemicals found in diesel emissions possess mutagenic activity in a variety of genetic assays. These genetic alterations can be produced by gene mutations, deletions, translocations, aneuploidy, or amplification of genes. hence no single genotoxicity assay should be expected to predict carcinogenicity. Also, because of the inherent biological differences of measured endpoints, both within genotoxicity assays and between genotoxicity assays and cancer bioassays, a direct extrapolation should not be expected. Indeed, most genotoxicity data are generated with in vitro assays that frequently employ test agent concentrations orders of magnitude greater than encountered in environmental situations. With diesel emissions or other mixtures, other complications also arise due to the complexity of the materials tested.

Since 1978, more than 100 publications have been reported for genotoxicity assays used with whole diesel emissions (DE), the volatile and particulate (DPM) fractions (including extracts), or individual chemicals found in diesel emissions. Interest in the contribution of mutagens to carcinogenicity was high in the early 1980s and the lack of long- term rodent carcinogenicity data for DE led to use of semiquantitative mutagenicity (and in vitro cell transformation) data for DE to augment epidemiology studies of diesel-related carcinogenic

effects. The number of chemicals in diesel emissions is very large; and many have been shown to exhibit mutagenic activity in a variety of assay systems (see Claxton, 1983). Among some of the mutagenically active compounds found in the gas phase of diesel exhaust are ethylene, benzene, 1,3-butadiene, acrolein and several PAHs, all of which are also present in comparable or greater amounts in gasoline exhaust. Of the diesel particle-associated chemicals, several PAHs and nitro-PAHs have been the focus of mutagenic investigations both in bacteria and in mammalian cell systems.

Numerous studies have evaluated mutagenic effects of DE and/or DPM. In one early study, Huisingh et al. (1978) showed that dichloromethane extracts from DPM were mutagenic in strains TA1537, TA1538, TA98, and TA100 of *S. typhimurium*, both with and without rat liver S9 activation, based on data from several fractions as well as DPM from different vehicles and fuels. Similar results with diesel extracts from various engines and fuels were reported by several others using the salmonella frameshift-sensitive strains TA1537, TA1538, and TA98 (Siak et al., 1981; Claxton, 1981; Dukovich et al., 1981; Brooks et al., 1984). Mutagenic activity was also seen in *Salmonella* forward mutation assays measuring 8-azaguanine resistance (Claxton and Kohan, 1981) and in *E. coli* mutation assays (Lewtas, 1983).

One approach to identifying significant mutagens in chemically complex environmental samples (e.g., DE or ambient PM extracts) is the combination of short-term bioassays with chemical fractionation (Scheutzle and Lewtas, 1986). The analysis is most frequently carried out by sequential extraction with increasingly polar or binary solvents. Fractionation by silica-column chromatography separates compounds by polarity or into acidic, basic, and neutral fractions. The resulting fractions are difficult to characterize by chemical methods, but the bioassay analysis can be used to determine fractions for further analysis. In most applications, salmonella strain TA98 without the addition of S9 has been used as the indicator for mutagenic activity.

Generally, a variety of nitrated polynuclear aromatic compounds have been found that account for a substantial portion of the mutagenicity (Liberti et al., 1984; Schuetzle and Frazier, 1986; Schuetzle and Perez, 1983). However, not all bacterial mutagenicity has been identified in this way, and the identity of the remaining mutagenic compounds remains unknown. The nitrated aromatics thus far identified in diesel engine exhaust (DE) were the subject of review in an IARC monograph on DE (International Agency for Research on Cancer, 1989). In addition to

qualitative identification of mutagenic chemicals, several investigators have used numerical data to express mutagenic activity as activity per distance driven or mass of fuel consumed. These types of calculations have been the basis for estimates that the nitroarenes (both mono- and dinitropyrenes) contribute a significant amount of the total mutagenic activity of the whole extract (Nishioka et al., 1982; Salmeen et al., 1982; Nakagawa et al., 1983). More recently, Crebelli et al. (1995) used salmonella to examine the effects of different fuel components. They reported that although mutagenicity was highly dependent on aromatic content, especially di- or triaromatics, there was no clear effect of sulfur content of the fuel. Later, however, Sjögren et al. (1996), using multivariate statistical methods with ten diesel fuels, concluded that the most influential chemical factors in salmonella mutagenicity were sulfur content, certain PAHs (1-nitropyrene), and naphthenes.

Matsushita et al. (1986) tested particle-free DE gas and benzene nitroderivatives and PAHs, identified as components of DE gas. The particle-free exhaust gas was positive in both TA100 and TA98, but only without S9 activation. Of the 94 nitrobenzene derivatives tested, 61 were mutagenic and most showed greatest activity in TA100 without S9; whereas 28 of 50 PAHs tested were mutagenic, all required the addition of S9 for detection, and most appeared to show a stronger response in TA100. When 1,6-dinitropyrene was mixed with various PAHs or an extract of heavy-duty (HD) DE, the mutagenic activity in TA98 was greatly reduced when S9 was absent but increased significantly with S9 present. These latter results suggest that caution should be used in estimating mutagenicity (or other toxic effects) of complex mixtures from the specific activity of individual components.

Mitchell et al. (1981) reported mutagenic activity of DPM extracts of diesel emissions in the mouse lymphoma L5178Y mutation assay. Positive results were seen both with and without S9 activation in extracts from several different vehicles, with mutagenic activity only slightly lower in the presence of S9. These findings were confirmed in a numerous other mammalian cell systems using several different genetic markers. Casto et al. (1981), Chescheir et al. (1981), Li and Royer (1982), and Brooks et al. (1984) all reported positive responses at the HPRT locus in Chinese hamster ovary (CHO) cells. Morimoto et al. (1986) used the APRT and Ouar loci in CHO cells; Curren et al. (1981) used Ouar in BALB/c 3T3 cells. In all of these studies, mutagenic activity was observed without S9 activation. Liber et al. (1981) used the thymidine kinase (TK) locus in the TK6 human lymphoblast cell line and observed induced mutagenesis

only in the presence of rat liver S9 when testing a methylene chloride extract of DE. Barfknecht et al. (1982) also used the TK6 assay to identify some of the chemicals responsible for this activation-dependent mutagenicity; and they suggested that 1-methylphenanthrene, 9-methylphenanthrene, and fluoranthene could account for over 40% of the observed activity.

Specific-locus mutations were not induced in (C3H × 101)F1 male mice exposed to DE 8 h/day, 7 days/week for either 5 or 10 weeks (Russell et al., 1980). The exhaust was a 1:18 dilution and the average particle concentration was 6 mg/m^3. After exposure, males were mated to T-stock females and matings continued for the reproductive life of the males. The results were unequivocally negative; no mutants were detected in 10,635 progeny derived from postspermatogonial cells or in 27,917 progeny derived from spermatogonial cells.

Additional evidence for cytotoxic and mutagenic effects of particles emitted from diesels comes from a study by Bunger et al. (2000). Filter sample particles, collected from diesel emissions generated by a tractor engine during combustion of conventional petroleum diesel fuel or diesel fuel containing rapeseed oil methyl ester (RME), were extracted by DCM and their cytotoxicity was then evaluated by the neutral red assay and their mutagenicity by the *S. typhimurium* assay. The diesel petroleum fuel emissions had much higher numbers of smaller particles than the RME emissions. However, 4-fold stronger toxic effects on mouse fibroblast cells were exerted by RME extracts from filters taken at "idling" but not at "rated" power load modes. Both types of extracts were significantly mutagenic at both load modes in both the TA98 and TA100 strain bioassays, but the petroleum fuel extracts had 4-fold more mutagenic effect in the TA98 and 2-fold more in the TA100 strain assays than did RME extracts. The authors attributed the lower mutagenic potency of the RME diesel emissions to lower sulfur and PAH content in the RME emissions.

Hou et al. (1995) measured DNA adducts and *hprt* mutations in peripheral lymphocytes of 47 bus maintenance workers and 22 control individuals. All were nonsmoking men from garages in the Stockholm area; the exposed group consisted of 16 garage workers, 25 mechanics, and 6 other garage workers. There were no exposure data, but the three groups were considered to be of higher to lower exposure to diesel engine exhaust, respectively. Levels of DNA adducts determined by ^{32}P-postlabeling were significantly higher in workers than controls (3.2 versus 2.3×10^{-8}), but not *hprt* mutant frequencies (8.6 versus 8.4×10^{-6}). Although group mean mutant frequencies were not different, both adduct level and mutagenicity were highest among the

16 most exposed, and mutant frequency was significantly correlated with adduct level. All individuals were genotyped for glutathione transferase GSTM1 and aromatic amino transferase NAT2 polymorphism. Neither GSTM1 nulls nor NAT2 slow acetylators exhibited effects on either DNA adducts or *hprt* mutant frequencies.

Driscoll et al. (1996) exposed Fischer 344 male rats to aerosols of CB (1.1, 7.1, and 52.8 mg/m^3) or air for 13 weeks (6 h/day, 5 days/week) and measured *hprt* mutations in alveolar type II cells in animals immediately after exposure and at 12 and 32 weeks after the end of exposure. The two higher exposures caused significant increases in mutant frequency. Whereas the mutant frequency from the 7.1 mg/m^3 group returned to control levels by 12 weeks, that of the high-exposure group was still higher than controls even after 32 weeks. Carbon black particles have very little adsorbed PAHs; hence a direct chemically induced mechanism is highly unlikely. Induction of *hprt* mutations were also seen for rat alveolar epithelial cells after intratracheal instillation with CB, quartz, and TiO_2 (Driscoll et al., 1997). All three types of particles elicited an inflammatory response as shown by significant increases of neutrophils in BAL fluid. The neutrophils in BAL are the source of ROS. DNA damage resulting from ROS is a secondary genotoxicity, and this effect is seen only at high doses. Culturing the BAL from exposed rats with a rat lung epithelial cell line also resulted in elevation of *hprt* mutational response. This response was effectively eliminated when catalase was included in the incubation mixture, providing evidence for cell-derived oxidative damage. The oxidative damage of CB appeared to be a threshold exposure dose-response phenomenon.

Recently, Sato et al. (2000) exposed male Big Blue transgenic F344 rats to diluted DE (1 and 6 mg/m^3 suspended particle concentration) for 4 weeks. Mutant frequency in lung DNA was significantly elevated (4.8× control) at 6 mg/m^3 but not at 1 mg/m^3. Lung DNA adduct levels measured by ^{32}P-postlabeling and 8-hydroxydeoxyguanosine measured by HPLC were elevated at both particle concentrations, but to a lesser extent than mutant frequencies. Sequence analysis of mutants indicated that some, but not all, of the mutations could be explained by an oxidative damage mechanism.

Other diesel studies have evaluated chromosome effects. Mitchell et al. (1981) and Brooks et al. (1984), for example, reported increased SCE in CHO cells exposed to DPM extracts of emissions from both LD and HD diesel engines. Morimoto et al. (1986) observed increased SCE from both LD and HD DPM extracts in PAH-stimulated human lymphocyte cultures. Tucker

et al. (1986) exposed human peripheral lymphocyte cultures from four donors to direct DE for up to 3 h. Samples were taken at 16, 48, and 160 min of exposure. Cell cycle delay was observed in all cultures; and significantly increased SCE levels were reported for two of the four cultures. Structural chromosome aberrations were induced in CHO cells by DPM extracts from a Nissan diesel engine (Lewtas, 1983) but not by similar extracts from an Oldsmobile diesel engine (Brooks et al., 1984).

DPM dispersed in an aqueous mixture containing dipalmitoyl lecithin (DPL), a component of pulmonary surfactant or extracted with DCM induced similar responses in SCE assays in Chinese hamster V79 cells (Keane et al., 1991), micronucleus tests in V79 and CHO cells (Gu et al., 1992), and unscheduled DNA synthesis (UDS) in V79 cells (Gu et al., 1994). After separating the samples into supernatant and sediment fractions, mutagenic activity was confined to the sediment fraction of the DPL sample and the supernatant of the DCM sample. These findings suggest that the mutagenic activity of DPM inhaled into the lungs could be made bioavailable through solubilization and dispersion of pulmonary surfactants. In a later study in the same laboratory, Liu et al. (1996) found increased micronuclei in V79 cells treated with crystalline quartz and a noncrystalline silica, but response was reduced after pretreatment of the particles with the simulated pulmonary surfactant.

Guerrero et al. (1981) observed a linear concentration-related increase in SCE in lung cells cultured after intratracheal instillation of DPM at doses up to 20 mg/hamster. However, they did not observe any increase in SCE after 3 mos of inhalation exposure to DE particles at 6 mg/m^3. Also, Pereira et al. (1981a) exposed female Swiss mice to by inhalation DE 8 h/day, 5 days/week for 1, 3, and 7 weeks. The incidence of micronuclei and structural aberrations was similar in bone marrow cells of both control and exposed mice.

Pereira et al. (1982) measured SCE in embryonic liver cells of Syrian hamsters. Pregnant females were exposed to DE diluted with air 1:9 to contain about 12 mg/m^3 particles from days 5 to 13 of gestation or injected intraperitoneally with diesel particles or particle extracts on gestational day 13 (18 h before sacrifice). Neither the incidence of SCE nor mitotic index was affected by exposure to DE. The injection of DPM extracts but not DPM resulted in a dose-related increase in SCE; however, the toxicity of the DPM was about 2-fold greater than the DPM extract.

In a study using mammalian germ cells, Russell et al. (1980) reported no increase in either dominant lethals or heritable translocations in males of T-stock mice exposed by inhalation to DE. In the dominant lethal test, T-stock males were exposed for 7.5 weeks and immediately mated to females of different genetic backgrounds. There were no differences from controls in any of the parameters measured. For heritable translocation analysis, T-stock males were exposed for 4.5 weeks and mated to (SEC × C57BL/6) females, and the F1 males were tested for the presence of heritable translocations. Although no translocations were detected among 358 progeny tested, the historical control incidence is ≤ 1/1,000.

A number of studies have measured other types of genotoxic effects (e.g., increased DNA adducts) in animals exposed to DPM, CB or other particles, as reviewed by Shirnamé-Moré (1995). Although modest increases in DNA adducts have been observed in lung tissue of rats after inhalation of DPM (Wong et al., 1986; Bond et al., 1990), the increases are small in comparison with those induced by chemical carcinogens present in DE (Smith et al., 1993). While Gallagher et al. (1994) found no increases in total DNA adducts in lung tissue of rats exposed to DE, CB, or titanium dioxide, they did observe an increase in an adduct with migration properties similar to nitrochrysene and nitro-benzo(a)pyrene adducts from diesel but not CB or TiO_2 exposures. The majority of the studies used the ^{32}P postlabeling assay to detect adducts. Although this method is sensitive, chemical identity of adducts can only be inferred if an adduct spot migrates to the same location as a known prepared adduct.

DNA adducts have also been measured in humans occupationally exposed to DE. Distinct adduct patterns were found among garage workers occupationally exposed to DE compared to nonexposed controls (Nielsen and Autrup, 1994). Furthermore, the findings were concordant with adduct patterns observed in groups exposed to low concentrations of PAHs from combustion processes. Hemminki et al. (1994) also reported significantly elevated levels of DNA adducts in lymphocytes from garage workers with known DE exposure compared with unexposed mechanics. Hou et al. (1995) found elevated adduct levels in bus maintenance workers exposed to DE. Although no difference in mutant frequency was observed between the groups, the adduct levels were significantly different (3.2 versus 2.3×10^{-8}). Nielsen et al. (1996) reported significantly increased levels of three biomarkers (lymphocyte DNA adducts, hydroxyethylvaline adducts in hemoglobin, and 1-hydroxypyrene in urine) in DE-exposed bus garage workers.

The role of oxidative damage in causing mutations has received increasing attention. More than 50 different chemicals have been studied in rodents usually measuring the formation of 8-hydroxydeoxyguanosine (8-OH-dG), a highly mutagenic adduct (Loft et al., 1998). Dose-dependent increases in that mutagenic DNA adduct were found in mouse lung DNA after intratracheal instillation of diesel particles (Nagashima et al., 1995). Mice fed on a high-fat diet showed an increased response, whereas the responses were partially reduced when the antioxidant, β-carotene, was included in the diet (Ichinose et al., 1997). Oxidative damage also has been measured in rat lung tissue after intratracheal instillation of quartz (Nehls et al., 1997) and in rat AMs after in vitro treatment with silica dust (Zhang et al., 2000). Arimoto et al. (1999) found that redissolved methanol extracts of DPM also induced the formation of 8-OH-dG adducts in L120 mouse cells. The response was dependent on both DPM concentration and P450 reductase. The potential role of oxidative damage in DE carcinogenesis is discussed in more detail in the U.S. EPA Diesel Document (U.S. Environmental Protection Agency, 2002).

7.8.3.2 Gasoline

In addition to the above studies of DE and DPM effects, other studies have also evaluated mutagenic/genotoxic effects of gasoline combustion emissions and/or compared the potencies of such emissions to DE or DPM potencies.

In an early study, Löfroth (1981) compared the mutagenic activity of PM from diesel and gasoline engine exhaust and found both to be mutagenic in the Ames assay, in the absence of mammalian metabolic activation. Both particulate and condensate fractions were tested. Expressed in units of revertants/g fuel used, diesel exhaust mutagenic response was 800 (PM fraction) and 210 (condensate fraction), which was far greater than the mutagenic response of gasoline (24 and 39, respectively). In another older study, Rannug (1983) collected both particulate and gas phase components from motor vehicle exhaust from medium- and heavy-duty diesel vehicles and light-duty cars burning gasoline and other fuels. The Ames assay was used with strains TA98 and TA100, both with and without S9 activation. The particulate phase of the exhaust created < 20,000 revertants/km (corresponding to 10 rev/L exhaust) in cars burning liquified petroleum and cars with catalysts, classified by the authors as the low mutagenicity group. Light-duty diesels produced > 100,000 rev/km with the highest effect of up to 700,000 rev/km seen with TA100−S9 (corresponding to 50-250 revertants/L exhaust) and were

classified by the authors as the high mutagenicity group. Engines burning gasoline or gasoline-alcohol fuels created exhaust from which the particulate phase gave 10,000 to 20,000 rev/km (or 10-50 rev/L exhaust). In general, the newer vehicles tested produced exhaust with slightly less mutagencity than older models. Also, more mutagenesis was seen in exhaust from cold starts (0 °C) than in starts at 23 °C.

Strandell et al. (1994) fractionated the extracts of gasoline and diesel exhaust from Volvos to find the most potent mutagens among the subfractions. Particle emission values for the vehicles were 0.021 g/km and 0.23 g/km, respectively. Mutagenicity testing was done with the Ames assay with strain TA98, both with and without S9 metabolic activation, and with strain TA98NR, the nitro reductase-deficient strain used to determine the presence of nitro aromatic mutagens. The subfraction that was most polar also demonstrated the most mutagenicity (51% of the total mutagenicity for gasoline and 39% of the total for diesel). This fraction contained low-boiling point components and some phenol derivatives. Quantitatively, this subfraction's mutagenicity using TA98–S9, TA98+S9 and TA98NR–S9 was 7.8, 3.3 and 3.7 rev/m^3, respectively, for gasoline and 6.1, 1.5, and 4.1 for diesel. The TA98NR response was generally lower than the TA98 response, which the authors suggested was due to the presence of nitro-PAH in the fractions. Both fuels had a similar TA98NR–S9 response, but differed significantly in their TA98–S9 response, which suggests difference in some nitro-reductase-dependent mutagens. A reduction in mutagenicity was observed with the addition of S9 activation, which the authors attribute to enzymatic deactivation of direct-acting mutagens or possible activation or deactivation of unknown compounds.

A more recent study (Seagrave, et al., 2002) using vehicles including automobiles, SUVs and pickup trucks from 1976 to 2000 evaluated the genotoxicity of gasoline and diesel emissions from normal vehicles, high emitters, and gasoline vehicles emitting smoke. Both PM and semivolatile organic compound (SVOC) fractions were collected, both at room temperature and in a cold environment. The PM and SVOC fractions were recombined and tested for mutagencity using the Ames assay with strains TA98 and TA100, both with and without S9 activation. All of the samples caused mutations in both strains with doses from 25 to 5000 μg/plate (LOEL not given). With most samples evidence pointed to a direct-acting mutagenesis effect due to the results of TA98 both with and without S9 activation. The assay using TA100 showed greater mutagenicity in the exhausts from the high emitter diesel, the white

smoker gasoline, and the black smoker gasoline. As seen in the Rannug (1983) study, emissions samples collected from cold engines were more mutagenic than those collected at room temperature. The authors ranked the mutagenic potency based on the TA98 results as: current diesel at 30 °F > high emitter diesel > gasoline engine emitting white smoke > normal gasoline > normal diesel 72 °F > gasoline engine emitting black smoke. The mutagenic potency based on the TA100 results were: current diesel at 30 °F > gasoline engine emitting white smoke > high emitter diesel > normal diesel 72 °F > gasoline engine emitting black smoke > normal gasoline 30 °F > normal gasoline 72 °F. The authors' goal with this work was to examine the various bioassays available to ascertain which are most useful in determining differences in mutagenicity, toxicity, and inflammation. Significant findings indicate that both diesel and gasoline exhaust emissions are mutagenic, with diesel being more mutagenic in general. The increase in mutagenicity of gasoline samples with S9 activation indicates the role of PAH in this effect. Decreased mutagenicity by the addition of S9 in the diesel sample collected at 30 °F suggested to the authors that the mutagenicity of the exhaust may be due to nitroarenes.

Pohjola et al., (2003) used the extractable organic material from the PM and SVOC gasoline and diesel exhaust fractions to examine their ability to induce mutations in *Salmonella* strain TA98 and to form adducts in calf thymus DNA. Doses used in the Ames assay were 30 to 500 µg/PM for the –S9 experiments and 10 to 1000 µg/PM for the +S9 experiments. Doses used for oxidative and reductive activation of PAHs were 18-300 µg PM for gasoline and 75-1,500 µg PM for diesel. Using the ^{32}P-postlabeling method, 4 µg of DNA was analyzed for bulky aromatic DNA adducts. Only the gasoline was tested in the Ames assay. The PM fraction had higher mutagenicity, which averaged 431 rev/mg PM (–S9) and 487 rev/mg PM (+S9). The SVOC fraction had only 106 rev/mg PM (–S9) and 98 rev/mg PM (+S9). However, the SVOC fraction formed more DNA adducts. PAH-DNA adduct formation with 150 µg PM gasoline extracts in calf thymus DNA ranged from 3.7 to 8.3 (–S9), 7.7 to 56 (+S9), 5.2 to 18 (-XO), and 19-60 (+XO) adducts/10^8 nucleotides/mg PM. Comparisons were made of PAH-DNA adduct levels using high doses (42 to 150 µg PM) and low doses (7.5 to 18.5 µg PM) of gasoline and diesel extracts. Diesel PM and gasoline extracts formed more S9-mediated adducts with increasing doses, but gasoline did not have a linear dose-response. The authors suggested that complex interactions and/or inhibition of S9 caused lower concentrations of both gasoline and diesel extracts to bind DNA with greater efficiency than 8-fold higher doses. Diesel extracts

formed higher levels of adducts than gasoline extracts, especially in the presence of XO (reductive activation), indicating possible high levels of nitro PAHs. Diesel extracts were also more mutagenic than gasoline extracts in the –S9 (direct-acting) assays, which further suggests higher concentrations of nitro-PAHs in diesel exhaust. This study corroborates earlier research suggesting that diesel exhausts extracts are more mutagenic than gasoline extracts, and that diesel's mutagencicity can be attributed, in part, to DNA adduct formation.

7.8.4 Summary of Mutagenic/Genotoxic Effects

A number of recent in vivo and in vitro studies have suggested that ambient urban PM is mutagenic. Research evaluating the mutagenicity of ambient PM from the Los Angeles area has pointed to ubiquitous emission sources as being responsible for mutagenic activity observed in vitro (Hannigan et al., 1997, 1998). Fractionation of those ambient samples and subsequent mutagenicity assessments have indicated that six unsubstituted polyaromatic compounds and two semi-polar compounds are the likely mutagens. Mutagenicity of urban air from Germany has also been demonstrated (Hornberg et al., 1996, 1998; Seemayer and Hornberg, 1998), with evidence showing that the fine fraction of PM exerted greater toxicity. Additionally, ambient PM from high traffic areas in the Netherlands also induced genotoxic activity.

Emissions from wood/biomass burning have been shown to be mutagenic. Studies of human exposures in China (Vinitketkumnuen et al., 2002) and the Netherlands (Heussen et al., 1994), examining both chronic seasonal and acute exposures, have demonstrated increased mutagenicity with environmental exposures. Characterization of wood smoke fractions to assign mutagenicity have shown that the organic fraction is mutagenic and that the condensate is not. Wood smoke emissions can cause both frameshift and base pair mutations but have not yet demonstrated the production of DNA adducts.

Emissions from coal combustion have been shown to be mutagenic, especially the polar and aromatic fractions. Research in China examining populations with high lung cancer rates have shown that emission samples from homes burning smoky coal are mutagenic in the Ames assay, and implicate PAHs as contributors to the mutagenicity (Mumford et al., 1987, 1999; Lan et al, 2002). Recent work (Granville et al., 2003) characterizing the mechanism of genotoxicity has examined the mutation spectra of coal smoke emissions from these Chinese homes. Sequencing the revertants has shown that the mutations in *Salmonella* exposed to coal smoke

extract are similar to mutations seen in lung tumors of women exposed environmentally to the coal smoke, which differs in notable ways from coal combustion emissions in the United States.

Extensive studies have demonstrated mutagenic activity in both particulate and gaseous fractions of DE. By sequential fractionation of DE, apportionment of the mutagenicity is possible, which has implicated nitrated polynuclear aromatic compounds as being responsible for a substantial portion of the mutagenicity. Other mutagenically active compounds include ethylene, benzene, 1,3-butadiene, acrolein, and several PAHs in the gas phase. In addition to Ames assay studies, the induction of gene mutations has been reported in several in vitro mammalian cell lines after exposure to extracts of DPM. Structural chromosome aberrations and SCE in mammalian cells have been induced by DE particles and extracts.

Early studies comparing the mutagenicity of gasoline and diesel exhaust showed that the PM component of the exhaust is more mutagenic than the condensate fraction, and that overall, diesel exhaust is more mutagenic than gasoline exhaust. More mutagenicity is also observed in exhaust from cold starts than from exhausts at room temperature. Examining the fractional mutagenicity of gasoline and diesel exhausts, it was shown that, as with coal smoke, the polar component has the most mutagenicity, and further, that nitro-PAH is present in the fraction. A comprehensive study comparing gasoline and diesel exhaust genotoxicity, using both the PM and SVOC fractions, demonstrated that both exhausts are mutagenic, but, in general, diesel exhaust is more mutagenic. Further, the study implicates PAH and nitroarenes in the genotoxicity. Another current study corroborates these finding, and includes data suggesting that DNA adduct formation is a component of the mutagenicity.

Exact comparisons of the mutagenicity of combustion emissions of these fuels are not possible because data provided in the studies vary so greatly in units in which mutagenicity is expressed. Thus, there is qualitative evidence for the mutagenic/genotoxic potential of both ambient PM and some fuel combustion products. Many of the published in vitro studies failed to provide details regarding the dose of PM extract delivered to the cells in vitro. In general, equal volumes of air or amounts of time were sampled and reported, but only limited, if any, characterization of the amount of PM mass or size was done or reported in many studies. Thus, any quantitative extrapolation of the reported findings would be quite difficult. Nevertheless, they collectively do appear to provide some evidence tending to substantiate the biologic

plausibility of, and/or elucidating potential mechanisms underlying, reported epidemiologic associations between long-term human exposure to ambient PM and lung cancer.

7.9 INHALED PARTICLES AS POTENTIAL CARRIERS OF TOXIC AGENTS

Particle-Bound Water

In Chapter 2, it was noted that, although water vapor is not considered a pollutant per se and particle-bound water is not measured as part of the ambient PM mass typically monitored for regulatory purposes, particle bound water may serve as a carrier for other pollutants. Wilson (1995) proposed that water-soluble gases that are usually largely removed by deposition to wet surfaces in the upper (ET) portion of the respiratory tract could be dissolved in particle bound water and, thereby, be carried into the lower regions of the respiratory tract. Such water-soluble gases commonly found in polluted air masses include: oxidant species (e.g., O_3, H_2O_2, and organic peroxides); acid gases (e.g., SO_2, HCl, HNO_3, HONO, and formic acid); and polar organic species (e.g., formaldehyde). Thus, water may be a vector by which these gases may be delivered in enhanced proportions to the TB and A regions of the deep lung.

Kao and Friedlander (1995) also noted that, in evaluating health effects of ambient aerosol components, it is "important to realize that the chemical analyses of routinely collected particulate samples are not necessarily an accurate representation of the atmosphere." They further noted that many short-lived chemical species in the gas or particle phase, such as free radicals, may not be present in the sampled materials when analyzed hours to weeks (or longer) after being collected on filters and stored. Also, the unmeasured metastable species may be much more biochemically active than "dead" components collected or remaining on analyzed filters. They concluded that, "since inhalation toxicology studies using both human and animal subjects often do not include the potential for metastable species and reactive intermediaries to be present, they could greatly underestimate the effects seen in field or epidemiologic studies." Friedlander and Yeh (1998) elaborated further on the fact that the aqueous component of the atmospheric submicron aerosol contains short-lived reactive chemical species. That is, they explained that submicron atmospheric aerosols contain several types of components, which importantly include very short-lived reaction intermediates, such as hydrogen peroxides,

aldehydes, and organic acids found in cloud and rain water. Friedlander and Yeh (1998) further noted (1) that particle phase concentrations of hydrogen peroxide fall in a range for which significant biochemical effects were elicited with treatment of respiratory tract epithelial calls; (2) that this may help to explain epidemiologic study results showing significant health effects to be associated with fine-mode aerosols or sulfate (the submicron sulfate-containing aerosol often being the product of atmospheric reactions involving hydrogen peroxide), and (3) that such aerosols may be serving as a surrogate or indicator for the hydrogen peroxide or other reactive species.

Wexler and Sarangapani (1998) used a physical model of "gas-particle-mucus heat and mass transport in the human airways" to investigate the transport by particles of soluble vapors to the tracheobronchial and air exchange regions of the lung. When the atmospheric aerosol is inhaled, water soluble gases will begin to dissolve in the mucus on the surface of the airways. However, hygroscopic particles will add particle-bound water in the high relative humidity of the respiratory tract and more soluble gas can dissolve in the particle. The amount of soluble gas in the particle will depend on the solubility of the gas (expressed as the Henry's Law coefficient), the size of the particle, and the position of the particle in the respiratory tract. In the presence of particles, the pattern of deposition of soluble gases may be moved deeper into the respiratory tract. Very soluble gases, such as H_2O_2 and formaldehyde will still be almost completely removed from the gas phase to the mucus on the airways. However, soluble gases dissolved in particles may be carried into the air exchange region. If equilibrium is reached rapidly, such highly soluble gases will evaporate from particles smaller than 0.1 μm diameter before the particles reach the air exchange region. However, particles larger than ~0.3 μm diameter can efficiently carry such gases into the air exchange region.

Wexler and Sarangapani (1998) point out that due to the small volume of particle-bound water, even in the case of highly soluble gases, only on the order of 1% of the soluble gas will be found in the particles. However, particles will change the pattern of vapor deposition and particles will carry dissolved gases deeper into the respiratory tract where the particles can deposit on air exchange surfaces not protected by mucus. Furthermore, the Wexler and Sarangapani (1998) analysis was based on considerations of physical solubility only. If adducts or complexes form, such peroxohydrates from H_2O_2 (Friedlander and Yeh, 1998; Elvers et al., 1991), or if the gas reacts chemically with water, as SO_2 does to form SO_2 (aq), H_2SO_3 (aq),

and HSO^{-3} (aq) (Schwartz, 1984), the solubility of the gas may be increased greatly and the time to reach equilibrium may be increased. Both factors would enable particles to transfer greater quantities of dissolved gases to the air exchange region.

Morio et al. (2001) evaluated whether hygroscopic components of PM may transport H_2O_2 into the lower respiratory tract and induce tissue injury. Rats were exposed via inhalation to $(NH_4)_2$ SO_4 (0.3 to 0.4 μm MMD) at 215 or 249 μg/m^3 or H_2O_2 at 10, 20, or 100 ppb alone or in combination for 2 h. No major effect was observed on BAL cell number or viability or on protein content or LDH levels immediately or 24 h post exposure. However, rats treated with the combination of sulfate and peroxide showed increased TNF∝ produced by AMs and increased numbers of neutrophils in pulmonary capillaries (as seen via EM). These results and other effects on NO levels were interpreted by the authors as showing that biological effects of inhaled PM are augmented by coexposure to sulfate and peroxide, including altered production of cytokine mediators by AM.

The information summarized above has substantial implications for interpreting and understanding the vast array of epidemiological and toxicologic results discussed in preceding sections of this chapter and earlier chapters of this document. Their full significance becomes more evident when considered in light of dosimetric information discussed in Chapter 6. It is worth restating a few basic points here from Chapter 6 and expanding on them further with regard to the importance of dosimetric considerations in relation to particles as carriers of other toxic agents.

First, particle size is one of the most basic parameters governing particle behavior and deposition in the respiratory tract. Particles between 0.3 and 0.7 μm in diameter have minimal deposition in the respiratory tract. Above and below this range of minimum deposition, the efficiency of deposition increases. The pattern of deposition within the respiratory tract also slowly shifts from the alveolar region to the TB and ET regions with increasing particle size over 1 to 2 μm MMAD and with decreasing particle size below 0.1 μm.

Hygroscopicity, the propensity of a material for taking up and retaining moisture, is an important property of some ambient particle species and affects respiratory tract deposition. Such particles can increase in size in humid air in the atmosphere or in the respiratory tract and, when inhaled, deposit according to their hydrated size rather than their initial size. Compared to nonhygroscopic particles of the same initial size, deposition of hygroscopic aerosols in different

regions varies, depending on initial size: hygroscopicity generally increases total deposition for particles with initial sizes larger than ~0.5 μm, but decreases deposition for particles between ~0.01 and 0.5 and again increases deposition for particles < 0.01 μm. Thus, under high humidity conditions, there is increased deposition of smaller (nucleation-mode; < 0.01 μm) ultrafine particles and of larger accumulation-mode (≥ 0.5 μm) particles, the latter of which can grow to sizes exceeding 1.0 μm and both of which would contain enhanced amounts of particle bound water and other toxic agents (e.g., SO_2, peroxide, formaldehyde) dissolved therein.

Enhanced particle retention occurs on carinal ridges in the trachea and segmental bronchi; and deposition "hot spots" occur at airway bifurcations or branching points. Peak deposition sites shift from distal to proximal sites as a function of particle size, with greater surface dose in conducting airways than in the A region for all particle sizes. To some extent then, the growth of ultrafine and accumulation mode particles under humid conditions would also likely increase "hot spot" deposition at airway branching points and thereby increase PM doses to tissues at those points.

Ventilation rate, gender, age, and respiratory disease status all affect total and regional respiratory tract particle deposition. Of likely most concern from among all these factors affecting respiratory particle deposit patterns are altered PM deposition patterns due to respiratory disease status that may put certain groups of adults (including some elderly) and children at greater risk for PM effects. Importantly, COPD contributes to more heterogenous deposition patterns and differences in regional deposition. One study indicates that people with COPD tend to breathe faster and deeper than those with normal lungs (i.e., about 50% higher resting ventilation) and have ~50% greater deposition than age-matched healthy adults under typical breathing conditions, with average deposition rates 2.5 times higher under elevated ventilation rates. Enhanced deposition appears to be associated more with the chronic bronchitic than the emphysematous component of COPD. In this and other new studies, fine-particle deposition increased markedly with increased degree of airway obstruction. With increasing airway obstruction and uneven airflow because of irregular obstruction patterns, particles tend to penetrate more into remaining better ventilated lung areas, leading to enhanced focal deposition at airway bifurcations and alveoli in those A region areas. In contrast, TB deposition increases with increasingly more severe bronchoconstrictive states, as occur with asthmatic conditions.

Disease states can also alter clearance rates for removal of deposited particles from the lung. Bronchial mucus transport is slowed by asthma, chronic bronchitis, bronchial carcinoma, and various acute respiratory infections - all being disease conditions expected to increase retention of deposited particle material and, thereby, increase the probability of toxic effects from inhaled ambient PM components reaching the TB region. Also, spontaneous coughing, an important TB region clearance mechanism, does not appear to fully compensate for impaired mucociliary clearance in small airways and may become depressed with worsening airway disease, as seen in COPD patients. Clearance of particles from the A region by AMs and their mucociliary transport is usually rapid (< 24 h), but alveolar region clearance rates are decreased in human COPD sufferers and slowed by acute respiratory infections; and the viability and functioning of AMs are reduced in human asthmatics and in animals with viral lung infections.

All this suggests that persons with asthma, chronic bronchitis, or acute lung infections are likely to experience increased deposition and retention of inhaled particles and to be at increased risk for ambient PM exposure effects. Such individuals can reasonably be expected to be put at even greater risk when inhaling ambient PM under high humidity conditions (with increased delivery of peroxides, SO_2, and other noxious agents into the deep lung in particle-bound water and enhanced "hot spot" deposition of hygroscopic aerosols at branching points in bronchial airways).

Bioaerosols as Contributors to Ambient PM Effects

Bioaerosols, from sources such as plants, fungi, and microorganisms, range in size from 0.01 μm to > 20 μm. They comprise a small fraction of ambient PM, but likely contribute to some types of ambient PM-related health effects exposure.

Intact pollen grains from flowering plants, trees and grasses are by far most abundant in warm/humid spring and summer months and can deposit in upper airways to induce allergic rhinitis. Allergen-laden cytoplasmic fragments (~0.1 to 0.4 μm in size) of pollen grains (which rupture under high moisture conditions) can enter the deep lung, where they can exacerbate asthma. Binding of allergen-laden pollen cytoplasmic fragments to ambient fine particles (e.g., DPM) has also been observed; and synergistic interactions between pollen debris and other ambient PM (e.g., the polycyclic hydrocarbon component of DE) are thought to be a mechanism that may explain the increased incidence of asthma morbidity and mortality. Pollen granules can

also act as vectors for binding of other bioaerosols (e.g., endotoxins, fungi or fragments, glucans) and thereby enhance their inhalation and deposition in the respiratory tract.

Fungal spores and fungi fragments are among the largest and most consistently present bioaerosols found outdoors (levels being higher during warm/humid months). They cause allergic rhinitis and asthma, which is highly dependent on seasonal variations in concentration. Exposures have been linked to asthma hospitalization and death.

Bacteria and viruses are significant bioaerosols. Much of the toxicity of bacteria is due to the endotoxins present in the outer cell membrane, which trigger production of cytokines and a cascade of inflammation. Ambient airborne concentrations of endotoxins vary with seasons (being higher in warm/humid periods and low in colder months) and tend to be higher in samples of coarse-mode than in fine-mode ambient PM. Another cell wall component of bacteria and fungi, (1→3)-β-D-glucan, has also been shown to cause respiratory inflammation.

Animals and insects produce bioaerosols capable of producing hypersensitivity diseases. Most notably, exposure to dust mite and cockroach material has been linked to sensitization in children. However, indoor exposures to such materials probably are of most importance with regard to human exposures to such materials.

It thus appears that certain ambient bioaerosols (e.g., pollen, fungi, endotoxins, glucans) that become abundant during warm/humid weather may contribute to seasonal increases in PM-associated risk during spring/summer months, but not during colder winter months. The copresence of nonbiological particles, serving as vectors concentrating such bioaerosols and enhancing their delivery into the deep lung, appears to likely be important.

Summary and Conclusions

It has been proposed that particles also may act as carriers to transport toxic gases into the deep lung. Water-soluble gases, which would be removed by deposition to wet surfaces in the upper respiratory system during inhalation, could dissolve in particle-bound water and be carried with the particles into the deep lung. Equilibrium calculations indicate that particles do not increase vapor deposition in human airways. However, these calculations do show that soluble gases are carried to higher generation airways (i.e., deeper into the lung) in the presence of particles than in the absence of particles. In addition, species such as SO_2 and formaldehyde react in water, reducing the concentration of the dissolved gas-phase species and providing a

kinetic resistence to evaporation of the dissolved gas. Thus, the concentration of the dissolved species may be greater than that predicted by the equilibrium calculations. Of much concern, particle-bound water appears to be a means by which dissolved hydrogen peroxide and other short-lived reactive oxygen species can be carried into lower respiratory tract regions and contribute to the induction of inflammatory responses. Also, certain other toxic species (e.g., NO, NO_2, benzene, PAHs, nitro-PAH, a variety of allergens) may be absorbed onto solid particles and carried into the lungs. Thus, ambient particles may play important roles not only in inducing direct health impacts of their constituent components but also in facilitating delivery of toxic gaseous pollutants or bioagents into the lung and may, thereby, serve as key mediators of health effects caused by the overall air pollutant mix.

7.10 INTERPRETIVE SUMMARY OF PM TOXICOLOGY FINDINGS

Toxicological studies can play an integral role in addressing several key important questions regarding ambient PM health effects:

(1) What types of pathophysiological effects are exerted by ambient PM or constituent substances and what are potential mechanisms that likely mediate various PM health effects?

(2) What PM characteristics (size, chemical composition, etc.) cause or contribute to health effects?

(3) What types of interactive effects of particles and gaseous co-pollutants have been demonstrated?

(4) What susceptible subgroups are at increased risk for ambient PM health effects and what factors contribute to increased susceptibility?

(5) What are the exposure-response relationships of ambient PM and how can that information be extrapolated to human exposures?

This summary focuses on highlighting salient findings that reflect the progress made by toxicological studies towards addressing these questions. All these questions have important implications bearing on the matter of biological plausibility of epidemiologically-observed ambient PM effects.

One overarching issue in the interpretation of toxicology study results is the relevance of findings from experimental human or animal studies using controlled exposure/dose concentrations that are high relative to the much lower ambient pollutant exposure levels that apply within the context of pertinent epidemiology studies. To provide insight on this issue, EPA conducted a series of illustrative analyses using dosimetric modeling of the type discussed in Chapter 6; these analyses are described in detail in Appendix 7A. First, taking into account certain key points regarding dose metrics, one of the publically available dosimetry models (the MMPD model) discussed in Section 6.6.4 of Chapter 6 and in Appendix 7A Section 3 was employed to compare estimates of deposited and/or retained respiratory tract PM doses in the human and rat lung using different dose metrics as described in Table 7A-4. The second approach involved application of the same publically-available model (a) to estimate likely respiratory tract doses (again using various dose metrics) resulting from experimental exposures (via PM inhalation or instillation) of human or laboratory animals (rats) actually employed in representative published PM toxicology studies assessed in this chapter and (b) to estimate likely ambient PM exposure concentrations that would be needed in order to obtain comparable human and rat PM respiratory tract doses. Rats clear PM from the respiratory tract much faster than humans, which is more important for long-term exposure comparisons. Rats also have a lower deposition fraction, which is more important for comparing acute effects. MPPD modeling indicates that higher exposure concentrations in the rat may be needed, in certain cases, in order to evaluate toxicological endpoints predictive of health outcomes in humans and to investigate biological mechanisms. The higher doses needed depend on the health endpoint measured. For example, the modeling results suggest that higher PM concentration exposures in rats may be needed to achieve nominally similar inflammatory responses relative to the human.

7.10.1 Particulate Matter Health Effects and Potential Mechanisms of Action

Numerous epidemiologic analyses discussed in Chapter 8 have shown associations between ambient PM levels and increased risk for cardiorespiratory effects, as well as for lung cancer. Findings since 1996 have provided evidence supporting many hypotheses regarding induction of PM effects; and this body of evidence has grown substantially. Various toxicologic studies using PM having diverse physicochemical characteristics have shown that such

characteristics have a great impact on the specific response that is observed. Thus, there appear to be multiple biological mechanisms that may be responsible for observed morbidity/mortality due to exposure to ambient PM, and these mechanisms appear to be highly dependent on the type and dose of particle in the exposure atmosphere. It also appears that many biological responses are produced by PM whether it is composed of a single component or a complex mixture.

The following discussion focuses on summarizing key lines of toxicological evidence useful in (a) delineating various types of health effects attributable to PM exposures, and (b) identifying potential pathophysiological mechanisms by which the effects of particle exposure are mediated. Major emphasis is placed on discussions of PM effects on the cardiopulmonary system, and some attention is accorded to PM-related mutagenic/genotoxic effects of relevance to evaluating the carcinogenic potential of ambient PM or constituent substances.

7.10.1.1 Direct Pulmonary Effects

When the 1996 PM AQCD was written, the lung was thought to be the primary organ affected by particulate air pollution. Although the lung still is a primary organ affected by PM inhalation, there is growing toxicological and epidemiologic evidence that the cardiovascular system is also affected and may be a co-primary organ system related to certain health endpoints such as mortality. Nonetheless, understanding how particulate air pollution affects respiratory system functions or exacerbates respiratory disease remains an important goal. The toxicological evidence from controlled exposures to ambient PM or constituents appear to support three hypothesized mechanisms for PM inducing direct pulmonary effects: (1) lung injury and inflammation; (2) increased airway reactivity and exacerbation of asthma; and (3) impaired lung defense mechanisms and increased susceptibility to respiratory infections.

An important caveat in interpretation of the toxicological data is that the high doses used in many of the studies may produce different effects on the lung than inhalation exposures at lower ambient concentrations. That is, “realistic” doses associated with ambient PM exposures may activate cells and pathways entirely disparate from those activated at high experimental doses.

Lung Injury and Inflammation

Particularly compelling evidence pointing towards ambient PM causing lung injury and inflammation derives from the study of extracts of ambient PM materials on filters collected from community air monitors before, during and after the temporary closing of a steel mill in Utah Valley. Ghio and Devlin (2001) found that intratracheal instillation of filter extract materials in human volunteers provoked greater lung inflammatory responses for materials obtained before and after the temporary closing versus that collected during the plant closing. The instilled dose of 500 μg of extract material was calculated by Ghio and Devlin to result in focal lung deposition in the lingula roughly equivalent to 5 times more than would be deposited if an active person experienced 24-h inhalation exposure to 100 $\mu g/m^3$ PM_{10} (during wintertime temperature inversions in Utah Valley 24-h PM_{10} levels can exceed 100 $\mu g/m^3$). Moreover, 100 μg of filter extract collected during the winter before the temporary plant closure similarly instilled into the lungs of human volunteers also increased levels of neutrophils, protein, and inflammatory cytokines. Dosimetric calculations presented in Appendix 7A suggest that the instilled dose used in the Ghio and Devlin (2001) study could be experienced by persons exposed for about 6 to 9 weeks to ambient PM in the Utah Valley. Further, the instillation in rats (Dye et al., 2001) of extract materials from before and after the plant closing resulted in a 50% increase in airway hyperresponsiveness to acetylcholine compared to 17 or 25% increases with saline or extract materials for the period when the plant was closed, respectively. Analysis of the extract materials revealed notably greater quantities of metals for when the plant was opened, thus suggesting that such metals (e.g., Cu, Zn, Fe, Pb, As, Mn, Ni) may importantly contribute to the pulmonary toxicity observed in the controlled exposure studies, as well as to health effects shown epidemiologically to vary with PM exposures of Utah Valley residents before, during, and after the steel mill closing.

Still other toxicological studies point towards lung injury and inflammation being associated with exposure of lung tissue to complex combustion-related PM materials, with metals again being among some ambient PM constituents identified as contributors. For example, in the last few years, numerous studies have shown that high doses/concentrations of instilled and inhaled ROFA, a product of fossil fuel combustion, can cause substantial lung injury and inflammation. The toxic effects of ROFA are largely caused by its high content of soluble metals including Fe, Ni, and V. Some of the pulmonary effects of ROFA can be

reproduced by equivalent exposures to soluble metal salts. In contrast, controlled exposures of animals to sulfuric acid aerosols, acid-coated carbon, and sulfate salts cause little lung injury or inflammation, even at high concentrations. Inhalation of concentrated ambient PM (which contains only small amounts of metals) by laboratory animals at concentrations in the range of 100 to 1000 $\mu g/m^3$ have been shown in some (but not all) studies to cause mild pulmonary injury and inflammation. Rats with SO_2-induced bronchitis and MCT-treated rats have been reported to have a greater inflammatory response to concentrated ambient PM than normal rats. These studies suggest that exacerbation of respiratory disease by ambient PM may be caused in part by lung injury and inflammation.

There are also new in vitro data indicating a potential neurogenic basis for the effects of particulate matter (Veronesi et al., 1999a,b; Oortgiesen et al., 2000; Veronesi et al., 2002b). More specifically, these researchers hypothesize that the proton cloud associated with negatively charged colloidal PM particles could activate acid sensitive VR1 receptors found on human airway epithelial cells and sensory terminals; this activation, in turn, results in an immediate influx of calcium and the release of inflammatory neuropeptides and cytokines, which initiate and sustain inflammatory events in the pathophysiology of neurogenic inflammation. This implies that a wide variety of particulate substances, from many different types of sources (both natural and anthropogenic), falling across wide size ranges (from ultrafine through accumulation mode and including small, < 10 μm, coarse fraction particles), and of highly diverse chemical composition could possibly exert neurogenically-mediated pathophysiological effects depending on shared physical properties of their surface molecules (i.e., negative charges surrounded by a proton cloud).

Increased Airway Reactivity and Exacerbation of Asthma

The strongest evidence supporting this hypothesis is from studies on DPM. Diesel particulate matter has been shown to increase production of antigen-specific IgE in mice and humans (summarized in Section 7.2.1.2). In vitro studies have suggested that both organic fraction and the CB fraction of DPM are involved in the increased IgE production. ROFA leachate also has been shown to enhance antigen-specific airway reactivity in mice (Goldsmith et al., 1999), indicating that soluble metals can also enhance an allergic response. However, in this same study, exposure of mice to concentrated ambient PM did not affect antigen-specific

airway reactivity. Thus the available evidence is inconclusive with regard to increased airway activity as a possible PM mechanism.

Increased Susceptibility to Respiratory Infections

A few newly published studies have provided some evidence for ambient PM potentially affecting lung defense mechanisms and increasing susceptibility to infection. The studies of Zelikoff et al. (2003) showed that brief exposures (3 to 5 h) of Fischer rats to New York City CAPs (~225 $\mu g/m^3$) either before or after IT-instillation of *Streptococcus pneumoniae* increased numbers of lavageable AMs and increased bacterial burden over control levels at 24 h postinfection. Similarly, Antonini et al. (2002) found that preexposure to ROFA (0.2 or 1.0 mg/100 g body weight) of SD rats 3 days before IT instillation of Listeria monocytogenes (a bacterial pathogen) led to notable lung injury, slowed clearance of the bacteria, and reduced AM NO production, although AM numbers were not reduced. Lastly, new studies by Ohtsuka et al. (2000a,b), showing decreased phagocytic activity of AMs in mice after a 4 h inhalation exposure to acid-coated carbon particles (albeit at a high mass concentration of 10 mg/m^3), are suggestive of possible impairment of an important lung defense mechanism even in the absence of lung injury.

7.10.1.2 Cardiovascular and Other Systemic Effects Secondary to Lung Injury

When the 1996 PM AQCD was written, it was thought that cardiovascular-related morbidity and mortality most likely would be sequelae occurring secondary to impairment of oxygenation or some other consequence of lung injury and inflammation. Newly available toxicologic studies provide evidence regarding such possibilities, as discussed below.

Impairment of Oxygenation and Increased Work of Breathing That Adversely Affect the Heart Secondary to Lung Injury

Results from most of the new toxicology studies in which animals (normal and compromised) were exposed to concentrated ambient PM (even at concentrations many times higher than would be encountered in the United States) indicate that ambient PM is unlikely to cause severe disturbances in oxygenation or pulmonary function. One study, of PM effects in a severely compromised animal model, may hint at possible PM pathophysiologic effects mediated via hypoxemia. Specifically, the instillation of ROFA (0, 0.25, 1.0, 2.5 mg) was

shown (Watkinson et al., 2000a,b) to increase (to 50%) the mortality rate observed in MCT-treated rats with pulmonary hypertension. Although blood oxygen levels were not measured in this study, there were ECG abnormalities consistent with severe hypoxemia in about half of the rats that subsequently died. Given the severe inflammatory effects of instilled ROFA at high doses and the fact that MCT-treated rats have increased lung permeability as well as pulmonary hypertension, it is plausible that instilled ROFA may cause severe hypoxemia leading to death in this rat model; but the relevance of such effects of high ROFA exposures in a severely compromised rat model to human ambient PM exposure effects is unclear. More research is needed on the effects of PM on arterial blood gases and pulmonary function to fully address the above hypothesis.

Systemic Hemodynamic Effects Secondary to Lung Inflammation and Increased Cytokine Production

It has been suggested that systemic effects of particulate air pollution may result from activation of cytokine production in the lung (Li et al., 1997). Results from some studies of compromised animal models provide some support for this idea. For example, there was a significant decrease in the time of onset of ischemic ECG changes following coronary artery occlusion in PM-exposed dogs compared to controls (Godleski et al., 2000). Analogously, Wellenius et al. (2002) found, in another animal model (i.e., left ventricular MI induced by thermocoagulation), that 41% of the MI rats exhibited one or more premature ventricular complexes (PVCs) during baseline periods 12 to 18 h after surgery; and exposure to ROFA (but not to CB or room air) increased arrhythmia frequency in animals with prior PVCs and decreased their HRV. Also, severely compromised MCT-treated rats exposed to high concentrations of inhaled ROFA (15,000 $\mu g/m^3$, 6 h/day for 3 days) showed increased pulmonary cytokine gene expression, bradycardia, hypothermia, and increased arrhythmias (Watkinson et al., 2000a,b). On the other hand, SH rats manifested similar cardiovascular responses to inhaled ROFA (except that they also developed ST segment depression), but without any increase in pulmonary cytokine gene expression.

Other studies of normal dogs exposed to concentrated ambient PM (322 $\mu g/m^3$, MMAD = 0.23 to 0.34 μm) showed minimal pulmonary inflammation and no positive staining for IL-8, IL-1, or TNF in airway biopsies (Godleski et al., 2000). In addition, several other studies (e.g., Muggenburg et al., 2000a,b) of normal dogs and/or rats failed to show changes in

ECG consistent with the types observed in the above studies of compromised models. Thus, the link between PM-induced changes in the production of cytokines in the lung and effects on cardiovascular function is not clear, and more basic information on the effects of mild pulmonary injury on cardiovascular function is needed to more fully evaluate this hypothesis.

Increased Blood Coagulability Secondary to Lung Inflammation

There is abundant evidence linking small prothrombotic changes in the blood coagulation system to increased long-term risk of heart attacks and strokes. However, the published toxicological evidence bearing on whether moderate lung inflammation causes increased blood coagulability is very mixed and inconsistent.

Several new studies have investigated possible effects of ambient PM or surrogate particles on blood chemistry constituents that would be indicative of increased blood coagulability. For example, Ghio et al. (2000a) have shown that inhalation of concentrated ambient PM (at $\geq$ 47 $\mu g/m^3$) in healthy nonsmokers causes increased levels of blood fibrinogen. Gardner et al. (2000) have also shown that a high dose (8300 $\mu g/kg$) of instilled ROFA in rats causes increased blood levels of fibrinogen, but no effect was seen at lower doses. Gordon et al. (1998) also reported increased blood platelets and neutrophils in control and MCT-treated rats on some, but not all, days when exposed to concentrated NYC ambient PM (150 to 400 $\mu g/m^3$) for 3 h. These differences in blood parameters were present at 3 h PE but not 24 h PE.

On the other hand, exposure of normal dogs to concentrated ambient PM from Boston (~100 to 1000 $\mu g/m^3$) had no effect on fibrinogen levels (Godleski et al., 2000). Nor were any significant effects on blood fibrinogen or other factors (e.g., blood platelets, tissue plasminogen activator, Factor VII, etc.) involved in the coagulation cascade seen with exposure of normal rats to concentrated NYC ambient PM (~130 to 900 $\mu g/m^3$), as reported by Nadziejko et al. (2002). Frampton (2001) also reported finding no effects on fibrinogen or clotting Factor VII in healthy, nonsmoking human adults exposed to 10 $\mu g/m^3$ ultrafine carbon for 2 h via mouthpiece inhalation while at rest. All these latter results, indicative of little effect of PM exposure on blood coagulation factors in healthy humans or laboratory animals, stand in contrast to the above-noted highly suggestive ambient PM-induced increases in fibrinogen seen by Ghio et al. (2000a) in healthy human adult volunteers.

The coagulation system is as multifaceted and complex as the immune system; and there are many other sensitive and clinically significant parameters that should, in addition to fibrinogen, show more extensive and consistent patterns of change reflective of PM effects on blood coagulation. Thus, it is premature to draw any strong conclusions about the relationship between PM and blood coagulation.

Hematopoiesis Effects Secondary to PM Interactions With the Lung

Terashima et al. (1997) found that instillation of fine carbon particles (20,000 μg/rabbit) stimulated release of PMNs from bone marrow. In further support of this hypothesis, Gordon and colleagues reported that the percentage of PMNs in the peripheral blood increased in rats exposed to ambient PM in some but not all exposures. On the other hand, Godleski et al. (2000) found no changes in peripheral blood counts of dogs exposed to concentrated ambient PM. Thus, consistent evidence that PM ambient concentrations can affect hematopoiesis remains to be demonstrated.

7.10.1.3 Direct Effects on the Heart

Although the data are still limited, two types of hypothesized direct effects of PM on the heart are noted below.

Effects on the Heart Secondary to Uptake of Particles into the Circulation and/or Release of Soluble Substances into the Circulation

Drugs can be rapidly and efficiently delivered to the systemic circulation by inhalation. This implies that the pulmonary vasculature absorbs inhaled materials, including charged substances such as small proteins and peptides. Such PM materials could conceivably be rapidly transported to the heart, where they might exert effects directly on cardiac vasculature or heart muscle itself. Alternatively, they could also exert very rapid effects on cardiac function through stimulation of nerve ending receptors in lung tissue, resulting in secretion of inflammatory messenger substances and/or activation of neurally-mediated autonomic reflexes. This raises the question of how inhaled particles could affect the autonomic nervous system. Activation of neural receptors in the lung is a logical area to investigate.

Epithelial cells lining lower respiratory tract airways are damaged or denuded in many common health disorders (e.g., asthma, viral infections, etc.), which may allow inhaled PM to directly encounter sensory nerve terminals and their acid-sensitive receptors. In vitro studies by Veronesi and colleagues provide interesting evidence indicating that (a) ROFA-induced inflammation is mediated by acid-sensitive VR1 receptors on sensory nerve fibers that innervate the airways and on surrounding bronchial epithelial cells (Veronesi et al., 1999a,b); (b) negatively-charged, but not neutrally-charged (i.e., zeta potential = 0 mV), particles in ROFA, synthetic polymer aerosols, or extracts from urban St. Louis, residential (woodstove), volcanic (Mt. St. Helens), and industrial (coal and oil fly ash) sources activate the VR1 receptors (Oortgiesen et al., 2000), with their zeta potential being the key physiochemical property correlated with consequent increases in Ca^{2+} and IL-6 release (Veronesi et al., 2002b); and (c) the receptor activation causing release of inflammatory cytokines and neuropeptides initiates and sustains inflammatory effects in the airways (Veronesi and Oortgeisen, 2001).

Inhaled Particulate Matter Effects on Autonomic Control of the Heart and Cardiovascular System

Besides the above studies, it is worth noting that earlier studies in conscious rats have shown that inhalation of wood smoke causes marked changes in sympathetic and parasympathetic input to the cardiovascular system that are mediated by neural reflexes (Nakamura and Hayashida, 1992).

While changes in heart rate variability and conduction system function with ambient PM exposure have been reported in some animal studies, not all studies have shown consistent alterations (Godleski et al., 2000; Gordon et al., 2000; Watkinson et al., 2000a,b; Campen et al., 2000; Muggenburg et al., 2000b; Frampton, 2001). In several human panel studies described in Chapter 8, similar discrepancies were noted. Some of these studies included endpoints related to respiratory effects but few significant adverse respiratory changes were detected. This raises the possibility that ambient PM may have effects on the heart that are independent of adverse changes in the lung. There is certainly precedent for this idea. For example, tobacco smoke (which is a mixture of combustion-generated gases and PM) causes cardiovascular disease by mechanisms that are independent of its effect on the lung.

7.10.1.4 Mutagenic/Genotoxic Effects of PM

As discussed in Chapter 8, the Pope et al. (2002) analysis of the American Cancer Society longer-term database provides evidence for chronic ambient PM exposure being associated with increased risk of lung cancer.

Ambient urban PM from sources such as the Los Angeles area, Germany, and the Netherlands has been shown to possess mutagenic activity in both in vivo and in vitro assays. The mutagenicity is dependent upon the chemical composition of the PM and also the size of the particles. Both unsubstituted polyaromatic compounds and semi-polar compounds are thought to be highly mutagenic components of urban ambient PM. Additionally, the fine fraction appears to be more mutagenic than the coarse fraction.

Emissions from wood/biomass burning have been shown to be mutagenic in studies of human exposures in China and the Netherlands. Mutagens from wood smoke emissions can cause both frameshift and base pair mutations but have not yet demonstrated the production of DNA adducts.

A large body of work examining emissions from coal combustion in China has demonstrated the mutagenicity of both the polar and aromatic fractions. Populations with high lung cancer rates have been linked to exposures of the PAH component of coal smoke. By sequencing of mutations, a direct link has been established between the mutagenesis assay results and human lung cancer.

The U.S. EPA Diesel Document (U.S. Environmental Protection Agency, 2002) was cited earlier in this chapter as discussing a number of studies utilizing mutagenicity/genotoxicity assays with diesel emissions; and key information from that document on a number of studies indicative of diesel emission particle-induced gene mutations, chromosome effects, or other genotoxic effects (e.g., altered DNA adduct patterns, increases in mutagenic DNA, adduct-related vulnerability to oxidative damage) was recounted. Additional findings were also noted which show that, although 50 to 90% of the total mutagenicity of diesel exhaust is likely attributable to its gaseous components, nitrated polynuclear aromatic compounds (PAHs) also appear to account for a notable portion of the mutagenicity. Some results (but not others) further appear to implicate sulfur in diesel emissions as contributing to mutagenic effects. Lastly, of much interest are findings by Driscoll et al. (1996, 1997) showing increased hprt mutations in rat alveolar type II cells with inhalation exposure to CB particles or with intratracheal instillation of

CB or two other (quartz, TiO_2) particles. All three types of particles elicited increased inflammatory responses, which the authors suggest leads to increased epithelial cell proliferation and consequently, mutations. Overall, the new studies are highly indicative of mutagenic and other secondary genotoxic effects of ambient PM and/or various specific constituents (e.g., comparisons of gasoline and diesel exhaust show that the PM component is more mutagenic than the condensate fraction in both exhausts). Additionally, the polar component has the most mutagenicity. Other components of both gasoline and diesel exhaust thought to contribute to the mutagenicity are PAHs, nitro-PAH, and nitroarenes. DNA adduct formation is one mechanism whereby these mobile combustion products are thought to induce carcinogenesis.

In summary, both ambient PM and combustion products of coal, wood, diesel, and gasoline are mutagenic/genotoxic, though exact comparisons of the mutagenicity of combustion emissions of these fuels are not possible. Additionally, the data currently available allow some clues as the to potential mechanisms underlying these health effects.

7.10.2 Links Between Specific Particulate Matter Components and Health Effects

The plausibility of epidemiologically-demonstrated associations between ambient PM and increases in morbidity and mortality has been questioned because adverse cardiopulmonary effects have been observed among human populations at very low ambient PM concentrations. To date, experimental toxicology studies have provided some intriguing, but limited, evidence for ambient PM mixes or specific PM components potentially being responsible for reported health effects of ambient PM. Overall, the new studies suggest that some of particles are more toxic than others. New findings substantiating the occurrence of health effects in response to controlled exposures to ambient PM mixes and/or their constituent substances are useful in demonstrating or clarifying potential contributions of physical/chemical factors of constituent particles are discussed below.

7.10.2.1 Ambient Particle Studies

Studies using concentrated ambient particles CAPs studies are probably most useful in helping to substantiate that particles present in “real-world” ambient air mixes are indeed capable of inducing notable pathophysiological effects under controlled exposure conditions and

to clarify further factors affecting increased susceptibility of "at risk" groups for PM effects. CAPs studies, on the other hand, tend to be somewhat less helpful than other toxicologic approaches in helping to delineate the specific characteristics of PM producing toxicity and potential underlying mechanisms. Some, but not all, studies with inhaled (CAPs) have found cardiopulmonary changes in rodents and dogs at high concentrations of fine PM. However, no comparative studies to examine the effects of ultrafine and coarse ambient PM have been done.

Studies using collected urban PM for intratracheal administration to healthy and compromised animals have also produced interesting new information. Despite the difficulties associated with extrapolating from the bolus delivery used in such studies, they have provided evidence indicating that the chemical composition of ambient particles can have a major influence on toxicity. Instillation of rats with filter extracts of ambient air particles collected from Ottawa CN air (Watkinson, et al., 2002a,b) at 2.5 mg, for example, induced pronounced biphasic hypothermia, severe drop in heart rate, and increased arrhythmias; this was in contrast to no cardiac effects seen with comparable instilled dose of Mt. St. Helens volcanic ash (shown by many studies to be relatively inert toxicologically). Similarly, dose-dependent increases in PMNs, other markers of lung inflammation, and decreases in AMs were seen with intratracheal exposures of hamsters to urban ambient particles from St. Louis or Kuwaiti oil fire particles (Brain et al., 1998).

Importantly, it has become evident that, although the concentrated ambient PM (CAPs) studies have provided important exposure-response information for some PM size fractions (especially $PM_{2.5}$), they have not, to date, been very helpful in identifying specific toxic components in urban PM. Insufficient attention has been accorded to characterization of day-to-day variations in specific PM constituents in order to relate such variations to observed variable health responses to CAPs exposures. Also, because only a limited number of exposures using CAPs can be reasonably conducted by a given laboratory in a particular urban environment, there may be insufficient information to conduct factor analyses on exposure/response matrices. This may also hinder principal component analysis techniques that are useful in identifying particle components responsible for health outcomes. New particle concentrator systems now coming on-line at the U.S. EPA and elsewhere that permit selective concentration of ultrafine, fine, and thoracic coarse PM hold promise for enhancing our understanding of PM characteristics producing toxicity. CAPs studies also hold promise for helping to identify

susceptibility factors in animal models, and permit examination of mechanisms related to PM toxicity.

7.10.2.2 Acid Aerosols

There is relatively little new information on the effects of acid aerosols. The 1996 PM AQCD previously assessed acid aerosol health effects and concluded that acid aerosols cause little or no change in pulmonary function in healthy subjects, but asthmatics may develop small changes in pulmonary function. This conclusion is further supported by the new study of Linn and colleagues (1997) in which children (26 children with allergy or asthma and 15 healthy children) were exposed to sulfuric acid aerosol (100 $\mu g/m^3$) for 4 h. There were no significant effects on symptoms or pulmonary function when data for the entire group were analyzed, but the allergy group had a significant increase in symptoms after the acid aerosol exposure. Thus, acid aerosol health effects may be a possible causal physical property for some types of PM-related respiratory symptoms. However, it is unlikely that particle acidity alone could account for the pulmonary function effects (Dreher, 2000).

7.10.2.3 Metals

The 1996 PM AQCD (U.S. Environmental Protection Agency, 1996a) mainly relied on data related to occupational exposures to evaluate the potential toxicity of metals in contributing to health effects associated with ambient PM exposures. Since that time, numerous newly published in vivo and in vitro studies using exposures to ambient PM extracts, ROFA, other combustion source emission materials (e.g., CFA, etc.), or specific soluble transition metals have contributed substantial further information on the health effects of particle-associated soluble metals. Although there are some uncertainties about differential effects of one transition metal versus another, some water soluble metals (e.g., Ni, V, Zn, Fe) leached from ambient filter extracts or ROFA have been shown consistently (albeit at high concentrations) to cause cell injury and inflammatory changes in vitro and in vivo.

Perhaps most notable in this argument are the Utah Valley studies that have linked the toxicology (in vitro cell culture as well as human and rodent instillation) with published epidemiological findings. In these studies, filter extracts of Utah Valley PM collected from the state/federal sampling sites yielding aerometric data used to ascribe the impact of PM on hospital

admissions and population mortality rates showed remarkable qualitative coherence with toxicological and clinical endpoints (BAL fluid markers, lung dysfunction) among the human and rodent test subjects. Moreover, the data were themselves consistent with the hypothesized underlying mode of action (oxidant generation, inflammation) for metal-associated PM cardiorespiratory effects (Frampton et al., 1999; Dye et al., 2001; Ghio and Devlin, 2001; Soukup et al., 2000; Wu et al., 2001; Pagan et al., 2003). Studies comparing human (Ghio and Devlin, 2001) and rat (Dye et al., 2001) exposures to both high and low metal content PM collected near a steel plant, showed convincingly that the metal content of the PM, and not the mass, was a major determinant of the toxicity of the PM. Both species showed similar inflammatory responses to exposures from PM with high metal content (collected while the steel mill was operating). Hence, this rich data set provides an important linkage across study disciplines used in the human and animal toxicology as well as in the in vitro studies.

Even though it is clear that combustion particles that have a high content of soluble metals can cause lung injury in compromised animals and correlate well with epidemiological findings in some cases (e.g., Utah Valley Studies), it has not been fully established that the small quantities of metals (typically $\leq$ 0.5 to 1.0 $\mu g/m^3$) associated with current U.S. ambient PM mass concentrations exhibit greater toxicity than other PM components typically present in ambient air. In studies in which various ambient and emission source particulates were instilled into rats, the soluble metal content did appear to be one important determinant of lung injury (Costa and Dreher, 1997). However, one published study (Kodavanti et al., 2000b) has compared the effects of inhaled ROFA (at 1 mg/m^3) to concentrated ambient PM (four experiments, at mean concentrations of 475 to 900 $\mu g/m^3$) in normal and SO_2-induced bronchitic rats. A statistically significant increase in at least one lung injury marker was seen in bronchitic rats with one out of four of the concentrated ambient exposures; whereas inhaled ROFA had no effect, even though the content of soluble Fe, V, and Ni was much higher in the ROFA sample than in the concentrated ambient PM.

Nevertheless, other particularly interesting new findings do point toward ambient PM exacerbation of allergic airway hyperresponsiveness and/or antigen-induced immune responses. Both metal and diesel particles have been implicated, with an expanding array of new studies showing DPM in particular as being effective in exacerbating allergic asthmatic responses.

7.10.2.4 Diesel Exhaust Particles

As described in Section 7.5.3, there is growing toxicological evidence that, analogously to several other types of PM (silica, CB, road dust, etc.), diesel PM may exacerbate allergic responses to inhaled antigens. The organic fraction of diesel exhaust PM has been linked to eosinophil degranulation and induction of cytokine production, suggesting that the organic constituents of diesel PM are the responsible part for the immune effects. It is important to compare the immune effects of diesel PM to other combustion source-specific emissions, as well as CAPs, to determine the relative potency of diesel exhaust PM in contributing to the incidence and severity of allergic rhinitis and asthma. It is also notable that rather direct evidence has been obtained which demonstrates adherence of allergen-laden pollen cytoplasm fragments to diesel particles, providing a likely mechanism by which diesel PM acts to concentrate bioaerosol materials and to increase their focal accumulation in lower regions of the respiratory tract. The adherence of allergen-laden pollen to other types of PM has not been investigated. Other evidence substantiates mutagenic/genotoxic effects of diesel emission particles (e.g., PAHs), consistent with qualitative findings in several studies of increased lung cancer effects being associated with long-term, occupational exposure to diesel emissions.

7.10.2.5 Organic Compounds

Published research on the acute effects of particle-associated organic carbon constituents is conspicuous by its relative absence, except for diesel exhaust particles. Like metals, organics are common constituents of combustion-generated particles and have been found in ambient PM samples over a wide geographical range. Organic carbon constituents comprise a substantial portion of the mass of ambient PM (10 to 70% of the total dry mass [Turpin, 1999]). The organic fraction of ambient PM has been evaluated for its mutagenic effects. Although the organic fraction of ambient PM is a poorly characterized heterogeneous mixture of an unknown number of different compounds, organic compounds remain a potential causal property for PM health effects due to the contribution of exhaust particles from various sources to the fine PM fraction (Dreher, 2000). Strategies have been proposed for examining the health effects of this potentially important constituent (Turpin, 1999).

7.10.2.6 Ultrafine Particles

Studies of various types of ultrafine particles have demonstrated a significantly greater inflammatory response than that seen with fine particles of the same chemical composition at similar mass doses (Oberdörster et al., 1992; Li et al., 1996, 1997, 1999).

In other more limited studies, ultrafines also have generated greater oxidative stress in experimental animals. Inhalation exposure of normal rats to ultrafine carbon particles generated by electric arc discharge (100 μg/m^3 for 6 h) caused minimal lung inflammation per unit mass (Elder et al., 2000a,b), compared to ultrafine PTFE or metal particles. On the other hand, instillation of 125 μg of ultrafine CB (20 nm) caused substantially more inflammation per unit mass than did the same dose of fine particles of CB (200 to 250 nm), suggesting that ultrafine particles may cause more inflammation per unit mass than larger particles (Li et al., 1997). However, the chemical constituents of the two sizes of CB used in this study were not analyzed, and it cannot be assumed that the chemical composition was the same. Further, when the particle surface area is used as a dose metric, the inflammatory response to both fine and ultrafine particles may be basically the same (Oberdörster, 1996b; Oberdörster et al., 2000; Li et al., 1996).

With regard to acid aerosols, studies of low concentrations of ultrafine sulfuric acid and metal oxide particles have demonstrated effects in the lung. However, it is possible that inhaled ultrafine particles may have systemic effects that are independent of effects on the lung. Thus, there is still insufficient toxicological evidence to elucidate clearly the extent to which ambient concentrations or high number counts of ultrafine particles may differentially contribute to increased health effects risks associated with ambient PM air pollution.

7.10.2.7 Bioaerosols

Bioaerosols, from sources such as plants, fungi, and microorganisms, range in size from 0.01 to μm to > 20 μm. They comprise a small fraction of ambient PM, but have been shown to contribute to the adverse health affects from PM exposure. Pollen from flowering plants, trees and grasses, deposits in upper airways to induce allergic rhinitis. Allergen-ladened cytoplasmic fragments of ruptured pollen grains can enter the deep lung, where they can exacerbate asthma. Synergistic interactions between pollen debris and other ambient PM (e.g., the polycyclic hydrocarbon component of DE) are thought to be a mechanism that may explain the increased

incidence of asthma morbidity and mortality. Human handling and burning of plant material contributes to increased bioaerosol levels, which have been shown to have adverse health effects. Fungi and fungal spores are the largest and the most consistently present outdoor bioaerosol. They cause allergic rhinitis and asthma, which is highly dependent on seasonal variations in concentration. Exposures have been linked to asthma hospitalization and death. Bacterial and viruses are significant bioaerosols. Much of the toxicity of bacteria is due to the endotoxins present in the outer cell membrane, which trigger production of cytokines and a cascade of inflammation. Concentrations of endotoxins are seasonal (higher under warm, humid conditions) and tend to be higher in samples of coarse-mode than in fine-mode ambient PM. Another cell wall component of bacteria and fungi, (1→3)-β-D-glucan, has also been shown to cause respiratory inflammation.

7.10.3 PM Interactions with Gaseous Co-Pollutants

Particulate matter exists in an atmospheric milieu of ubiquitous co-pollutant gases, all of which have the potential for antagonistic, additive, or synergistic interactions with PM and which can modify the toxicologic health effects. The mechanisms by which interactions between PM and gases are thought likely to occur are by: (1) formation of secondary products by chemical interactions between the gas and the particle, (2) adherence of material to the particle and subsequent transport to sensitive sites, and/or 3) pollutant-induced change in the local microenviroment of the lung (e.g., by decreasing the pH). All of these interactions have the potential to create antagonistic, additive, or synergistic interactions between PM and gases, which could potentially greatly modify their individual effects.

New controlled human exposure toxicology studies provide interesting findings on effects of combined exposures to PM and other pollutants. One study, by Linn et al. (1997), found a positive association between acid concentration and respiratory symptoms (but not spirometry) among allergic/asthmatic children (in comparison to clean-air exposure results) following a single 4-h exposure to 60 to 140 $\mu g/m^3$ H_2SO_4, 0.1 ppm SO_2, and 0.1 ppm O_3 while undergoing intermittent exercise. No changes were seen among healthy children. However, the experimental design did not include comparison of effects of the overall mixture versus those of individual components (e.g., H_2SO_4 alone, O_3 alone), thus precluding discernment of possible interactive effects.

Recent animal studies have also evaluated effects of coexposures to particles and gases. In one study, both combined CAPs/O_3 and O_3-alone exposure in a mouse asthma model (Kobzik et al., 2001) showed similar increases in airway responsiveness and pulmonary resistance, thus indicating a lack of synergism with the combined exposure. Mixtures of elemental carbon particles, O_3, and ammonium bisulfate showed enhanced changes in lung collagen, AM respiratory burst, and phagocytosis (Kleinman et al, 2000), although the results were ambiguous as to whether PM was enhancing the effects of O_3 or the converse. A short exposure of combined carbon particle/SO_2 caused depressed AM phagocytosis and suppressed intrapulmonary bactericidal activity which lasted for a week (Jakab et al., 1996; Clarke et al., 2000c). Other studies using co-exposures of PM and gases have demonstrated no changes in histopathological (Moss et al., 2001) or biochemical and morphometric endpoints (Last and Pinkerton, 1997). Additionally, 4-week exposures of rats to a mixture of carbon particles, ammonium bisulfate, and O_3 caused no changes in BAL parameters and only a small decrease in plasma fibronectin compared to O_3 alone (Bolarin et al., 1997).

7.10.4 Susceptibility

Progress has been made in understanding the role of individual susceptibility to ambient PM effects. Studies have consistently shown that older animals or animals with certain types of compromised health, either genetic or induced, are more susceptible to instilled or inhaled particles, although the increased animal-to-animal variability in these models has created greater uncertainty for the interpretation of the findings (Clarke et al., 1999, 2000a,b; Kodavanti et al, 1998b, 2000a, 2001; Gordon et al., 2000; Ohtsuka et al., 2000b; Wesselkamper et al., 2000; Leikauf et al., 2000; Saldiva et al., 2002). Moreover, because PM seems to affect broad categories of disease states, ranging from cardiac arrhythmias to pulmonary infection, it is difficult to know what disease models to use in evaluating the biological plausibility of adverse health effects of PM.

Compromised hosts are a significant susceptible population which includes individuals with asthma, individuals with pneumonia or other lung infections, and the elderly with chronic cardiopulmonary disease. To better understand the effects of PM in this population, researchers are increasingly using compromised host models such as a rat model of cardiopulmonary disease that utilize MCT-treatment to induce pulmonary vasculitis/hypertension. This model has

demonstrated ROFA-induced increased neutrophilic inflammation, exacerbated lung lesions, increased lung edema, alveolar thickening, and decreased phagocytosis of particles in some studies (Costa and Dreher, 1997; Kodavanti et al., 1999; Madl et al., 1998). Another report using MCT-treated rats did not find similar inflammatory responses or changes in pulmonary function following CAPs exposures (Gordon et al., 2000). Though the MCT-treated rat has been used extensively for modeling human cardiopulmonary disease, it does have limitations. There is clearly a need for new and better animal models to examine human pathophysiology associated with PM exposure.

Animals infected with bacteria or viruses are used to model humans with respiratory infections; and they have been shown to have increased inflammatory response with PM exposure (Kodavanti et al., 1998b; Elder et al., 2000a,b). Rats pre-treated with high SO_2 exposures have been used to model chronic bronchitis and have shown interaction of CAPs with preexisting lung injury which produce changes in cellular and biochemical markers in lavage fluid and increases in tidal volume (Clarke et al., 1999; Saldiva et al., 2002; Kodavanti et al., 1998b).

Genetic susceptibility to the effects of PM are becoming increasingly apparent as various strains of rodents are characterized for strain-specific responses. Rat strains such as SD, Fischer-344, and Wistar demonstrate unique inflammatory and histological responses to ROFA (Kodavanti et al., 1996, 1997b). Also, genetically predisposed SH rats have been used to model cardiovascular disease to evaluate potential increased susceptibility to PM-associated effects. SH rats demonstrate greater oxidative stress and cardiovascular responses than their normal counterparts in response to ROFA exposure. Inter-strain differences in airway hyperresponsiveness, inflammation, Fc-receptor-mediated AM phagocytosis, and mortality, too, have been demonstrated in mouse strains such as BALB/c, C57BL/6, C3H/HeJ, and others (Veronesi et al., 2000; Ohtsuka et al., 2000a,b; Prows et al., 1997; Leikauf et al., 2000, Wesselkamper, et al., 2000) in response to PM exposure. The extent to which genetic susceptibility plays a role in humans remains to be determined. Use of genomics, proteomics, and bioinformatics technologies will allow further characterization of the differences in susceptibility to PM.

Newly available studies also suggest that individuals with allergic disorders are likely more susceptible to PM effects than are nonallergic persons. Relatively little is known about the effects of inhaled PM on humoral (antibody) or cell-mediated immunity. However, both in vivo and in vitro studies have shown that various types of PM can alter immune responses to challenge to antigens and may act as an adjuvant (Van Zijverden et al., 2000; Van Zijverdan and Granum, 2000). Steerenberg et al. (2003) found adjuvant activity to be associated with several types of PM tested (e.g., road tunnel dust, ROFA, DPM).

ROFA has been shown to enhance allergic sensitization in a number of studies (e.g., Hamada et al., 1999; Lambert., 1999; Gilmour et al., 2001), but the applicability of these findings to ambient PM is not certain. A study has shown that a single exposure to ROFA elicits a greater effect on airway hyperresponsiveness than a 3-day exposure to CAPs (Goldsmith et al., 1999).

Particularly interesting new findings point toward ambient PM exacerbation of allergic airway hyperresponsiveness and/or antigen-induced immune responses. Both metals and diesel particles have been implicated, with an expanding array of new studies showing DPM as one particle that is effective in exacerbating allergic asthma responses (Takano et al., 1997; Nel et al., 2001; Van Zijerden et al., 2000, 2001; Walters et al., 2001; Nordenhall et al., 2001; Hamada et al., 1999, 2000; Lambert et al., 1999; Gilmour et al., 2001).

REFERENCES

Adamson, I. Y. R.; Prieditis, H.; Hedgecock, C.; Vincent. R. (2000) Zinc is the toxic factor in the lung response to an atmospheric particulate sample. Toxicol. Appl. Pharmacol. 166: 111-119.

Agopyan, N.; Li, L.; Yu, S.; Simon, S. A. (2003) Negatively charged 2- and 10-μm particles activate vanilloid receptors, increase cAMP, and induce cytokine release. Toxicol. Appl. Pharmacol. 186: 63-76.

Alink, G. M.; Sjögren, M.; Bos, R. P.; Doekes, G.; Kromhout, H.; Scheepers, P. T. J. (1998) Effect of airborne particles from selected indoor and outdoor environments on gap-junctional intercellular communication. Toxicol. Lett. 96/97: 209-213.

Amdur, M. O.; Chen, L. C. (1989) Furnace-generated acid aerosols: speciation and pulmonary effects. In: Symposium on the health effects of acid aerosols; October 1987; Research Triangle Park, NC. Environ. Health Perspect. 79: 147-150.

Amdur, M. O.; Dubriel, M.; Creasia, D. A. (1978) Respiratory response of guinea pigs to low levels of sulfuric acid. Environ. Res. 15: 418-423.

Andrews, N. P.; Gralnick, H. R.; Merryman, P.; Vail, M.; Quyyumi, A. A. (1996) Mechanisms underlying the morning increase in platelet aggregation: a flow cytometry study. J. Am. Coll. Cardiol. 28: 1789-1795.

Antonini, J. M.; Roberts, J. R.; Jernigan, M. R.; Yang, H.-M.; Ma, J. Y. C.; Clarke, R. W. (2002) Residual oil fly ash increases the susceptibility to infection and severely damages the lungs after pulmonary challenge with a bacterial pathogen. Toxicol. Sci. 70: 110-119.

Arimoto, T.; Yoshikawa, T.; Takano, H.; Kohno, M. (1999) Generation of reactive oxygen species and 8-hydroxy-2'-deoxyguanosine formation from diesel exhaust particle components in L1210 cells. Jpn. J. Pharmacol. 80: 49-54.

Ball, B. R.; Smith, K. R.; Veranth, J. M.; Aust, A. E. (2000) Bioavailability of iron from coal fly ash: mechanisms of mobilization and of biological effects. In: Grant, L. D., ed. PM2000: particulate matter and health. Inhalation Toxicol. 12(suppl. 4): 209-225.

Baluk, P.; Nadel, J. A.; McDonald, D. M. (1992) Substance P-immunoreactive sensory axons in the rat respiratory tract: a quantitative study of their distribution and role in neurogenic inflammation. J. Compar. Neurol. 319: 586-598.

Barfknecht, T. R.; Hites, R. A.; Cavaliers, E. L.; Thilly, W. G. (1982) Human cell mutagenicity of polycyclic aromatic hydrocarbon components of diesel emissions. In: Lewtas, J., ed. Toxicological effects of emissions from diesel engines: proceedings of the Environmental Protection Agency 1981 diesel emissions symposium; October 1981; Raleigh, NC. New York, NY: Elsevier Biomedical; pp. 277-294. (Developments on toxicology and environmental science: v. 10).

Barnhart, M. I.; Chen, S.-T.; Salley, S. O.; Puro, H. (1981) Ultrastructure and morphometry of the alveolar lung of guinea pigs chronically exposed to diesel engine exhaust: six month's experience. J. Appl. Toxicol. 1: 88-103.

Barnhart, M. I.; Salley, S. O.; Chen, S.-T.; Puro, H. (1982) Morphometric ultrastructural analysis of alveolar lungs of guinea pigs chronically exposed by inhalation to diesel exhaust (DE). In: Lewtas, J., ed. Toxicological effects of emissions from diesel engines: proceedings of the Environmental Protection Agency diesel emissions symposium; October, 1981; Raleigh, NC. New York, NY: Elsevier Biomedical; pp. 183-200. (Developments in toxicology and environmental science: v. 10).

Bayram, H.; Devalia, J. L.; Khair, O. A.; Abdelaziz, M. M.; Sapsford, R. J.; Sagai, M.; Davies, R. J. (1998a) Comparison of ciliary activity and inflammatory mediator release from bronchial epithelial cells of nonatopic nonasthmatic subjects and atopic asthmatic patients and the effect of diesel exhaust particles *in vitro*. J. Allergy Clin. Immunol. 102: 771-782.

Bayram, H.; Devalia, J. L.; Sapsford, R. J.; Ohtoshi, T.; Miyabara, Y.; Sagai, M.; Davies, R. J. (1998b) The effect of diesel exhaust particles on cell function and release of inflammatory mediators from human bronchial epithelial cells *in vitro*. Am. J. Respir. Cell Mol. Biol. 18: 441-448.

Becker, S.; Soukup, J. M. (1998) Decreased CD11B expression, phagocytosis, and oxidative burst in urban particulate pollution-exposed human monocytes and alveolar macrophages. J. Toxicol. Environ. Health Part A 55: 455-477.

Becker, S.; Soukup, J. M.; Gilmour, M. I.; Devlin, R. B. (1996) Stimulation of human and rat alveolar macrophages by urban air particulates: effects on oxidant radical generation and cytokine production. Toxicol. Appl. Pharmacol. 141: 637-648.

Becker, S.; Fenton, M. J.; Soukup, J. M. (2002) Involvement of microbial components and toll-like receptors 2 and 4 in cytokine responses to air pollution particles. Am. J. Respir. Cell Mol. Biol. 27: 611-618.

Becker, S.; Soukup, J. M.; Sioutas, C.; Cassee, F. R. (2003) Response of human alveolar macrophages to ultrafine, fine and coarse urban air pollution particles. Exp. Lung Res. 29: 29-44.

Behrendt, H.; Becker, W. M.; Friedrichs, K. H.; Darsow, U.; Tomingas, R. (1992) Interaction between aeroallergens and airborne particulate matter. Int. Arch. Allergy Immunol. 99: 425-428.

Behrendt, H.; Friedrichs, K.-H.; Krämer, U.; Hitzfeld, B.; Becker, W.-M.; Ring, J. (1995) The role of indoor and outdoor air pollution in allergic diseases. In: Johansson, S. G. O., ed. Prog. Allergy Clin. Immunol., Proceedings of the 15th international congress, Allergol. Clin. Immunol.; 1994. Seattle, WA: Hogrefe & Huber; pp. 83-89.

Behrendt, H.; Becker, W. M.; Fritzsche, C.; Sliwa-Tomczok, W.; Tomczok, J.; Friedrichs, K. H.; Ring, J. (1997) Air pollution and allergy: experimental studies on modulation of allergen release from pollen by air pollutants. Int. Arch. Allergy Immunol. 113: 69-74.

Behrendt, H.; Krämer, U.; Schäfer, T.; Kasche, A.; Eberlein-König, B.; Darsow, U.; Ring, J. (2001) Allergotoxicology–a research concept to study the role of environmental pollutants in allergy. Allergy Clin. Immunol. Int. 13: 122-128.

Belisario, M. A.; Buonocore, V.; De Marinis, E.; De Lorenzo, F. (1984) Biological availability of mutagenic compounds adsorbed onto diesel exhaust particulate. Mutat. Res. 135: 1-9.

Bellomo, R.; Gigliotti, P.; Treloar, A.; Holmes, P.; Suphioglu, C.; Singh, M. B.; Knox, Bruce. (1992) Two consecutive thunderstorm associated epidemics of asthma in the city of Melbourne: the possible role of rye grass pollen. Med. J. Aust. 156: 834-837.

Bice, D. E.; Seagrave, JC.; Green, F. H. Y. (2000) Animal models of asthma: potential usefulness for studying health effects of inhaled particles. Inhalation Toxicol. 12: 829-862.

Blomberg, A.; Sainsbury, C.; Rudell, B.; Frew, A. J.; Holgate, S. T.; Sandström, T.; Kelly, F. J. (1998) Nasal cavity lining fluid ascorbic acid concentration increases in healthy human volunteers following short term exposure to diesel exhaust. Free Radical Res. 28: 59-67.

Bolarin, D. M.; Bhalla, D. K.; Kleinman, M. T. (1997) Effects of repeated exposures of geriatric rats to ozone and particle-containing atmospheres: an analysis of bronchoalveolar lavage and plasma proteins. Inhalation Toxicol. 9: 423-434.

Bond, J. A.; Mauderly, J. L.; Wolff, R. K. (1990) Concentration- and time-dependent formation of DNA adducts in lungs of rats exposed to diesel exhaust. Toxicology 60: 127-135.

Bonner, J. C.; Rice, A. B.; Lindroos, P. M.; O'Brien, P. O.; Dreher, K. L.; Rosas, I.; Alfaro-Moreno, E.; Osornio-Vargas, A. R. (1998) Induction of the lung myofibroblast PDGF receptor system by urban ambient particles from Mexico City. Am. J. Respir. Cell Mol. Biol. 19: 672-680.

Bouthillier, L.; Vincent, R.; Goegan, P.; Adamson, I. Y. R.; Bjarnason, S.; Stewart, M.; Guénette, J.; Potvin, M.; Kumarathasan, P. (1998) Acute effects of inhaled urban particles and ozone: lung morphology, macrophage activity, and plasma endothelin-1. Am. J. Pathol. 153: 1873-1884.

Brain, J. D.; Long, N. C.; Wolfthal, S. F.; Dumyahn, T.; Dockery, D. W. (1998) Pulmonary toxicity in hamsters of smoke particles from Kuwaiti oil fires. Environ. Health Perspect. 106: 141-146.

Braunwald, E. (1997) Cardiovascular medicine at the turn of the millennium: triumphs, concerns, and opportunities. N. Engl. J. Med. 337: 1360-1369.

Brightwell, J.; Fouillet, X.; Cassano-Zoppi, A.-L.; Gatz, R.; Duchosal, F. (1986) Neoplastic and functional changes in rodents after chronic inhalation of engine exhaust emissions. In: Ishinishi, N.; Koizumi, A.; McClellan, R. O.; Stöber, W., eds. Carcinogenic and mutagenic effects of diesel engine exhaust: proceedings of the international satellite symposium on toxicological effects of emissions from diesel engines; July; Tsukuba Science City, Japan. Amsterdam, Holland: Elsevier Science Publishers B. V.; pp. 471-485. (Developments in toxicology and environmental science: v. 13).

Broeckaert, F.; Buchet, J. P.; Huaux, F.; Lardot, C.; Lison, D.; Yager, J. W. (1997) Reduction of the ex vivo production of tumor necrosis factor alpha by alveolar phagocytes after administration of coal fly ash and copper smelter dust. J. Toxicol. Environ. Health 51: 189-202.

Brook, R. D.; Brook, J. R.; Urch, B.; Vincent, R.; Rajagopalan, S.; Silverman, F. (2002) Inhalation of fine particulate air pollution and ozone causes acute arterial vasoconstriction in health adults. Circulation 105: 1534-1536.

Brooks, A. L.; Li, A. P.; Dutcher, J. S.; Clark, C. R.; Rothenberg, S. J.; Kiyoura, R.; Bechtold, W. E.; McClellan, R. O. (1984) A comparison of genotoxicity of automobile exhaust particles from laboratory and environmental sources. Environ. Mutagen. 6: 651-668.

Brunekreef, B.; Hoek, G.; Fischer, P.; Spieksma, F. T. M. (2000) Relation between airborne pollen concentrations and daily cardiovascular and respiratory-disease mortality. Lancet 355: 1517-1518.

Bünger, J.; Krahl, J.; Baum, K.; Schröder, O.; Müller, M.; Westphal, G.; Ruhnau, P.; Schulz, T. G.; Hallier, E. (2000) Cytotoxic and mutagenic effects, particle size and concentration analysis of diesel engine emissions using biodiesel and petrol diesel as fuel. Arch. Toxicol. 74: 490-498.

Burge, H. A. (1995) Bioaerosols in the residential environment. In: Cox, C. S.; Wathes, C. M., eds. Bioaerosols handbook. Boca Raton, FL: CRC Press, Inc.; pp. 579-597.

Campen, M. J.; Costa, D. L.; Watkinson, W. P. (2000) Cardiac and thermoregulatory toxicity of residual oil fly ash in cardiopulmonary-compromised rats. In: Phalen, R. F., ed. Inhalation Toxicology: proceedings of the third colloquium on particulate air pollution and human health (second special issue); June, 1999; Durham, NC. Inhalation Toxicol. 12(suppl. 2): 7-22.

Campen, M. J.; Nolan, J. P.; Schladweiler, M. C. J.; Kodavanti, U. P.; Evansky, P. A.; Costa, D. L.; Watkinson, W. P. (2001) Cardiovascular and thermoregulatory effects of inhaled PM-associated transition metals: a potential interaction between nickel and vanadium sulfate. Toxicol. Sci. 64: 243-252.

Campen, M. J.; Nolan, J. P.; Schladweiler, M. C. J.; Kodavanti, U. P.; Costa, D. L.; Watkinson, W. P. (2002) Cardiac and thermoregulatory effects of instilled particulate matter-associated transition metals in healthy and cardiopulmonary-compromised rats. J. Toxicol. Environ. Health Part A 65:1615-1631.

Campen, M. J.; McDonald, J. D.; Gigliotti, A. P.; Seilkop, S. K.; Reed, M. D.; Benson, J. M. (2003) Cardiovascular effects of inhaled diesel exhaust in spontaneously hypertensive rats. Cardiovasc. Toxicol. 3: 353-361.

Carter, J. D.; Ghio, A. J.; Samet, J. M.; Devlin, R. B. (1997) Cytokine production by human airway epithelial cells after exposure to an air pollution particle is metal-dependent. Toxicol. Appl. Pharmacol. 146: 180-188.

Cassee, F. R.; Dormans, J. A. M. A.; Van Loveren, H.; Van Bree, L.; Rombout, P. J. A. (1998a) Toxicity of ambient particulate matter (PM_{10}). I. Acute toxicity study in asthmatic mice following 3-day exposure to ultrafine and fine ammonium bisulfate, a model compounds for secondary aerosol fraction of PM_{10}. Bilthoven, The Netherlands: National Institute of Public Health and the Environment (RIVM); report no. 650010 010.

Cassee, F. R.; Dormans, J. A. M. A.; Van Loveren, H.; Van Bree, L.; Rombout, P. J. A. (1998b) Toxicity of ambient particulate matter. II. Acute toxicity study in asthmatic mice following 3-day exposure to fine ammonium ferrosulfate, a model compounds for secondary aerosol fraction of PM_{10}. Bilthoven, The Netherlands: National Institute of Public Health and the Environment (RIVM); report no. 650010 011.

Cassee, F. R.; Dormans, J. A. M. A.; Van Loveren, H.; Van Bree, L.; Rombout, P. J. A. (1998c) Toxicity of ambient particulate matter. III. Acute toxicity study in (asthmatic) mice following 3-day exposure to ultrafine and fine ammonium nitrate, a model compound for secondary aerosol fraction of PM_{10}. Bilthoven, The Netherlands: National Institute of Public Health and the Environment (RIVM); report no. 651101 013.

Cassee, F. R.; Arts, J. H. E.; Fokkens, P. H. B.; Spoor, S. M.; Boere, A. J. F.; Van Bree, L.; Dormans, J. A. M. A. (2002) Pulmonary effects of ultrafine and fine ammonium salts aerosols in healthy and monocrotaline-treated rats following short-term exposure. Inhalation Toxicol. 14: 1215-1229.

Castellan, R. M.; Olenchock, S. A.; Hankinson, J. L.; Millner, P. D.; Cocke, J. B.; Bragg, C. K.; Perkins, H. H., Jr.; Jacobs, R. R. (1984) Acute bronchoconstriction induced by cotton dust: dose-related responses to endotoxin and other dust factors. Ann. Intern. Med. 102: 157-163.

Castellan, R. M.; Olenchock, S. A.; Kinsley, K. B.; Hankinson, J. L. (1987) Inhaled endotoxin and decreased spirometric values: an exposure-response relation for cotton dust. N. Engl. J. Med. 317: 605-610.

Casto, B. C.; Hatch, G. G.; Huang, S. L.; Lewtas, J.; Nesnow, S.; Waters, M. D. (1981) Mutagenic and carcinogenic potency of extracts of diesel and related environmental emissions: *in vitro* mutagenesis and oncogenic transformation. Environ. Int. 5: 403-409.

Celenza, A.; Fothergill, J.; Kupek, E.; Shaw R. J. (1996) Thunderstorm associated asthma: a detailed analysis of environmental factors. Br. Med. J. 312: 604-607.

Chang, M. C.; Sioutas, C.; Kim, S.; Gong, H., Jr.; Linn, W. S. (2000) Reduction of nitrate losses from filter and impactor samplers by means of concentration enrichment. Atmos. Environ. 34: 85-98.

Chapman, R. S.; Mumford, J. L.; Harris, D. B.; He, X.; Jiang, W.; Yang, R. (1988) The epidemiology of lung cancer in Xuan Wei, China: current progress, issues, and research strategies. Arch. Environ. Health 43: 180-185.

Chen, L. C.; Fine, J. M.; Qu, Q.-S.; Amdur, M. O.; Gordon, T. (1992) Effects of fine and ultrafine sulfuric acid aerosols in guinea pigs: alterations in alveolar macrophage function and intracellular pH. Toxicol. Appl. Pharmacol. 113: 109-117.

Chescheir, G. M., III; Garrett, N. E.; Shelburne, J. D.; Huisingh, J. L.; Waters, M. D. (1981) Mutagenic effects of environmental particulates in the CHO/HGPRT system. In: Waters, M. D.; Sandhu, S. S.; Huisingh, J. L.; Claxton, L.; Newnow, S., eds. Short-term bioassays in the analysis of complex environmental mixtures II. New York, NY: Plenum Press; pp. 337-350. (Environmental science research: v. 22).

Churg, A.; Brauer, M.; Keeling, B. (1996) Ozone enhances the uptake of mineral particles by tracheobronchial epithelial cells in organ culture. Am. J. Respir. Crit. Care Med. 153: 1230-1233.

Churg, A.; Stevens, B.; Wright, J. L. (1998) Comparison of the uptake of fine and ultrafine TiO_2 in a tracheal explant system. Am. J. Physiol. 274: L81-L86.
Clark, S. (1986) Report on prevention and control. Am. J. Ind. Med. 10: 267-273.
Clarke, R. W.; Catalano, P. J.; Koutrakis, P.; Krishna Murthy, G. G.; Sioutas, C.; Paulauskis, J.; Coull, B.; Ferguson, S.; Godleski, J. J. (1999) Urban air particulate inhalation alters pulmonary function and induces pulmonary inflammation in a rodent model of chronic bronchitis. Inhalation Toxicol. 11: 637-656.
Clarke, R. W.; Coull, B.; Reinisch, U.; Catalano, P.; Killingsworth, C. R.; Koutrakis, P.; Kavouras, I.; Murthy, G. G. K.; Lawrence, J.; Lovett, E.; Wolfson, J. M.; Verrier, R. L.; Godleski, J. J. (2000a) Inhaled concentrated ambient particles are associated with hematologic and bronchoalveolar lavage changes in canines. Environ. Health Perspect. 108: 1179-1187.
Clarke, R. W.; Catalano, P.; Coull, B.; Koutrakis, P.; Krishna Murthy, G. G.; Rice, T.; Godleski, J. J. (2000b) Age-related responses in rats to concentrated urban air particles (CAPs). Inhalation Toxicol. 12(suppl. 1): 73-84.
Clarke, R. W.; Antonini, J. M.; Hemenway, D. R.; Frank, R.; Kleeberger, S. R.; Jakab, G. J. (2000c) Inhaled particle-bound sulfate: effects on pulmonary inflammatory responses and alveolar macrophage function. Inhalation Toxicol. 12: 169-186.
Claxton, L. D. (1981) Mutagenic and carcinogenic potency of diesel and related environmental emissions: *Salmonella* bioassay. Environ. Int. 5: 389-391.
Claxton, L. D. (1983) Characterization of automotive emissions by bacterial mutagenesis bioassay: a review. Environ. Mutagen. 5: 609-631.
Claxton, L.; Kohan, M. (1981) Bacterial mutagenesis and the evaluation of mobile-source emissions. In: Waters, M. D.; Sandhu, S. S.; Huisingh, J. L.; Claxton, L.; Nesnow, S., eds. Short-term bioassays in the analysis of complex environmental mixtures II: proceedings of the second symposium on the application of short-term bioassays in the fractionation and analysis of complex environmental mixtures; March 1980; Williamsburg, VA. New York, NY: Plenum Press; pp. 299-317. (Hollaender, A.; Welch, B. L.; Probstein, R. F., eds. Environmental science research series: v. 22).
Cohen, M. D.; Becker, S.; Devlin, R.; Schlesinger, R. B.; Zelikoff, J. T. (1997) Effects of vanadium upon polyI:C-induced responses in rat lung and alveolar macrophages. J. Toxicol. Environ. Health 51: 591-608.
Conn, C. A.; Green, F. H. Y.; Nikula, K. J. (2000) Animal models of pulmonary infection in the compromised host: potential usefulness for studying health effects of inhaled particles. Inhalation Toxicol. 12: 783-827.
Costa, D. L. (2000) Particulate matter and cardiopulmonary health: a perspective. Inhalation Toxicol. 12(suppl. 3): 35-44.
Costa, D. L.; Dreher, K. L. (1997) Bioavailable transition metals in particulate matter mediate cardiopulmonary injury in healthy and compromised animal models. In: Driscoll, K. E.; Oberdörster, G., eds. Proceedings of the sixth international meeting on the toxicology of natural and man-made fibrous and non-fibrous particles; September 1996; Lake Placid, NY. Environ. Health Perspect. Suppl. 105(5): 1053-1060.
Crebelli, R.; Conti, L.; Crochi, B.; Carera, A.; Bertoli, C.; Del Giacomo, N. (1995) The effect of fuel composition on the mutagenicity of diesel engine exhaust. Mutat. Res. 346: 167-172.
Curren, R. D.; Kouri, R. E.; Kim, C. M.; Schechtman, L. M. (1981) Mutagenic and carcinogenic potency of extracts from diesel related environmental emissions: simultaneous morphological transformation and mutagenesis in BALB/c 3T3 cells. Environ. Int. 5: 411-415.
Dalal, N. S.; Suryan, M. M.; Vallyathan, V.; Green, F. H.; Jafari, B.; Wheeler, R. (1989) Detection of reactive free radicals in fresh coal mine dust and their implication for pulmonary injury. Ann. Occup. Hyg. 33: 79-84.
Delfino, R. J.; Coate, B. D.; Zeiger, R. S.; Seltzer, J. M.; Street, D. H.; Koutrakis, P. (1996) Daily asthma severity in relation to personal ozone exposure and outdoor fungal spores. Am. J. Respir. Crit. Care Med. 154: 633-641.
Delfino, R. J.; Murphy-Moulton, A. M.; Burnett, R. T.; Brook, J. R.; Becklake, M. R. (1997) Effects of air pollution on emergency room visits for respiratory illnesses in Montreal, Quebec. Am. J. Respir. Crit. Care Med. 155: 568-576.
Diaz-Sanchez, D.; Tsien, A.; Casillas, A.; Dotson, A. R.; Saxon, A. (1996) Enhanced nasal cytokine production in human beings after in vivo challenge with diesel exhaust particles. J. Allergy Clin. Immunol. 98: 114-123.
Diaz-Sanchez, D.; Tsien, A.; Fleming, J.; Saxon, A. (1997) Combined diesel exhaust particulate and ragweed allergen challenge markedly enhances human in vivo nasal ragweed-specific IgE and skews cytokine production to a T helper cell 2-type pattern. J. Immunol. 158: 2406-2413.
Di Minno, G.; Mancini, M. (1990) Measuring plasma fibrinogen to predict stroke and mycardial infarction. Arteriosclerosis 10: 1-7.

Diociaiuti, M.; Balduzzi, M.; De Berardis, B.; Cattani, G.; Stacchini, G.; Ziemacki, G.; Marconi, A.; Paoletti, L. (2001) The two $PM_{2.5}$ (fine) and $PM_{2.5\text{-}10}$ (coarse) fractions: evidence of different biological activity. Environ. Res. A 86: 254-262.

Donaldson, K.; Brown, D. M.; Mitchell, C.; Dineva, M.; Beswick, P. H.; Gilmour, P.; MacNee, W. (1997) Free radical activity of PM_{10}: iron-mediated generation of hydroxyl radicals. In: Driscoll, K. E.; Oberdörster, G., eds. Proceedings of the sixth international meeting on the toxicology of natural and man-made fibrous and non-fibrous particles; September 1996; Lake Placid, NY. Environ. Health Perspect. Suppl. 105(5): 1285-1289

Dong, W.; Lewtas, J.; Luster, M. I. (1996) Role of endotoxin in tumor necrosis factor α expression from alveolar macrophages treated with urban air particles. Exp. Lung Res. 22: 577-592.

Dormans, J. A. M. A.; Steerenberg, P. A.; Arts, J. H. E.; Van Bree, L.; De Klerk, A.; Verlaan, A. P. J.; Bruijntjes, J. P.; Beekhof, P.; Van Soolingen, D.; Van Loveren, H. (1999) Pathological and immunological effects of respirable coal fly ash in male wistar rats. Inhalation Toxicol. 11: 51-69.

Douwes, J.; Zuidhof, A.; Doekes, G.; Van der Zee, S.; Wouters, I.; Boezen, H. M.; Brunekreef, B. (2000) (1–>3)-β-D-glucan and endotoxin in house dust and peak flow variability in children. Am. J. Respir. Crit. Care Med. 162: 1348-1354.

Dreher, K. L. (2000) Particulate matter physicochemistry and toxicology: in search of causality—a critical perspective. Inhalation Toxicol. 12(suppl. 3): 45-57.

Dreher, K. L.; Jaskot, R. H.; Lehmann, J. R.; Richards, J. H.; McGee, J. K.; Ghio, A. J.; Costa, D. L. (1997) Soluable transition metals mediate residual oil fly ash induced acute lung injury. J. Toxicol. Environ. Health 50: 285-305.

Driscoll, K. E.; Carter, J. M.; Howard, B. W.; Hassenbein, D. G.; Pepelko, W. I.; Baggs, R. B.; Oberdörster, G. (1996) Pulmonary inflammatory, chemokine, and mutagenic responses in rats after subchronic inhalation of carbon black. Toxicol. Appl. Pharmacol. 136: 372-380.

Driscoll, K. E.; Deyo, K. C.; Carter, J. M.; Howard, B. W.; Hassenbein, D. G.; Bertram, T. A. (1997) Effects of particle exposure and particle-elicited inflammatory cells on mutation in rat alveolar epithelial cells. Carcinogenesis 18: 423-430.

Driscoll, K. E.; Costa, D. L.; Hatch, G.; Henderson, R.; Oberdorster, G.; Salem, H.; Schlesinger, R. B. (2000) Intratracheal instillation as an exposure technique for the evaluation of respiratory tract toxicity: uses and limitations. Toxicol. Sci. 55: 24-35.

Dukovich, M.; Yasbin, R. E.; Lestz, S. S.; Risby, T. H.; Zweidinger, R. B. (1981) The mutagenic and SOS-inducing potential of the soluble organic fraction collected from diesel particulate emissions. Environ. Mutagen. 3: 253-264.

Dye, J. A.; Adler, K. B.; Richards, J. H.; Dreher, K. L. (1997) Epithelial injury induced by exposure to residual oil fly-ash particles: role of reactive oxygen species? Am. J. Respir. Cell Mol. Biol. 17: 625-633.

Dye, J. A.; Adler, K. B.; Richards, J. H.; Dreher, K. L. (1999) Role of soluble metals in oil fly ash-induced airway epithelial injury and cytokine gene expression. Am. J. Physiol. 277: L498-L510.

Dye, J. A.; Lehmann, J. R.; McGee, J. K.; Winsett, D. W.; Ledbetter, A. D.; Everitt, J. I.; Ghio, A. J.; Costa, D. L. (2001) Acute pulmonary toxicity of particulate matter filter extracts in rats: coherence with epidemiological studies in Utah Valley residents. Environ. Health Perspect. Suppl. 109(3): 395-403.

Elder, A. C. P.; Gelein, R.; Finkelstein J. N.; Cox, C.; Oberdörster, G. (2000a) Endotoxin priming affects the lung response to ultrafine particles and ozone in young and old rats. In: Phalen, R. F., ed. Inhalation Toxicology: proceedings of the third colloquium on particulate air pollution and human health (first special issue); June, 1999; Durham, NC. Inhalation Toxicol. 12(suppl. 1): 85-98.

Elder, A. C. P.; Gelein, R.; Finkelstein, J. N.; Cox, C.; Oberdörster, G. (2000b) Pulmonary inflammatory response to inhaled ultrafine particles is modified by age, ozone exposure, and bacterial toxin. In: Grant, L. D., ed. PM2000: particulate matter and health. Inhalation Toxicol. 12(suppl. 4): 227-246.

Elvers, B.; Hawkins, S.; Schulz, G., eds. (1991) Peroxo compounds, inorganic. In: Ullmann's encyclopedia of industrial chemistry. V. A19. 5th ed. New York, NY: VCH Publishers; pp. 177-197.

Fabiani, R.; Pampanella, L.; Minelli, A.; Mezzasoma, I.; Vecchiarelli, A.; Morozzi, G. (1997) Effect of airborne particulate extracts on monocyte oxidative metabolism. J. Environ. Pathol. Toxicol. Oncol. 16: 195-199.

Federal Register. (1997) National ambient air quality standards for particulate matter; final rule. F. R. (July 18) 62: 38,652-38,752.

Ferin, J.; Oberdörster, G.; Penney, D. P.; Soderholm, S. C.; Gelein, R.; Piper, H. C. (1990) Increased pulmonary toxicity of ultrafine particles? I. Particle clearance, translocation, morphology. J. Aerosol Sci. 21: 381-384.

Ferin, J.; Oberdörster, G.; Penney, D. P. (1992) Pulmonary retention of ultrafine and fine particles in rats. Am. J. Respir. Cell Mol. Biol. 6: 535-542.

Finkelstein, J. N.; Johnston, C.; Barrett, T.; Oberdörster, G. (1997) Particulate-cell interactions and pulmonary cytokine expression. In: Driscoll, K. E.; Oberdörster, G., eds. Proceedings of the sixth international meeting on the toxicology of natural and man-made fibrous and non-fibrous particles; September 1996; Lake Placid, NY. Environ. Health Perspect. Suppl. 105(5): 1179-1182.

Folinsbee, L. J.; Kim, C. S.; Kehrl, H. R.; Prah, J. D.; Devlin, R. B. (1997) Methods in human inhalation toxicology. In: Massaro, E. J., ed. Handbook of human toxicology. Boca Raton, FL: CRC Press LLC; pp. 607-670.

Frampton, M. W. (2001) Systemic and cardiovascular effects of airway injury and inflammation: ultrafine particle exposure in humans. Environ. Health Perspect. Suppl. 109(4): 529-532.

Frampton, M. W.; Voter, K. Z.; Morrow, P. E.; Roberts, N. J., Jr.; Culp, D. J.; Cox, C.; Utell, M. J. (1992) Sulfuric acid aerosol exposure in humans assessed by bronchoalveolar lavage. Am. Rev. Respir. Dis. 146: 626-632.

Frampton, M. W.; Morrow, P. E.; Cox, C.; Levy, P. C.; Condemi, J. J.; Speers, D.; Gibb, F. R.; Utell, M. J. (1995) Sulfuric acid aerosol followed by ozone exposure in healthy and asthmatic subjects. Environ. Res. 69: 1-14.

Frampton, M. W.; Ghio, A. J.; Samet, J. M.; Carson, J. L.; Carter, J. D.; Devlin, R. B. (1999) Effects of aqueous extracts of PM_{10} filters from the Utah Valley on human airway epithelial cells. Am. J. Physiol. 277: L960-L967.

Friedlander, S. K.; Yeh, E. K. (1998) The submicron atmospheric aerosol as a carrier of reactive chemical species: case of peroxides. Appl. Occup. Environ. Hyg. 13: 416-420.

Fujimaki, H.; Katayama, N.; Wakamori, K. (1992) Enhanced histamine release from lung mast cells of guinea pigs exposed to sulfuric acid aerosols. Environ. Res. 58: 117-123.

Fujimaki, H.; Nohara, O.; Ichinose, T.; Watanabe, N.; Saito, S. (1994) IL-4 production in mediastinal lymph node cells in mice intratracheally instilled with diesel exhaust particulates and antigen. Toxicology 92: 261-268.

Galatius-Jensen, S.; Wroblewski, H.; Emmeluth, C.; Bie, P.; Haunsø, S.; Kastrup, J. (1996) Plasma endothelin in congestive heart failure: a predictor of cardiac death? J. Card. Failure 2: 71-76.

Gallagher, J.; Heinrich, U.; George, M.; Hendee, L.; Phillips, D. H.; Lewtas, J. (1994) Formation of DNA adducts in rat lung following chronic inhalation of diesel emissions, carbon black and titanium dioxide particles. Carcinogenesis (London) 15: 1291-1299.

Gardner, S. Y.; Lehmann, J. R.; Costa, D. L. (2000) Oil fly ash-induced elevation of plasma fibrinogen levels in rats. Toxicol. Sci. 56: 175-180.

Gavett, S. H.; Madison, S. L.; Dreher, K. L.; Winsett, D. W.; McGee, J. K.; Costa, D. L. (1997) Metal and sulfate composition of residual oil fly ash determines airway hyperreactivity and lung injury in rats. Environ. Res. 72: 162-172.

Gavett, S. H.; Madison, S. L.; Stevens, M. A.; Costa, D. L. (1999) Residual oil fly ash amplifies allergic cytokines, airway responsiveness, and inflammation in mice. Am. J. Respir. Crit. Care Med. 160: 1897-1904.

Gearhart, J. M.; Schlesinger, R. B. (1986) Sulfuric acid-induced airway hyperresponsiveness. Fundam. Appl. Toxicol. 7: 681-689.

Gercken, G.; Berg, I.; Dörger, M.; Schlüter, T. (1996) Mechanisms of particle-induced activation of alveolar macrophages. Toxicol. Lett. 88: 121-129.

Ghio, A. J.; Devlin, R. B. (2001) Inflammatory lung injury after bronchial instillation of air pollution particles. Am. J. Respir. Crit. Care Med. 164: 704-708.

Ghio, A. J.; Meng, Z. H.; Hatch, G. E.; Costa, D. L. (1997a) Luminol-enhanced chemiluminescence after in vitro exposures of rat alveolar macrophages to oil fly ash is metal dependent. Inhalation Toxicol. 9: 255-271.

Ghio, A. J.; Piantadosi, C. A.; Crumbliss, A. L. (1997b) Hypothesis: iron chelation plays a vital role in neutrophilic inflammation. BioMetals 10: 135-142.

Ghio, A. J.; Richards, J. H.; Dittrich, K. L.; Samet, J. M. (1998a) Metal storage and transport proteins increase after exposure of the rat lung to an air pollution particle. Toxicol. Pathol. 26: 388-394.

Ghio, A. J.; Carter, J. D.; Richards, J. H.; Brighton, L. E.; Lay, J. C.; Devlin, R. B. (1998b) Disruption of normal iron homeostasis after bronchial instillation of an iron-containing particle. Am. J. Physiol. 274: L396-L403.

Ghio, A. J.; Carter, J. D.; Samet, J. M.; Reed, W.; Quay, J.; Dailey, L. A.; Richards, J. H.; Devlin, R. B. (1998c) Metal-dependent expression of ferritin and lactoferrin by respiratory epithelial cells. Am. J. Physiol. 274: L728-L736.

Ghio, A. J.; Stonehuerner, J.; Dailey, L. A.; Carter, J. D. (1999a) Metals associated with both the water-soluble and insoluble fractions of an ambient air pollution particle catalyze an oxidative stress. Inhalation Toxicol. 11: 37-49.

Ghio, A. J.; Carter, J. D.; Dailey, L. A.; Devlin, R. B.; Samet, J. M. (1999b) Respiratory epithelial cells demonstrate lactoferrin receptors that increase after metal exposure. Am. J. Physiol. 276: L933-L940.

Ghio, A. J.; Stoneheurner, J.; McGee, J. K.; Kinsey, J. S. (1999c) Sulfate content correlates with iron concentrations in ambient air pollution particles. Inhalation Toxicol. 11: 293-307.

Ghio, A. J.; Kim, C.; Devlin, R. B. (2000a) Concentrated ambient air particles induce mild pulmonary inflammation in healthy human volunteers. Am. J. Respir. Crit. Care Med. 162: 981-988.
Ghio, A. J.; Carter, J. D.; Richards, J. H.; Crissman, K. M.; Bobb, H. H.; Yang, F. (2000b) Diminished injury in hypotransferrinemic mice after exposure to a metal-rich particle. Am. J. Physiol. 278: L1051-L1061.
Ghio, A. J.; Richards, J. H.; Carter, J. D.; Madden, M. C. (2000c) Accumulation of iron in the rat lung after tracheal instillation of diesel particles. Toxicol. Pathol. 28: 619-627.
Ghio, A. J.; Gilbey, J. G.; Roggli, V. L.; Richards, J. H.; McGee, J. K.; Carson, J. L.; Devlin, R. B.; Cascio, W. E. (2001) Diffuse alveolar damage after exposure to an oil fly ash. Am. J. Respir. Crit. Care Med. 164: 1514-1518.
Gift, J. S.; Faust, R. A. (1997) Noncancer inhalation toxicology of crystalline silica: exposure-response assessment. J. Exposure Anal. Environ. Epidemiol. 7: 345-358.
Gilmour, M. I.; Taylor, F. G. R.; Baskerville, A.; Wathes, C. M. (1989a) The effect of titanium dioxide inhalation on the pulmonary clearance of *Pasteurella haemolytica* in the mouse. Environ. Res. 50: 157-172.
Gilmour, M. I.; Taylor, F. G. R.; Wathes, C. M. (1989b) Pulmonary clearance of *Pasteurella haemolytica* and immune responses in mice following exposure to titanium dioxide. Environ. Res. 50: 184-194.
Gilmour, P. S.; Brown, D. M.; Lindsay, T. G.; Beswick, P. H.; MacNee, W.; Donaldson, K. (1996) Adverse health effects of PM_{10} particles: involvement of iron in generation of hydroxyl radical. Occup. Environ. Med. 53: 817-822.
Gilmour, M. I.; Daniels, M.; McCrillis, R. C.; Winsett, D.; Selgrade, M. K. (2001) Air pollutant-enhanced respiratory disease in experimental animals. Environ. Health Perspect. Suppl. 109(4): 619-622.
Godleski, J. J.; Verrier, R. L.; Koutrakis, P.; Catalano, P. (2000) Mechanisms of morbidity and mortality from exposure to ambient air particles. Cambridge, MA: Health Effects Institute; research report no. 91.
Goldsmith, C.-A.; Frevert, C.; Imrich, A.; Sioutas, C.; Kobzik, L. (1997) Alveolar macrophage interaction with air pollution particulates. In: Driscoll, K. E.; Oberdörster, G., eds. Proceedings of the sixth international meeting on the toxicology of natural and man-made fibrous and non-fibrous particles; September 1996; Lake Placid, NY. Environ. Health Perspect. Suppl. 105(5): 1191-1195.
Goldsmith, C.-A. W.; Imrich, A.; Danaee, H.; Ning, Y. Y.; Kobzik, L. (1998) Analysis of air pollution particulate-mediated oxidant stress in alveolar macrophages. J. Toxicol. Environ. Health Part A 54: 529-545.
Goldsmith, C.-A. W.; Hamada, K.; Ning, Y. Y.; Qin, G.; Catalano, P.; Murthy, G. G. K.; Lawrence, J.; Kobzik, L. (1999) The effects of environmental aerosols on airway hyperresponsiveness in a murine model of asthma. Inhalation Toxicol. 11: 981-998.
Gong, H., Jr.; Sioutas, C.; Linn, W. S.; Clark, K. W.; Terrell, S. L.; Terrell, L. L.; Anderson, K. R.; Kim, S.; Chang, M.-C. (2000) Controlled human exposures to concentrated ambient fine particles in metropolitan Los Angeles: methodology and preliminary health-effect findings. In: Phalen, R. F., ed. Inhalation Toxicology: proceedings of the third colloquium on particulate air pollution and human health (first special issue); June, 1999; Durham, NC. Inhalation Toxicol. 12(suppl. 1): 107-119.
Gong, H., Jr.; Linn, W. S.; Sioutas, C.; Terrell, S. L.; Clark, K. W.; Anderson, K. R.; Terrell, L. L. (2003) Controlled exposures of healthy and asthmatic volunteers to concentrated ambient fine particles in Los Angeles. Inhalation Toxicol. 15: 305-325.
Gordon, T.; Nadziejko, C.; Schlesinger, R.; Chen, L. C. (1998) Pulmonary and cardiovascular effects of acute exposure to concentrated ambient particulate matter in rats. Toxicol. Lett. 96-97: 285-288.
Gordon, T.; Nadziejko, C.; Chen, L. C.; Schlesinger, R. (2000) Effects of concentrated ambient particles in rats and hamsters: an exploratory study. Cambridge, MA: Health Effects Institute; research report no. 93.
Granville, C. A.; Hanley, N. M.; Mumford, J. L.; DeMarini, D. M. (2003) Mutation spectra of smoky coal combustion emissions in *Salmonella* reflect the *TP*53 and *KRAS* mutations in lung tumor from smoky coal-exposed individuals. Mutat. Res. 525: 77-83.
Gross, K. B. (1981) Pulmonary function testing of animals chronically exposed to diluted diesel exhaust. J. Appl. Toxicol. 1: 116-123.
Gu, Z. W.; Zhong, B. Z.; Nath, B.; Whong, W.-Z.; Wallace, W. E.; Ong, T.-M. (1992) Micronucleus induction and phagocytosis in mammalian cells treated with diesel emission particles. Mutat. Res. 279: 55-60.
Gu, Z. W.; Zhong, B. Z.; Keane, M. J.; Whong, W. Z.; Wallace, W. E.; Ong, T. (1994) Induction of unscheduled DNA synthesis in V79 cells by diesel emission particles dispersed in simulated pulmonary surfactant. In: Dodgson, J.; McCallum, R. I., eds. Inhaled Particles VII: proceedings of an international symposium on inhaled particles organised by the British Occupational Hygiene Society; September 1991; Cambridge, UK. Ann. Occup. Hyg. 38(suppl. 1): 345-349.
Guerrero, R. R.; Rounds, D. E.; Orthoefer, J. (1981) Genotoxicity of Syrian hamster lung cells treated *in vivo* with diesel exhaust particulates. Environ. Int. 5: 445-454.

Hahon, N.; Booth, J. A.; Green, F.; Lewis, T. R. (1985) Influenza virus infection in mice after exposure to coal dust and diesel engine emissions. Environ. Res. 37: 44-60.
Hamada, K.; Goldsmith, C.-A.; Kobzik, L. (1999) Increased airway hyperresponsiveness and inflammation in a juvenile mouse model of asthma exposed to air-pollutant aerosol. J. Toxicol. Environ. Health 58: 129-143.
Hamada, K.; Goldsmith, C.-A.; Goldman, A.; Kobzik, L. (2000) Resistance of very young mice to inhaled allergen sensitization Is overcome by coexposure to an air-pollutant aerosol. Am. J. Respir. Crit. Care Med. 161: 1285-1293.
Hamers, T.; Van Schaardenburg, M. D.; Felzel, E. C.; Murk, A. J.; Koeman, J. H. (2000) The application of reporter gene assays for the determination of the toxic potency of diffuse air pollution. Sci. Total Environ. 262: 159-174.
Hannigan, M. P.; Cass, G. R.; Penman, B. W.; Crespi, C. L.; Lafleur, A. L.; Busby, W. F., Jr.; Thilly, W. G. (1997) Human cell mutagens in Los Angeles air. Environ. Sci. Technol. 31: 438-447.
Hannigan, M. P.; Cass, G. R.; Penman, B. W.; Crespi, C. L.; Lafleur, A. L.; Busby, W. F., Jr.; Thilly, W. G.; Simoneit, B. R. T. (1998) Bioassay-directed chemical analysis of Los Angeles airborne particulate matter using a human cell mutagenicity assay. Environ. Sci. Technol. 32: 3502-3514.
Harder, S. D.; Soukup, J. M.; Ghio, A. J.; Devlin, R. B.; Becker, S. (2001) Inhalation of $PM_{2.5}$ does not modulate host defense or immune parameters in blood or lung of normal human subjects. Environ. Health Perspect. Suppl. 109(4): 599-604.
Hastie, A. T.; Peters, S. P. (2001) Interactions of allergens and irritants in susceptible populations in producing lung dysfunction: implications for future research. Environ. Health Perspect. 109(suppl. 4): 605-607.
Health Effects Institute. (1995) Diesel exhaust: a critical analysis of emissions, exposure, and health effects: a special report of the Institute's Diesel Working Group. Cambridge, MA: Health Effects Institute.
Heck, J. D.; Costa, M. (1983) Influence of surface charge and dissolution on the selective phagocytosis of potentially carcinogenic particulate metal compounds. Cancer Res. 43: 5652-5656.
Heederik, D.; Douwes, J.; Wouters, I.; Doekes, G. (2000) Organic dusts: beyond endotoxin. Inhalation Toxicol. 12(suppl. 3): 27-33.
Heinrich, U.; Muhle, H.; Takenaka, S.; Ernst, H.; Fuhst, R.; Mohr, U.; Pott, F.; Stöber, W. (1986a) Chronic effects on the respiratory tract of hamsters, mice, and rats after long-term inhalation of high concentrations of filtered and unfiltered diesel engine emissions. J. Appl. Toxicol. 6: 383-395.
Heinrich, U.; Pott, F.; Rittinghausen, S. (1986b) Comparison of chronic inhalation effects in rodents after long-term exposure to either coal oven flue gas mixed with pyrolized pitch or diesel engine exhaust. In: Ishinishi, N.; Koizumi, A.; McClellan, R. O.; Stöber, W., eds. Carcinogenic and mutagenic effects of diesel engine exhaust: proceedings of the international satellite syposium on toxicological effects of emissions from diesel engines; July; Tsukuba Science City, Japan. Amsterdam, Holland: Elsevier Science Publishers B. V.; pp. 441-457. (Developments in toxicology and environmental science: v. 13).
Heinrich, U.; Fuhst, R.; Rittinghausen, S.; Creutzenberg, O.; Bellmann, B.; Koch, W.; Levsen, K. (1995) Chronic inhalation exposure of Wistar rats and two different strains of mice to diesel engine exhaust, carbon black, and titantium dioxide. Inhalation Toxicol. 7: 533-556.
Heinrich, J.; Hoelscher, B.; Frye, C.; Meyer, I.; Pitz, M.; Cyrys, J.; Wjst, M.; Neas, L.; Wichmann, H.-E. (2002a) Improved air quality in reunified Germany and decreases in respiratory symptoms. Epidemiology 13: 394-401.
Heinrich, J.; Hoelscher, B.; Frye, C.; Meyer, I.; Wjst, M.; Wichmann, H. E. (2002b) Trends in prevalence of atopic diseases and allergic sensitization in children in eastern Germany. Eur. Respir. J. 19: 1040-1046.
Heinrich, J.; Pitz, M.; Bischof, W.; Krug, N.; Borm, P. J. A. (2003) Endotoxin in fine ($PM_{2.5}$) and coarse ($PM_{2.5-10}$) particle mass of ambient aerosols. A tempero-spatial analysis. Atmos. Environ. 37: 3659-3667.
Hemminki, K.; Söderling, J.; Ericson, P.; Norbeck, H. E.; Segerbäck, D. (1994) DNA adducts among personnel servicing and loading diesel vehicles. Carcinogenesis 15: 767-769.
Heussen, G. A. H.; Bouman, H. G. M.; Roggeband, R.; Baan, R. A.; Alink, G. M. (1994) ^{32}P-postlabelling analysis of DNA adducts in white blood cells of humans exposed to residential wood combustion particulate matter. Environ. Mol. Mutagen. 23: 121-127.
Heyder, J.; Beck-Speier, I.; Busch, B.; Dirscherl, P.; Heilmann, P.; Ferron, G. A.; Josten, M.; Karg, E.; Kreyling, W. G.; Lenz, A.-G.; Maier, K. L.; Miaskowski, U.; Platz, S.; Reitmeir, P.; Schulz, H.; Takenaka, S.; Ziesenis, A. (1999) Health effects of sulfur-related environmental air pollution. I. Executive summary. Inhalation Toxicol. 11: 343-359.
Hitzfeld, B.; Friedrichs, K. H.; Ring, J.; Behrendt, H. (1997) Airborne particulate matter modulates the production of reactive oxygen species in human polymorphonuclear granulocytes. Toxicology 120: 185-195.

Hodgson, M. J.; Morey, P.; Leung, W. Y.; Morrow, L.; Miller, D.; Jarvis, B. B.; Robbins, H.; Halsey, J. F.; Storey, E. (1998) Building-associated pulmonary disease from exposure to *Stachybotrys chartarum* and *Aspergillus versicolor*. J. Occup. Environ. Med. 40:241-249.

Holian, A.; Hamilton, R. F., Jr.; Morandi, M. T.; Brown, S. D.; Li, L. (1998) Urban particle-induced apoptosis and phenotype shifts in human alveolar macrophages. Environ. Health Perspect. 106: 127-132.

Holma, B. (1989) Effects of inhaled acids on airway mucus and its consequences for health. In: Symposium on the health effects of acid aerosols; October 1987; Research Triangle Park, NC. Environ. Health Perspect. 79: 109-113.

Hornberg, C.; Maciuleviciute, L.; Seemayer, N. H. (1996) Sister chromatid exchanges in rodent tracheal epithelium exposed in vitro to environmental pollutants. Toxicol. Lett. 88: 45-53.

Hornberg, C.; Maciuleviciute, L.; Seemayer, N. H.; Kainka, E. (1998) Induction of sister chromatid exchanges (SCE) in human tracheal epithelial cells by the fractions PM-10 and PM-2.5 of airborne particulates. Toxicol. Lett. 96/97: 215-220.

Hou, S.; Lambert, B.; Hemminki, K. (1995) Relationship between hprt mutant frequency, aromatic DNA adducts and genotypes for *GSTM1* and *NAT2* in bus maintenance workers. Carcinogenesis 16: 1913-1917.

Houk, V. S.; Early, G.; Claxton, L. D. (1991) Use of the spiral Salmonella assay to detect the mutagenicity of complex environmental mixtures. Environ. Mol. Mutagen. 17: 112-121.

Huang, S. L.; Cheng, W. L.; Lee, C. T.; Huang, H. C.; Chan, C. C. (2002) Contribution of endotoxin in macrophage cytokine response to ambient particles in vitro. J. Toxicol. Environ. Health A 65: 1261-1272.

Huisingh, J.; Bradow, R.; Jungers, R.; Claxton, L.; Zweidinger, R.; Tejada, S.; Bumgarner, J.; Duffield, F.; Waters, M.; Simmon, V. F.; Hare, C.; Rodriguez, C.; Snow, L. (1978) Application of bioassay to the characterization of diesel particle emissions. In: Waters, M. D.; Nesnow, S.; Huisingh, J. L.; Sandhu, S. S.; Claxton, L., eds. Application of short-term bioassays in the fractionation and analysis of complex environmental mixtures: [proceedings of a symposium; February; Williamsburg, VA]. New York, NY: Plenum Press; pp. 383-418. (Hollaender, A.; Probstein, F.; Welch, B. L., eds. Environmental science research: v. 15).

Hunter, R. J. (1981) Zeta potential in colloid science: principles and applications. Orlando, FL: Academic Press, pp. 1-124. (Ottewill, R. H.; Rowell, R. L., eds. Colloid Science).

Ichinose, T.; Yajima, Y.; Nagashima, M.; Takenoshita, S.; Nagamachi, Y.; Sagai, M. (1997) Lung carcinogenesis and formation of 8-hydroxydeoxyguanosine in mice by diesel exhaust particles. Carcinogenesis 18: 185-192.

Imrich, A.; Ning, Y. Y.; Kobzik, L. (2000) Insoluble components of concentrated air particles mediate alveolar macrophage responses *in vitro*. Toxicol. Appl. Pharmacol. 167: 140-150.

International Agency for Research on Cancer. (1989) Diesel and gasoline engine exhausts and some nitroarenes. Lyon, France: International Agency for Research on Cancer; pp. 41-185. (IARC monographs on the evaluation of carcinogenic risks to humans: v. 46).

Ishinishi, N.; Kuwabara, N.; Nagase, S.; Suzuki, T.; Ishiwata, S.; Kohno, T. (1986) Long-term inhalation studies on effects of exhaust from heavy and light duty diesel engines on F344 rats. In: Ishinishi, N.; Koizumi, A.; McClellan, R. O.; Stöber, W., eds. Carcinogenic and mutagenic effects of diesel engine exhaust: proceedings of the international satellite symposium on toxicological effects of emissions from diesel engines; July; Tsukuba Science City, Japan. Amsterdam, Holland: Elsevier Science Publishers B. V.; pp. 329-348. (Developments in toxicology and environmental science: v. 13).

Ishinishi, N.; Kuwabara, N.; Takaki, Y.; Nagase, S.; Suzuki, T.; Nakajima, T.; Maejima, K.; Kato, A.; Nakamura, M. (1988) Long-term inhalation experiments on diesel exhaust. In: Diesel exhaust and health risks: results of the HERP studies. Tsukuba, Ibaraki, Japan: Japan Automobile Research Institute, Inc., Research Committee for HERP Studies; pp. 11-84.

Jacobs, J.; Kreutzer, R.; Smith, D. (1997) Rice burning and asthma hospitalizations, Butte County, California, 1983-1992. Environ. Health Perspect. 105: 980-985.

Jakab, G. J. (1992) Relationship between carbon black particulate-bound formaldehyde, pulmonary antibacterial defenses, and alveolar macrophage phagocytosis. Inhalation Toxicol. 4: 325-342.

Jakab, G. J. (1993) The toxicologic interactions resulting from inhalation of carbon black and acrolein on pulmonary antibacterial and antiviral defenses. Toxicol. Appl. Pharmacol. 121: 167-175.

Jakab, G. J.; Hemenway, D. R. (1993) Inhalation coexposure to carbon black and acrolein suppresses alveolar macrophage phagocytosis and TNF-α release and modulates peritoneal macrophage phagocytosis. Inhalation Toxicol. 5: 275-289.

Jakab, G. J.; Clarke, R. W.; Hemenway, D. R.; Longphre, M. V.; Kleeberger, S. R.; Frank, R. (1996) Inhalation of acid coated carbon black particles impairs alveolar macrophage phagocytosis. Toxicol. Lett. 88: 243-248.

Jiang, N.; Dreher, K. L.; Dye, J. A.; Richards, J. H.; Martin, L. D.; Adler, K. B. (2000) Residual oil fly ash induces cytotoxicity and mucin secretion by guinea pig tracheal epithelial cells via an oxidant-mediated mechanism. Toxicol. Appl. Pharmacol. 163: 221-230.

Kadiiska, M. B.; Mason, R. P.; Dreher, K. L.; Costa, D. L.; Ghio, A. J. (1997) *In vivo* evidence of free radical formation in the rat lung after exposure to an emission source air pollution particle. Chem. Res. Toxicol. 10: 1104-1108.

Kao, A. S.; Friedlander, S. K. (1995) Temporal variations of particulate air pollution: a marker for free radical dosage and adverse health effects? Inhalation Toxicol. 7: 149-156.

Keane, M. J.; Xing, S.-G.; Harrison, J. C.; Ong, T.; Wallace, W. E. (1991) Genotoxicity of diesel-exhaust particles dispersed in simulated pulmonary surfacta t. Mutat. Res. 260: 233-238.

Kennedy, T.; Ghio, A. J.; Reed, W.; Samet, J.; Zagorski, J.; Quay, J.; Carter, J.; Dailey, L.; Hoidal, J. R.; Devlin, R. B. (1998) Copper-dependent inflammation and nuclear factor-κB activation by particulate air pollution. Am. J. Respir. Cell Mol. Biol. 19: 366-378.

Killingsworth, C. R.; Alessandrini, F.; Krishna Murthy, G. G.; Catalano, P. J.; Paulauskis, J. D.; Godleski, J. J. (1997) Inflammation, chemokine expression, and death in monocrotaline-treated rats following fuel oil fly ash inhalation. Inhalation Toxicol. 9: 541-565.

Kim, S.; Chang, M.-C.; Kim, D.; Sioutas, C. (2000a) A new generation of portable coarse, fine, and ultrafine particle concentrators for use in inhalation toxicology. In: Phalen, R. F., ed. Inhalation Toxicology: proceedings of the third colloquium on particulate air pollution and human health (first special issue); June, 1999; Durham, NC. Inhalation Toxicol. 12(suppl. 1): 121-137.

Kim, S.; Sioutas, C.; Chang, M.-C.; Gong, H., Jr. (2000b) Factors affecting the stability of the performance of ambient fine-particle concentrators. In: Grant, L. D., ed. PM2000: particulate matter and health. Inhalation Toxicol. 12(suppl. 4): 281-298.

Kimmel, T. A.; Chen, L. C.; Bosland, M. C.; Nadziejko, C. (1997) Influence of acid aerosol droplet size on structural changes in the rat lung caused by acute exposure to sulfuric acid and ozone. Toxicol. Appl. Pharmacol. 144: 348-355.

Kim Oanh, N. T.; Nghiem, L. H.; Phyu, Y. L. (2002) Emission of polycyclic aromatic hydrocarbons, toxicity, and mutagenicity from domestic cooking using sawdust briquettes, wood, and kerosene. Environ. Sci. Technol. 36: 833-839.

Kitabatake, M.; Imai, M.; Kasama, K.; Kobayashi, I.; Tomita, Y.; Yoshida, K. (1979) Effects of air pollutants on the experimental induction of asthma attacks in guinea pigs: sulfuric acid mist and mixture of the mist and sulfur dioxide. Mie Med. J. 29: 29-36.

Kleeberger, S. R.; Levitt, R. C.; Zhang, L.-Y.; Longphre, M.; Harkema, J.; Jedlicka, A.; Eleff, S. M.; DiSilvestre, D.; Holroyd, K. J. (1997) Linkage analysis of susceptibility to ozone-induced lung inflammation in inbred mice. Nat. Genet. 17: 475-478.

Kleiger, R. E.; Bigger, J. T.; Bosner, M. S.; Chung, M. K.; Cook, J. R.; Rolnitzky, L. M.; Steinman, R.; Fleiss, J. L. (1991) Stability over time of variables measuring heart rate variability in normal subjects. Am. J. Cardiol. 68: 626-630.

Kleinman, M. T.; Leaf, D. A.; Kelly, E.; Caiozzo, V.; Osann, K.; O'Niell, T. (1998) Urban angina in the mountains: effects of carbon monoxide and mild hypoxemia on subjects with chronic stable angina. Arch. Environ. Health 53: 388-397.

Kleinman, M. T.; Mautz, W. J.; Bjarnason, S. (1999) Adaptive and non-adaptive responses in rats exposed to ozone, alone and in mixtures, with acidic aerosols. Inhalation Toxicol. 11: 249-264.

Kleinman, M. T.; Bufalino, C.; Rasmussen, R.; Hyde, D.; Bhalla, D. K.; Mautz, W. J. (2000) Toxicity of chemical components of ambient fine particulate matter ($PM_{2.5}$) inhaled by aged rats. J. Appl. Toxicol. 20: 357-364.

Knox, R. B.; Suphioglu, C.; Taylor, P.; Desai, R.; Watson, H. C.; Peng, J. L.; Bursill, L. A. (1997) Major grass pollen allergen Lol p 1 binds to diesel exhaust particles: implications for asthma and air pollution. Clin. Exp. Allergy 27: 246-251.

Kobzik, L. (1995) Lung macrophage uptake of unopsonized environmental particulates: role of scavenger-type receptors. J. Immunol. 155: 367-376.

Kobzik, L.; Goldsmith, C.-A. W.; Ning, Y. Y.; Qin, G.; Morgan, B.; Imrich, A.; Lawrence J.; Murthy, G. G. K.; Catalano, P. J. (2001) Effects of combined ozone and air pollution particle exposure in mice. Boston, MA: Health Effects Institute; research report no. 106. Available: http://www.healtheffects.org/Pubs/Kobzik.pdf [27 January 2003].

Kodavanti, U. P.; Costa, D. L. (1999) Animal models to study for pollutant effects. In: Holgate, S. T.; Samet, J. M.; Koren, H. S.; Maynard, R. L., eds. Air pollution and health. New York, NY: Academic Press; pp. 165-197.

Kodavanti, U. P.; Jaskot, R. H.; Bonner, J.; Badgett, A.; Dreher, K. L. (1996) Eosinophilic lung inflammation in particulate-induced lung injury: technical consideration in isolating RNA for gene expression studies. Exp. Lung Res. 22: 541-554.

Kodavanti, U. P.; Jaskot, R. H.; Costa, D. L.; Dreher, K. L. (1997a) Pulmonary proinflammatory gene induction following acute exposure to residual oil fly ash: roles of particle-associated metals. Inhalation Toxicol. 9: 679-701.

Kodavanti, U. P.; Jaskot, R. H.; Su, W. Y.; Costa, D. L.; Ghio, A. J.; Dreher, K. L. (1997b) Genetic variability in combustion particle-induced chronic lung injury. Am. J. Physiol. 272: L521-L532.

Kodavanti, U. P.; Hauser, R.; Christiani, D. C.; Meng, Z. H.; McGee, J.; Ledbetter, A.; Richards, J.; Costa, D. L. (1998a) Pulmonary responses to oil fly ash particles in the rat differ by virtue of their specific soluble metals. Toxicol. Sci. 43: 204-212.

Kodavanti, U. P.; Costa, D. L.; Bromberg, P. A. (1998b) Rodent models of cardiopulmonary disease: their potential applicability in studies of air pollutant susceptibility. Environ. Health Perspect. Suppl. 106(1): 111-130.

Kodavanti, U. P.; Jackson, M. C.; Ledbetter, A. D.; Richards, J. R.; Gardner, S. Y.; Watkinson, W. P.; Campen, M. J.; Costa, D. L. (1999) Lung injury from intratracheal and inhalation exposures to residual oil fly ash in a rat model of monocrotaline-induced pulmonary hypertension. J. Toxicol. Environ. Health Part A 57: 101-121.

Kodavanti, U. P.; Schladweiler, M. C.; Ledbetter, A. D.; Watkinson, W. P.; Campen, M. J.; Winsett, D. W.; Richards, J. R.; Crissman, K. M.; Hatch, G. E.; Costa, D. L. (2000a) The spontaneously hypertensive rat as a model of human cardiovascular disease: evidence of exacerbated cardiopulmonary injury and oxidative stress from inhaled emission particulate matter. Toxicol. Appl. Pharmacol. 164: 250-263.

Kodavanti, U. P.; Mebane, R.; Ledbetter, A.; Krantz, T.; McGee, J.; Jackson, M. C.; Walsh, L.; Hilliard, H.; Chen, B. Y.; Richards, J.; Costa, D. L. (2000b) Variable pulmonary responses from exposure to concentrated ambient air particles in a rat model of bronchitis. Toxicol. Sci. 54: 441-451.

Kodavanti, U. P.; Schladweiler, M. C. J.; Richards, J. R.; Costa, D. L. (2001) Acute lung injury from intratracheal exposure to fugitive residual oil fly ash and its constituent metals in normo- and spontaneously hypertensive rats. Inhalation Toxicol. 13: 37-54.

Kodavanti, U. P.; Schladweiler, M. C.; Ledbetter, A. D.; Hauser, R.; Christiani, D. C.; McGee, J.; Richards, J. R.; Costa, D. L. (2002a) Temporal association between pulmonary and systemic effects of particulate matter in healthy and cardiovascular compromised rats. J. Toxicol. Environ. Health Part A 65: 1545-1569.

Kodavanti, U. P.; Schladweiler, M. C. J.; Ledbetter, A. D.; Hauser, R.; Christiani, D. C.; Samet, J. M.; McGee, J.; Richards, J. H.; Costa, D. L. (2002b) Pulmonary and systemic effects of zinc-containing emission particles in three rat strains: multiple exposure scenarios. Toxicol. Sci. 70: 73-85.

Kodavanti, U. P.; Moyer, C. F.; Ledbetter, A. D.; Schladweiler, M. C.; Costa, D. L.; Hauser, R.; Christiani, D. C.; Nyska, A. (2003) Inhaled environmental combustion particles cause myocardial injury in the Wistar Kyoto rat. Toxicol. Sci. 71: 237-245.

Lambert, A. L.; Dong, W.; Winsett, D. W.; Selgrade, M. K.; Gilmour, M. I. (1999) Residual oil fly ash exposure enhances allergic sensitization to house dust mite. Toxicol. Appl. Pharmacol. 158: 269-277.

Lambert, A. L.; Dong, W.; Selgrade, M. K.; Gilmour, M. I. (2000) Enhanced allergic sensitization by residual oil fly ash particles is mediated by soluble metal constituents. Toxicol. Appl. Pharmacol. 165: 84-93.

Lan, Q.; Chapman, R. S.; Schreinemachers, D. M.; Tian, L. W.; He, X. Z. (2002) Household stove improvement and risk of lung cancer in Xuanwei, China. J. Nat. Cancer Inst. 94: 826-835.

La Rovere, M. T.; Pinna, G. D.; Maestri, R.; Mortara, A.; Capomolla, S.; Febo, O.; Ferrari, R.; Franchini, M.; Gnemmi, M.; Opasich, C.; Riccardi, P. G.; Traversi, E.; Cobelli, F. (2003) Short-term heart rate variability strongly predicts sudden cardiac death in chronic heart failure patients. Circulation 107: 565-570.

Larsen, F. O.; Christensen, L. H. R.; Clementsen, P.; Gravesen, S.; Stahl Skov, P.; Norn, S. (1996) Microfungi in indoor air are able to trigger histamine release by non-IgE-mediated mechanisms. Inflammation Res. 45(suppl. 1): S23-S24.

Last, J. A.; Pinkerton, K. E. (1997) Chronic exposure of rats to ozone and sulfuric acid aerosol: biochemical and structural responses. Toxicology 116: 133-146.

Last, J. A.; Hyde, D. M.; Chang, D. P. Y. (1984) A mechanism of synergistic lung damage by ozone and a respirable aerosol. Exp. Lung Res. 7: 223-235.

Laurie, R. D.; Boyes, W. K. (1980) Neurophysiological alterations due to diesel exhaust exposure during the neonatal life of the rat. In: Pepelko, W. E.; Danner, R. M.; Clarke, N. A., eds. Health effects of diesel engine emissions: proceedings of an international symposium, v. 2; December 1979; Cincinnati, OH. Cincinnati, OH: U.S. Environmental Protection Agency, Health Effects Research Laboratory; pp. 713-727; EPA report no. EPA-600/9-80-057b. Available from: NTIS, Springfield, VA; PB81-173817.

Laurie, R. D.; Boyes, W. K. (1981) Neurophysiological alterations due to diesel exhaust exposure during the neonatal life of the rat. Environ. Int. 5: 363-368.

Laurie, R. D.; Boyes, W. K.; Wessendarp, T. (1980) Behavioral alterations due to diesel exhaust exposure. In: Pepelko, W. E.; Danner, R. M.; Clarke, N. A., eds. Health effects of diesel engine emissions: proceedings of an international symposium, v. 2; December 1979; Cincinnati, OH. Cincinnati, OH: U.S. Environmental Protection Agency, Health Effects Research Laboratory; pp. 698-712; EPA report no. EPA-600/9-80-057b. Available from: NTIS, Springfield, VA; PB81-173817.

Lay, J. C.; Bennett, W. D.; Kim, C. S.; Devlin, R. B.; Bromberg, P. A. (1998) Retention and intracellular distribution of instilled iron oxide particles in human alveolar macrophages. Am. J. Respir. Cell Mol. Biol. 18: 687-695.

Lay, J. C.; Zeman, K. L.; Ghio, A. J.; Bennett, W. D. (2001) Effects of inhaled iron oxide particles on alveolar epithelial permeability in normal subjects. Inhalation Toxicol. 13: 1065-1078.

Leduc, D.; Fally, S.; De Vuyst, P.; Wollast, R.; Yernault, J.-C. (1995) Acute exposure to realistic acid fog: effects on respiratory function and airway responsiveness in asthmatics. Environ. Res. 71: 89-98.

Lee, M. M.; Green, F. H. Y.; Roth, S. H.; Karkhanis, A.; Bjarnason, S. G.; Schürch, S. (1999) Sulfuric acid aerosol induces changes in alveolar surface tension in the guinea pig but not in the rat. Exp. Lung Res. 25: 229-244.

Leikauf, G. D.; McDowell, S. A.; Gammon, K.; Wesselkamper, S. C.; Bachurski, C. J.; Puga, A.; Wiest, J. S.; Leikauf, J. E.; Prows, D. R. (2000) Functional genomics of particle-induced lung injury. Inhalation Toxicol. 12: 59-73.

Leikauf, G.; McDowell, S. A.; Wesselkamper, S. C.; Miller, C. R.; Hardie, W. D.; Gammon, K.; Biswas, P. P.; Korfhagen, T. R.; Bachurski, C. J.; Wiest, J. S.; Willeke, K.; Bingham, E.; Leikauf, J. E.; Aronow, B. J.; Prows, D. R. (2001) Pathogenomic mechanisms for particulate matter induction of acute lung injury and inflammation in mice. Boston, MA: Health Effects Institute; research report no. 105. Available: http://www.healtheffects.org/pubs-research.htm [15 May, 2003].

Lewis, T. R.; Green, F. H. Y.; Moorman, W. J.; Burg, J. R.; Lynch, D. W. (1989) A chronic inhalation toxicity study of diesel engine emissions and coal dust, alone and combined. J. Am. Coll. Toxicol. 8: 345-375.

Lewtas, J. (1983) Evaluation of the mutagenicity and carcinogenicity of motor vehicle emissions in short-term bioassays. Environ. Health Perspect. 47: 141-152.

Li, A. P.; Royer, R. E. (1982) Diesel-exhaust-particle extract enhancement of chemical-induced mutagenesis in cultured Chinese hamster ovary cells: possible interaction of diesel exhaust with environmental chemicals. Mutat. Res. 103: 349-355.

Li, X. Y.; Gilmour, P. S.; Donaldson, K.; MacNee, W. (1996) Free radical activity and pro-inflammatory effects of particulate air pollution (PM_{10}) *in vivo* and *in vitro*. Thorax 51: 1216-1222.

Li, X. Y.; Gilmour, P. S.; Donaldson, K.; MacNee, W. (1997) *In vivo* and *in vitro* proinflammatory effects of particulate air pollution (PM_{10}). In: Driscoll, K. E.; Oberdörster, G., eds. Proceedings of the sixth international meeting on the toxicology of natural and man-made fibrous and non-fibrous particles; September 1996; Lake Placid, NY. Environ. Health Perspect. Suppl. 105(5): 1279-1283.

Li, X. Y.; Brown, D.; Smith, S.; MacNee, W.; Donaldson, K. (1999) Short-term inflammatory responses following intratracheal instillation of fine and ultrafine carbon black in rats. Inhalation Toxicol. 11: 709-731.

Liber, H. L.; Andon, B. M.; Hites, R. A.; Thilly, W. G. (1981) Diesel soot: mutation measurements in bacterial and human cells. Environ. Int. 5: 281-284.

Liberti, A.; Ciccioli, P.; Cecinato, A.; Brancaleoni, E.; Di Palo, C. (1984) Determination of nitrated-polyaromatic hydrocarbons (nitro-PAHs) in environmental samples by high resolution chromatographic techniques. J. High Resolut. Chromatogr. Chromatogr. Commun. 7: 389-397.

Linn, W. S.; Shamoo, D. A.; Anderson, K. R.; Peng, R.-C.; Avol, E. L.; Hackney, J. D. (1994) Effects of prolonged, repeated exposure to ozone, sulfuric acid, and their combination in healthy and asthmatic volunteers. Am. J. Respir. Crit. Care Med. 150: 431-440.

Linn, W. S.; Gong, H., Jr.; Shamoo, D. A.; Anderson, K. R.; Avol, E. L. (1997) Chamber exposures of children to mixed ozone, sulfur dioxide, and sulfuric acid. Arch. Environ. Health 52: 179-187.

Lipsett, M.; Hurley, S.; Ostro, B. (1997) Air pollution and emergency room visits for asthma in Santa Clara County, California. Environ. Health Perspect. 105: 216-222.

Lison, D.; Lardot, C.; Huaux, F.; Zanetti, G.; Fubini, B. (1997) Influence of particle surface area on the toxicity of insoluble manganese dioxide dusts. Arch. Toxicol. 71: 725-729.

Liu, X.; Keane, M. J.; Zong, B.-Z.; Ong, T.-M.; Wallace, W. E. (1996) Micronucleus formation in V79 cells treated with respirable silica dispersed in medium and simulated pulmonary surfactant. Mutat. Res. 361: 89-94.

Löfroth, G. (1981) Comparison of the mutagenic activity in carbon particulate matter and in diesel and gasoline engine exhaust. In: Waters, M. D.; Sandhu, S. S.; Huisingh, J. L.; Claxton, L.; Nesnow, S., eds. Short-term bioassays in the analysis of complex environmental mixtures II: proceedings of the second symposium on the application of short-term bioassays in the fractionation and analysis of complex environmental mixtures; March 1980; Williamsburg, VA. New York, NY: Plenum Press; pp. 319-336. (Hollaender, A.; Welch, B. L.; Probstein, R. F., eds. Environmental science research series: v. 22).

Löfroth, G.; Lazaridis, G.; Rudling, L. (1986) Mutagenicity assay of emission extracts from wood stoves: comparison with other emission parameters. Sci. Total Environ. 58: 199-208.

Loft, S.; Deng, X. S.; Tuo, J.; Wellejus, A.; Sørensen, M.; Poulsen, H. E. (1998) Experimental study of oxidative DNA damage. Free Rad. Res. 29: 525-539.

Long, C. M.; Suh, H. H.; Kobzik, L.; Catalano, P. J.; Ning, Y. Y.; Koutrakis, P. (2001) A pilot investigation of the relative toxicity of indoor and outdoor fine particles: *in vitro* effects of endotoxin and other particulate properties. Environ. Health Perspect. 109: 1019-1026.

Longphre, M.; Li, D.; Matovinovic, E.; Gallup, M.; Samet, J. M.; Basbaum, C. B. (2000) Lung mucin production is stimulated by the air pollutant residual oil fly ash. Toxicol. Appl. Pharmacol. 162: 86-92.

Lowe, G. D. O.; Lee, A. J.; Rumley, A.; Price, J. F.; Fowkes, F. G. R. (1997) Blood viscosity and risk of cardiovascular events: The Edinburgh Study. Br. J. Haematol. 96: 168-173.

Madden, M. C.; Thomas, M. J.; Ghio, A. J. (1999) Acetaldehyde (CH_3CHO) production in rodent lung after exposure to metal-rich particles. Free Radical Biol. Med. 26: 1569-1577.

Madden, M. C.; Richards, J. H.; Dailey, L. A.; Hatch, G. E.; Ghio, A. J. (2000) Effect of ozone on diesel exhaust particle toxicity in rat lung. Toxicol. Appl. Pharmacol. 168: 140-148.

Madl, A. K.; Wilson, D. W.; Segall, H. J.; Pinkerton, K. E. (1998) Alteration in lung particle translocation, macrophage function, and microfilament arrangement in monocrotaline-treated rats. Toxicol. Appl. Pharmacol. 153: 28-38.

Matsushita, H.; Goto, S.; Endo, O.; Lee, J.-H.; Kawai, A. (1986) Mutagenicity of diesel exhaust and related chemicals. In: Ishinishi, N.; Koizumi, A.; McClellan, R. O.; Stöber, W., eds. Carcinogenic and mutagenic effects of diesel engine exhaust: proceedings of the international satellite symposium on toxicological effects of emissions from diesel engines; July; Tsukuba Science City, Japan. Amsterdam, The Netherlands: Elsevier Science Publishers B. V.; pp. 103-118. (Developments on toxicology and environmental science: v. 13).

Mauderly, J. L. (1993) Toxicological approaches to complex mixtures. Environ. Health Perspect. Suppl. 101(4): 155-165.

Mauderly, J. L. (2000) Animal models for the effect of age on susceptibility to inhaled particulate matter. Inhalation Toxicol. 12: 863-900.

Mauderly, J. L.; Gillett, N. A.; Henderson, R. F.; Jones, R. K.; McClellan, R. O. (1988) Relationships of lung structural and functional changes to accumulation of diesel exhaust particles. In: Dodgson, J.; McCallum, R. I.; Bailey, M. R.; Fisher, D. R., eds. Inhaled particles VI: proceedings of an international symposium and workshop on lung dosimetry; September 1985; Cambridge, United Kingdom. Ann. Occup. Hyg. 32(suppl. 1): 659-669.

Mautz, W. J.; Kleinman, M. T.; Bhalla, D. K.; Phalen, R. F. (2001) Respiratory tract responses to repeated inhalation of an oxidant and acid gas-particle air pollutant mixture. Toxicol. Sci. 61: 331-341.

McClellan, R. O.; Bice, D. E.; Cuddihy, R. G.; Gillett, N. A.; Henderson, R. F.; Jones, R. K.; Mauderly, J. L.; Pickrell, J. A.; Shami, S. G.; Wolff, R. K. (1986) Health effects of diesel exhaust. In: Lee, S. D.; Schneider, T.; Grant, L. D.; Verkerk, P. J., eds. Aerosols: research, risk assessment and control strategies: proceedings of the second U.S.-Dutch international symposium; May 1985; Williamsburg, VA. Chelsea, MI: Lewis Publishers, Inc.; pp. 597-615.

McDowell, S. A.; Gammon, K.; Bachurski, C. J.; Weist, J. S.; Leikauf, J. E.; Prows, D. R. Leikauf, G. D. (2000) Differential gene expression in the initiation and progression of nickel-induced acute lung injury. Am. J. Respir. Cell Mol. Biol. 23: 466-474.

McKenna, I. M.; Gordon, T.; Chen, L. C.; Anver, M. R.; Waalkes, M. P. (1998) Expression of metallothionein protein in the lungs of Wistar rats and C57 and DBA mice exposed to cadmium oxide fumes. Toxicol. Appl. Pharmacol. 153: 169-178.

Meade, T. W.; Ruddock, V.; Stirling, Y.; Chakrabarti, R.; Miller, G. J. (1993) Fibrinolytic activity, clotting factors, and long-term incidence of ischaemic heart disease in The Northwick Park Heart Study. Lancet 342: 1076-1079.

Menetrez, M. Y.; Foarde, K. K.; Ensor, D. S. (2001) An analytical method for the measurement of nonviable bioaerosols. J. Air Waste Manage. Assoc. 51: 1436-1442.

Michel, O.; Nagy, A.-M.; Schroeven, M.; Duchateau, J.; Nève, J.; Fondu, P.; Sergysels, R. (1997) Dose-response relationship to inhaled endotoxin in normal subjects. Am. J. Respir. Crit. Care Med. 156: 1157-1164.

Miller, F. J. (2000) Dosimetry of particles in laboratory animals and humans in relationship to issues surrounding lung overload and human health risk assessment: a critical review. Inhalation Toxicol. 12: 19-57.

Mitchell, A. D.; Evans, E. L.; Jotz, M. M.; Riccio, E. S.; Mortelmans, K. E.; Simmon, V. F. (1981) Mutagenic and carcinogenic potency of extracts of diesel and related environmental emissions: *in vitro* mutagenesis and DNA damage. Environ. Int. 5: 393-401.

Molinelli, A. R.; Madden, M. C.; McGee, J. K.; Stonebuerner, J. G.; Ghio, A. J. (2002) Effect of metal removal on the toxicity of airborne particulate matter from the Utah Valley. Inhalation Toxicol. 14: 1069-1086.

Monini, P.; de Lellis, L.; Barbanti-Brodano, G. (1995) Association of BK and JC human Polyomaviruses and SV40 with human tumors. In: Barbanti-Brodano, G.; Bendinelli, M.; Friedman, H., eds. DNA tumor viruses–oncogenic mechanisms. New York, NY: Plenum; pp. 51-73.

Monn, C.; Becker, S. (1999) Cytotoxicity and induction of proinflammatory cytokines from human monocytes exposed to fine ($PM_{2.5}$) and coarse particles ($PM_{10-2.5}$) in outdoor and indoor air. Toxicol. Appl. Pharmacol. 155: 245-252.

Monn, C.; Naef, R.; Koller, T. (2003) Reactions of macrophages exposed to particles <10 μm. Environ. Res. 91: 35-44.

Morimoto, K.; Kitamura, M.; Kondo, H.; Koizumi, A. (1986) Genotoxicity of diesel exhaust emissions in a battery of in-vitro short-term bioassays. In: Ishinishi, N.; Koizumi, A.; McClellan, R. O.; Stöber, W., eds. Carcinogenic and mutagenic effects of diesel engine exhaust: proceedings of the international satellite symposium on toxicological effects of emissions from diesel engines; July; Tsukuba Science City, Japan. Amsterdam, The Netherlands: Elsevier Science Publishers B. V.; pp. 85-102. (Developments in toxicology and environmental science: v. 13).

Morio, L. A.; Hooper, K. A.; Brittingham, J.; Li, T.-H.; Gordon, R. E.; Turpin, B. J.; Laskin, D. L. (2001) Tissue injury following inhalation of fine particulate matter and hydrogen perioxide is associated with altered production of inflammatory mediators and antioxidants by alveolar macrophages. Toxicol. Appl. Pharmacol. 177: 188-199.

Morrow, P. E. (1988) Possible mechanisms to explain dust overloading of the lungs. Fundam. Appl. Toxicol. 10: 369-384.

Moss, O. R.; Gross, E. A.; James, R. A.; Janszen, D. B.; Ross, P. W.; Roberts, K. C.; Howard, A. M.; Harkema, J. R.; Calderón-Garcidueñas, L.; Morgan, K. T. (2001) Respiratory tract toxicity in rats exposed to Mexico City air. Cambridge, MA: Health Effects Institute; research report no. 100. Available: http://www.healtheffects.org/pubs-research.htm [15 May, 2003].

Muggenburg, B. A.; Tilley, L.; Green, F. H. Y. (2000a) Animal models of cardiac disease: potential usefulness for studying health effects of inhaled particles. Inhalation Toxicol. 12: 901-925.

Muggenburg, B. A.; Barr, E. B.; Cheng, Y. S.; Seagrave, JC.; Tilley, L. P.; Mauderly, J. L. (2000b) Effect of inhaled residual oil fly ash on the electrocardiogram of dogs. In: Grant, L. D., ed. PM2000: particulate matter and health. Inhalation Toxicol. 12(suppl. 4): 189-208.

Muggenburg, B. A.; Benson, J. M.; Barr, E. B.; Kubatko, J.; Tilley, L. P. (2003) Short-term inhalation of particulate transition metals has little effect on the electrocardiograms of dogs having preexisting cardiac abnormalities. Inhalation Toxicol. 15: 357-371.

Mukae, H.; Hogg, J. C.; English, D.; Vincent, R.; Van Eeden, S. F. (2000) Phagocytosis of particulate air pollutants by human alveolar macrophages stimulates the bone marrow. Am. J. Physiol. 279: L924-L931.

Mukae, H.; Vincent, R.; Quinlan, K.; English, D.; Hards, J.; Hogg, J. C.; Van Eeden, S. F. (2001) The effect of repeated exposure to particulate air pollution (PM_{10}) on the bone marrow. Am. J. Respir. Crit. Care Med. 163: 201-209.

Mumford, J. L.; Lewtas, J. (1982) Mutagenicity and cytotoxicity of coal fly ash from fluidized bed and conventional combustion. J. Toxicol. Environ. Health 10: 565-586.

Mumford, J. L.; He, X. Z.; Chapman, R. S.; Cao, S. R.; Harris, D. B.; Li, X. M.; Xian, Y. L.; Jiang, W. Z.; Xu, C. W.; Chuang, J. C.; Wilson, W. E.; Cooke, M. (1987) Lung cancer and indoor air pollution in Xuan Wei, China. Science (Washington, DC) 235: 217-220.

Mumford, J. L.; Tian, D.; Younes, M.; Hu, F.; Lan, Q.; Ostrowski, M. L.; He, X.; Feng, Z. (1999) Detection of p53 protein accumulation in sputum and lung adenocarcinoma associated with indoor exposure to unvented coal smoke in China. Anticancer Res. 19: 951-958.

Murphy, S. A.; BéruBé, K. A.; Pooley, F. D.; Richards, R. J. (1998) The response of lung epithelium to well characterised fine particles. Life Sci. 62: 1789-1799.

Nadadur, S. S.; Kodavanti, U. P. (2002) Altered gene expression profiles of rat lung in response to an emission particulate and its metal constituents. J. Toxicol. Environ. Health Part A 65:1333-1350.
Nadadur, S. S.; Schladweiler, M. C. J.; Kodavanti, U. P. (2000) A pulmonary rat gene array for screening altered expression profiles in air pollutant-induced lung injury. Inhalation Toxicol. 12: 1239-1254.
Nadeau, D.; Vincent, R.; Kumarathasan, P.; Brook, J.; Dufresne, A. (1996) Cytotoxicity of ambient air particles to rat lung macrophages: comparison of cellular and functional assays. Toxicol. in Vitro 10: 161-172.
Nadziejko, C.; Fang, K.; Chen, L. C.; Cohen, B.; Karpatkin, M.; Nadas, A. (2002) Effect of concentrated ambient particulate matter on blood coagulation parameters in rats. Boston, MA: Health Effects Institute. Available: http://www.healtheffects.org/Pubs/Nadziejko.pdf.
Nagashima, M.; Kasai, H.; Yokota, J.; Nagamachi, Y.; Ichinose, T.; Sagai, M. (1995) Formation of an oxidative DNA damage, 8-hydroxydeoxyguanosine, in mouse lung DNA after intratracheal instillation of diesel exhaust particles and effects of high dietary fat and beta-carotene on this process. Carcinogenesis 16: 1441-1445.
Nakagawa, R.; Kitamori, S.; Horikawa, K.; Nakashima, K.; Tokiwa, H. (1983) Identification of dinitropyrenes in diesel-exhaust particles: their probable presence as the major mutagens. Mutat. Res. 124: 201-211.
Nakamura, T.; Hayashida, Y. (1992) Autonomic cardiovascular responses to smoke exposure in conscious rats. Am. J. Physiol. 262: R738-745.
National Institutes of Health. (1997) Guidelines for the diagnosis and management of asthma: expert panel report 2. Bethesda, MD: U.S. Department of Health and Human Services, National Heart, Lung, and Blood Institute; publication no. 97-4051.
Nehls, P.; Seiler, F.; Rehn, B.; Greferath, R.; Bruch, J. (1997) Formation and persistence of 8-oxoguanine in rat lung cells as an important determinant for tumor formation following particle exposure. In: Driscoll, K. E.; Oberdörster, G., eds. Proceedings of the sixth international meeting on the toxicology of natural and man-made fibrous and non-fibrous particles; September 1996; Lake Placid, NY. Environ. Health Perspect. Suppl. 105(5): 1291-1296.
Nel, A. E.; Diaz-Sanchez, D.; Li, N. (2001) The role of particulate pollutants in pulmonary inflammation and asthma: evidence for the involvement of organic chemicals and oxidative stress. Curr. Opin. Pulm. Med. 7: 20-26.
Nemmar, A.; Delaunois, A.; Nemery, B.; Dessy-Doizé, C.; Beckers, J.-F.; Sulon, J.; Gustin, P. (1999) Inflammatory effect of intratracheal instillation of ultrafine particles in the rabbit: role of C-fiber and mast cells. Toxicol. Appl. Pharmacol. 160: 250-261.
Nemmar, A.; Hoylaerts, M. F.; Hoet, P. H. M.; Dinsdale, D.; Smith, T.; Xu, H.; Vermylen, J.; Nemery, B. (2002) Ultrafine particles affect experimental thrombosis in an *in vivo* hamster model. Am. J. Respir. Crit. Care Med. 166: 998-1004.
Nielsen, P. S.; Autrup, H. (1994) Diesel exhaust-related DNA adducts in garage workers. Clin. Chem. 40: 1456-1458.
Nielsen, P. S.; Andreassen, Å.; Farmer, P. B.; Øvrebø, S.; Autrup, H. (1996) Biomonitoring of diesel exhaust-exposed workers. DNA and hemoglobin adducts and urinary 1-hydroxypyrene as markers of exposure. Toxicol. Lett. 86: 27-37.
Nightingale, J. A.; Maggs, R.; Cullinan, P.; Donnelly, L. E.; Rogers, D. F.; Kinnersley, R.; Chung, K. F.; Barnes, P. J.; Ashmore, M.; Newman-Taylor, A. (2000) Airway inflammation after controlled exposure to diesel exhaust particulates. Am. J. Respir. Crit. Care Med. 162: 161-166.
Nikula, K. J.; Snipes, M. B.; Barr, E. B.; Griffith, W. C.; Henderson, R. F.; Mauderly, J. L. (1995) Comparative pulmonary toxicities and carcinogenicities of chronically inhaled diesel exhaust and carbon black in F344 rats. Fundam. Appl. Toxicol. 25: 80-94.
Ning, Y.; Imrich, A.; Goldsmith, C. A.; Qin, G.; Kobzik, L. (2000) Alveolar macrophage cytokine production in response to air particles in vitro: role of endotoxin. J. Toxicol. Environ. Health A 59: 165-180.
Nishioka, M. G.; Petersen, B. A.; Lewtas, J. (1982) Comparison of nitro-aromatic content and direct-acting mutagenicity of diesel emissions. In: Cooke, M.; Dennis, A. J.; Fisher, G. L., eds. Polynuclear aromatic hydrocarbons: physical and biological chemistry, proceedings of the sixth international symposium on polynuclear aromatic hydrocarbons; October 1981; Columbus, OH. Columbus, OH: Battelle Press; pp. 603-613.
Nordenhäll, C.; Pourazar, J.; Ledin, M. C.; Levin, J. O.; Sandström, T.; Ädelroth, E. (2001) Diesel exhaust enhances airway responsiveness in asthmatic subjects. Eur. Respir. J. 17: 909-915.
Norwood, J., Jr.; Ledbetter, A. D.; Doerfler, D. L.; Hatch, G. E. (2001) Residual oil fly ash inhalation in guinea pigs: influence of absorbate and glutathione depletion. Toxicol. Sci. 61: 144-153.

Oberdörster, G. (1996a) Effects of ultrafine particles in the lung and potential relevance to environmental particles. In: Marijnissen, J. C. M.; Gradon, L., eds. Proceedings of Aerosol inhalation, lung transport, deposition and the relation to the environment: recent research frontiers, an international workshop; September,1995; Warsaw, Poland. London, United Kingdom: Kluwer Academic; pp. 165-174.

Oberdörster, G. (1996b) Significance of particle parameters in the evaluation of exposure-dose-response relationships of inhaled particles. Inhalation Toxicol. 8(suppl.): 73-89.

Oberdörster, G.; Ferin, J.; Gelein, R.; Soderholm, S. C.; Finkelstein, J. (1992) Role of the alveolar macrophage in lung injury: studies with ultrafine particles. Environ. Health Perspect. 97: 193-199.

Oberdörster, G.; Cox, C.; Gelein, R. (1997) Intratracheal instillation versus intratracheal inhalation of tracer particles for measuring lung clearance function. Exp. Lung Res. 23: 17-34.

Oberdörster, G.; Finkelstein, J. N.; Johnston, C.; Gelein, R.; Cox, C.; Baggs, R.; Elder, A. C. P. (2000) Acute pulmonary effects of ultrafine particles in rats and mice. Cambridge, MA: Health Effects Institute; research report no. 96.

Oettinger, R.; Drumm, K.; Knorst, M.; Krinyak, P.; Smolarski, R.; Kienast, K. (1999) Production of reactive oxygen intermediates by human macrophages exposed to soot particles and asbestos fibers and increase in NF-kappa B p50/p105 mRNA. Lung 177: 343-354.

Ohtoshi, T.; Takizawa, H.; Okazaki, H.; Kawasaki, S.; Takeuchi, N.; Ohta, K.; Ito, K. (1998) Diesel exhaust particles stimulate human airway epithelial cells to produce cytokines relevant to airway inflammation *in vitro*. J. Allergy Clin. Immunol. 101: 778-785.

Ohtsuka, Y.; Clarke, R. W.; Mitzner, W.; Brunson, K.; Jakab, G. J.; Kleeberger, S. R. (2000a) Interstrain variation in murine susceptibility to inhaled acid-coated particles. Am. J. Physiol. L469-L476.

Ohtsuka, Y.; Brunson, K. J.; Jedlicka, A. E.; Mitzner, W.; Clarke, R. W.; Zhang, L.-Y.; Eleff, S. M.; Kleeberger, S. R. (2000b) Genetic linkage analysis of susceptibility to particle exposure in mice. Am. J. Respir. Cell Mol. Biol. 22: 574-581.

Omland, T.; Lie, R. T.; Aakvaag, A.; Aarsland, T.; Dickstein, K. (1994) Plasma endothelin determination as a prognostic indicator of 1-year mortality after acute myocardial infarction. Circulation 89: 1573-1579.

Ong, E. K. (1994) Grass pollen allergens: molecular characterization and environmental monitoring [dissertation]. Melbourne, Australia: The University of Melbourne.

Ong, T.; Whong, W. Z.; Xu, J.; Burchell, B.; Green, F. H.; Lewis, T. (1985) Genotoxicity studies of rodents exposed to coal dust and diesel emission particulates. Environ. Res. 37: 399-409.

Oortgiesen, M.; Veronesi, B.; Eichenbaum, G.; Kiser, P. F.; Simon, S. A. (2000) Residual oil fly ash and charged polymers activate epithelial cells and nociceptive sensory neurons. Am. J. Physiol. 278: L683-L695.

Ormstad, H.; Johansen, B. V.; Gaarder, P. I. (1998) Airborne house dust particles and diesel exhaust particles as allergen carriers. Clin. Exp. Allergy 28: 702-708.

Osier, M.; Oberdörster, G. (1997) Intratracheal inhalation vs intratracheal instillation: differences in particle effects. Fundam. Appl. Toxicol. 40: 220-227.

Osier, M.; Baggs, R. B.; Oberdörster, G. (1997) Intratracheal instillation versus intratracheal inhalation: influence of cytokines on inflammatory response. In: Driscoll, K. E.; Oberdörster, G., eds. Proceedings of the sixth international meeting on the toxicology of natural and man-made fibrous and non-fibrous particles; September 1996; Lake Placid, NY. Environ. Health Perspect. Suppl. 105(5): 1265-1271.

Osornio-Vargas, Á. R.; Bonner, J. C.; Alfaro-Moreno, E.; Martínez, L.; García-Cuellar, C.; Rosales, S. P.; Miranda, J.; Rosas, I. (2003) Proinflammatory and cytotoxic effects of Mexico City air pollution particulate matter *in vitro* are dependent on particle size and composition. Environ. Health Perspect. 111: 1289-1293.

Pagan, I.; Costa, D. L.; McGee, J. K.; Richards, J. H.; Dye, J. A. (2003) Metals mimic airway epithelial injury induced by in vitro exposure to Utah Valley ambient particulate matter extracts. J. Toxicol. Environ. Health A 66: 1087-1112.

Palchak, R. B.; Cohen, R.; Ainslie, M.; Hoerner, C. L. (1988) Airborne endotoxin associated with industrial-scale production of protein products in gram-negative bacteria. Am. Ind. Hyg. Assoc. J. 49: 420-421.

Pepelko, W. E.; Mattox, J. K.; Yang, Y. Y.; Moore, W., Jr. (1980a) Pulmonary function and pathology in cats exposed 28 days to diesel exhaust. J. Environ. Pathol. Toxicol. 4: 449-458.

Pepelko, W. E.; Mattox, J.; Moorman, W. J.; Clark, J. C. (1980b) Pulmonary function evaluation of cats after one year of exposure to diesel exhaust. In: Pepelko, W. E.; Danner, R. M.; Clarke, N. A., eds. Health effects of diesel engine emissions: proceedings of an international symposium, v. 2; December 1979; Cincinnati, OH. Cincinnati, OH: U.S. Environmental Protection Agency, Health Effects Research Laboratory; pp. 757-765; EPA report no. EPA-600/9-80-057b. Available from: NTIS, Springfield, VA; PB81-173817.

Pepelko, W. E.; Mattox, J.; Moorman, W. J.; Clark, J. C. (1981) Pulmonary function evaluation of cats after one year of exposure to diesel exhaust. Environ. Int. 5: 373-376.

Pereira, M. A.; Connor, T. H.; Meyne, J.; Legator, M. S. (1981a) Metaphase analysis, micronuclei assay, and urinary mutagenicity assay of mice exposed to diesel emissions. Environ. Int. 5: 435-438.

Pereira, M. A.; Sabharwal, P. S.; Gordon, L.; Wyrobek, A. J. (1981b) The effect of diesel exhaust on sperm-shape abnormalities in mice. Environ. Int. 5: 459-460.

Pereira, M. A.; Sabharwal, P. S.; Kaur, P.; Ross, C. B.; Choi, A.; Dixon, T. (1981c) *In vivo* detection of mutagenic effects of diesel exhaust by short-term mammalian bioassays. Environ. Int. 5: 439-443.

Pereira, M. A.; McMillan, L.; Kaur, P.; Gulati, D. K.; Sabharwal, P. S. (1982) Effect of diesel exhaust emissions, particulates, and extract on sister chromatid exchange in transplacentally exposed fetal hamster liver. Environ. Mutagen. 4: 215-220.

Peters, A.; Wichmann, H. E.; Tuch, T.; Heinrich, J.; Heyder, J. (1997) Respiratory effects are associated with the number of ultrafine particles. Am. J. Respir. Crit. Care Med. 155: 1376-1383.

Petrovic, S.; Urch, B.; Brook, J.; Datema, J.; Purdham, J.; Liu, L.; Lukic, Z.; Zimmerman, B.; Tofler, G.; Downar, E.; Corey, P.; Tarlo, S.; Broder, I.; Dales, R.; Silverman, F. (2000) Cardiorespiratory effects of concentrated ambient PM2.5: a pilot study using controlled human exposures. Inhalation Toxicol. 12(suppl. 1): 173-188.

Piecková, E.; Kunová, Z. (2002) Indoor fungi and their ciliostatic metabolites. Ann. Agric. Environ. Med. 9: 59-63.

Piedimonte, G.; Hoffman, J. I. E.; Husseini, W. K.; Hiser, W. L.; Nadel, J. A. (1992) Effect of neuropeptides released from sensory nerves on blood flow in the rat airway microcirculation. J. Appl. Physiol. 72: 1563-1570.

Pierce, L. M.; Alessandrini, F.; Godleski, J. J.; Paulauskis, J. D. (1996) Vanadium-induced chemokine mRNA expression and pulmonary inflammation. Toxicol. Appl. Pharmacol. 138: 1-11.

Pinto, M.; Birnbaum, S. C.; Kadar, T.; Goldberg, G. M. (1979) Lung injury in mice induced by factors acting synergistically with inhaled particulate antigen. Clin. Immunol. Immunopathol. 13: 361-368.

Pohjola, S. K.; Lappi, M.; Honkanen, M.; Savela, K. (2003) Comparison of mutagenicity and calf thymus DNA adducts formed by the particulate and semivolatile fractions of vehicle exhausts. Environ. Mol. Mutagen. 42: 26-36.

Pope, C. A., III. (1989) Respiratory disease associated with community air pollution and a steel mill, Utah Valley. Am. J. Public Health 79: 623-628.

Pope, C. A., III. (1991) Respiratory hospital admissions associated with PM_{10} pollution in Utah, Salt Lake, and Cache Valleys. Arch. Environ. Health 46: 90-97.

Pope, C. A., III; Burnett, R. T.; Thun, M. J.; Calle, E. E.; Krewski, D.; Ito, K.; Thurston, G. D. (2002) Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. JAMA J. Am. Med. Assoc. 287: 1132-1141.

Prahalad, A. K.; Soukup, J. M.; Inmon, J.; Willis, R.; Ghio, A. J.; Becker, S.; Gallagher, J. E. (1999) Ambient air particles: effects on cellular oxidant radical generation in relation to particulate elemental chemistry. Toxicol. Appl. Pharmacol. 158: 81-91.

Pritchard, R. J.; Ghio, A. J.; Lehmann, J. R.; Winsett, D. W.; Tepper, J. S.; Park, P.; Gilmour, M. I.; Dreher, K. L.; Costa, D. L. (1996) Oxidant generation and lung injury after particulate air pollutant exposure increase with the concentrations of associated metals. Inhalation Toxicol. 8: 457-477.

Prows, D. R.; Leikauf, G. D. (2001) Quantitative trait analysis of nickel-induced acute lung injury in mice. Am. J. Respir. Cell Mol. Biol. 24: 740-746.

Prows, D. R.; Shertzer, H. G.; Daly, M. J.; Sidman, C. L.; Leikauf, G. D. (1997) Genetic analysis of ozone-induced acute lung injury in sensitive and resistant strains of mice. Nat. Genet. 17: 471-474.

Putnam, K. P.; Bombick, D. W.; Avalos, J. T.; Doolittle, D. J. (1999) Comparison of the cytotoxic and mutagenic potential of liquid smoke food flavourings, cigarette smoke condensate and wood smoke condensate. Food Chem. Toxicol. 37: 1113-1118.

Quay, J. L.; Reed, W.; Samet, J.; Devlin, R. B. (1998) Air pollution particles induce IL-6 gene expression in human airway epithelial cells via NF-κB activation. Am. J. Respir. Cell Mol. Biol. 19: 98-106.

Rannug, U.; Sundvall, A.; Westerholm, R.; Alsberg, T.; Stenberg, U. (1983) Some aspects of mutagenicity testing of the particulate phase and the gas phase of diluted and undiluted automobile exhaust. In: Waters, M. D.; Sandhu, S. S.; Lewtas, J.; Claxton, L.; Chernoff, N.; Newnow, S., eds. Short-term bioassays in the analysis of complex environmental mixtures III. New York, NY: Plenum Press; pp. 3-16. (Environmental science research: v. 27).

Renwick, L. C.; Donaldson, K.; Clouter, A. (2001) Impairment of alveolar macrophage phagocytosis by ultrafine particles. Toxicol. Appl. Pharmacol. 172: 119-127.

Rosas, I.; McCartney, H. A.; Payne, R. W.; Calderón, C.; Lacey, J.; Chapela, R.; Ruiz-Velazco, S. (1998) Analysis of the relationships between environmental factors (aeroallergens, air pollution, and weather) and asthma emergency admissions to a hospital in Mexico City. Allergy 53: 394-401.

Rose, C. S.; Martyny, J. W.; Newman, L. S.; Milton, D. K.; King, T. E., Jr.; Beebe, J. L.; McCammon, J. B.; Hoffman, R. E.; Kreiss, K. (1998) "Lifeguard lung": endemic granulomatous pneumonitis in an indoor swimming pool. Am. J. Public Health 88: 1795-1800.

Rothenberg, S. J.; Nagy, P. A.; Pickrell, J. A.; Hobbs, C. H. (1989) Surface area, adsorption, and desorption studies on indoor dust samples. Am. Ind. Hyg. Assoc. J. 50: 15-23.

Rudell, B.; Sandström, T.; Stjernberg, N.; Kolmodin-Hedman, B. (1990) Controlled diesel exhaust exposure in an exposure chamber: pulmonary effects investigated with bronchoalveolar lavage. J. Aerosol Sci. 21(suppl. 1): S411-S414.

Rudell, B.; Sandström, T.; Hammarström, U.; Ledin, M.-L.; Hörstedt, P.; Stjernberg, N. (1994) Evaluation of an exposure setup for studying effects of diesel exhaust in humans. Int. Arch. Occup. Environ. Health 66: 77-83.

Rudell, B.; Ledin, M.-C.; Hammarström, U.; Stjernberg, N.; Lundbäck, B.; Sandström, T. (1996) Effects on symptoms and lung function in humans experimentally exposed to diesel exhaust. Occup. Environ. Med. 53: 658-662.

Rudell, B.; Blomberg, A.; Helleday, R.; Ledin, M.-C.; Lundbäck, B.; Stjernberg, N.; Hörstedt, P.; Sandström, T. (1999) Bronchoalveolar inflammation after exposure to diesel exhaust: comparison between unfiltered and particle trap filtered exhaust. Occup. Environ. Med. 56: 527-534.

Russell, L. B.; Generoso, W. M.; Oakberg, E. F.; Russell, W. L.; Bangham, J. W.; Stelzner, K. F. (1980) Tests for heritable effects induced by diesel exhaust in the mouse. In: Biology division progress report: for period of October 1, 1978 - May 31, 1980. Oak Ridge, TN: Oak Ridge National Laboratory; report no. ORNL-5685.

Rylander, R. (1996) Airway responsiveness and chest symptoms after inhalation of endotoxin or (1 → 3)-β-D-glucan. Indoor Built Environ. 5: 106-111.

Sagai, M.; Furuyama, A.; Ichinose, T. (1996) Biological effects of diesel exhaust particles (DEP). III. Pathogenesis of asthma like symptoms in mice. Free Radical Biol. Med. 21: 199-209.

Saldiva, P. H. N.; Clarke, R. W; Coull, B. A.; Stearns, R. C.; Lawrence, J.; Krishna-Murthy, G. G.; Diaz, E.; Koutrakis, P.; Suh, H.; Tsuda, A.; Godleski, J. J. (2002) Lung inflammation induced by concentrated ambient air particles is related to particle composition. Am. J. Respir. Crit. Care Med. 165: 1610-1617.

Salmeen, I.; Durisin, A. M.; Prater, T. J.; Riley, T.; Schuetzle, D. (1982) Contribution of 1-nitropyrene to direct-acting Ames assay mutagenicities of diesel particulate extracts. Mutat. Res. 104: 17-23.

Salvi, S.; Blomberg, A.; Rudell, B.; Kelly, F.; Sandström, T.; Holgate, S. T.; Frew, A. (1999) Acute inflammatory responses in the airways and peripheral blood after short-term exposure to diesel exhaust in healthy human volunteers. Am. J. Respir. Crit. Care Med. 159: 702-709.

Salvi, S. S.; Nordenhall, C.; Blomberg, A.; Rudell, B.; Pourazar, J.; Kelly, F. J.; Wilson, S.; Sandström, T.; Holgate, S. T.; Frew, A. J. (2000) Acute exposure to diesel exhaust increases IL-8 and GRO-αproduction in healthy human airways. Am. J. Respir. Crit. Care Med. 161: 550-557.

Samet, J. M.; Reed, W.; Ghio, A. J.; Devlin, R. B.; Carter, J. D.; Dailey, L. A.; Bromberg, P. A.; Madden, M. C. (1996) Induction of prostaglandin H synthase 2 in human airway epithelial cells exposed to residual oil fly ash. Toxicol. Appl. Pharmacol. 141: 159-168.

Samet, J. M.; Stonehuerner, J.; Reed, W.; Devlin, R. B.; Dailey, L. A.; Kennedy, T. P.; Bromberg, P. A.; Ghio, A. J. (1997) Disruption of protein tyrosine phosphate homeostasis in bronchial epithelial cells exposed to oil fly ash. Am. J. Physiol. 272: L426-L432.

Samet, J. M.; Graves, L. M.; Quay, J.; Dailey, L. A.; Devlin, R. B.; Ghio, A. J.; Wu, W.; Bromberg, P. A.; Reed, W. (1998) Activation of MAPKs in human bronchial epithelial cells exposed to metals. Am. J. Physiol. 275: L551-L558.

Samet, J. M.; Ghio, A. J.; Costa, D. L.; Madden, M. C. (2000) Increased expression of cyclooxygenase 2 mediates oil fly ash-induced lung injury. Exp. Lung Res. 26: 57-69.

Sarangapani, R.; Wexler, A. S. (1996) Growth and neutralization of sulfate aerosols in human airways. J. Appl. Physiol. 81: 480-490.

Sato, H.; Sone, H.; Sagai, M.; Suzuki, K. T.; Aoki, Y. (2000) Increase in mutation frequency in lung of Big Blue® rat by exposure to diesel exhaust. Carcinogenesis 21: 653-661.

Schäppi, G. F.; Taylor, P. E.; Pain, M. C. F.; Cameron, P. A.; Dent, A. W.; Staff, I. A.; Suphioglu, C. (1999) Concentrations of major grass group 5 allergens in pollen grains and atmospheric particles: implications for hay fever and allergic asthma sufferers sensitized to grass pollen allergens. Clin. Exp. Allergy 29: 633-641.

Schlesinger, R. B.; Cassee, F. (2003) Atmospheric secondary in organic particulate matter: the toxicological perspective as a basis for health effects risk assessment. Inhalation Toxicol. 15: 197-235.

Schlüter, T.; Berg, I.; Dörger, M.; Gercken, G. (1995) Effect of heavy metal ions on the release of reactive oxygen intermediates by bovine alveolar macrophages. Toxicology 98: 47-55.

Schuetzle, D.; Frazier, J. A. (1986) Factors influencing the emission of vapor and particulate phase components from diesel engines. In: Ishinishi, N.; Koizumi, A.; McClellan, R. O.; Stöber, W., eds. Carcinogenic and mutagenic effects of diesel engine exhaust: proceedings of the international satellite symposium on toxicological effects of emissions from diesel engines; July; Tsukuba Science City, Japan. Amsterdam, The Netherlands: Elsevier Science Publishers B. V.; pp. 41-63. (Developments in toxicology and environmental science: v. 13).

Schuetzle, D.; Lewtas, J. (1986) Bioassay-directed chemical analysis in environmental research. Anal. Chem. 58: 1060A-1076A.

Schuetzle, D.; Perez, J. M. (1983) Factors influencing the emissions of nitrated-polynuclear aromatic hydrocarbons (nitro-PAH) from diesel engines. J. Air Pollut. Control Assoc. 33: 751-755.

Schwartz, S. E. (1984) Gas- and aqueous-phase chemistry of HO_2 in liquid water clouds. J. Geophys. Res. [Atmos.] 89: 11,589-11,598.

Seagrave, J. C.; Nikula, K. J. (2000) Multiple modes of responses to air pollution particulate materials in A549 alveolar type II cells. In: Grant, L. D., ed. PM2000: particulate matter and health. Inhalation Toxicol. 12(suppl. 4): 247-260.

Seagrave, J.; McDonald, J. D.; Gigliotti, A. P.; Nikula, K. J.; Seilkop, S. K.; Gurevic, M.; Mauderly, J. L. (2002) Mutagenicity and in vivo toxicity of combined particulate and semivolatile organic fractions of gasoline and diesel engine emissions. Toxicol. Sci. 70: 212-226.

Seaton, A.; MacNee, W.; Donaldson, K.; Godden, D. (1995) Particulate air pollution and acute health effects. Lancet (8943): 176-178.

Seemayer, N. H.; Happel, A.; Behrendt, H.; Hadnagy, W.; Tomingas, R. (1990) Comparison of cytotoxicity of airborne particulates to rat and human macrophages. J. Aerosol Sci. 21: 387-391.

Seemayer, N. H.; Hornberg, C. (1998) Malignant transformation of Syrian hamster kidney cells in vitro by interaction of airborne particulates and simian virus (SV-) 40. Toxicol. Lett. 96/97: 231-238.

Shirnamé-Moré, L. (1995) Genotoxicity of diesel emissions. Part 1: mutagenicity and other genetic effects. Diesel exhaust: a critical analysis of emissions, exposure, and health effects. A special report of the Institute's Working Group. Cambridge, MA: Health Effects Institute, pp. 222-242.

Shukla, A.; Timblin, C.; BeruBe, K.; Gordon, T.; McKinney, W.; Driscoll, K.; Vacek, P.; Mossman, B. T. (2000) Inhaled particulate matter causes expression of nuclear factor (NF)-κB-related genes and oxidant-dependent NF-κB activation *in vitro*. Am. J. Respir. Cell Mol. Biol. 23: 182-187.

Siak, J. S.; Chan, T. L.; Lees, P. S. (1981) Diesel particulate extracts in bacterial test systems. Environ. Int. 5: 243-248.

Silbajoris, R.; Ghio, A. J.; Samet, J. M.; Jaskot, R.; Dreher, K. L.; Brighton, L. E. (2000) In vivo and in vitro correlation of pulmonary map kinase activation following metallic exposure. Inhalation Toxicol. 12: 453-468.

Sindhu, R. K.; Mautz, W. J.; Kikkawa, Y. (1998) Chronic exposure to ozone and nitric acid vapor results in increased levels of rat pulmonary putrescine. Arch. Toxicol. 72: 445-449.

Sioutas, C.; Koutrakis, P.; Burton, R. M. (1995a) A technique to expose animals to concentrated fine ambient aerosols. Environ. Health Perspect. 103: 172-177.

Sioutas, D.; Koutrakis, P.; Ferguson, S. T.; Burton, R. M. (1995b) Development and evaluation of a prototype ambient particle concentrator for inhalation exposure studies. Inhalation Toxicol. 7: 633-644.

Sioutas, C.; Kim, S.; Chang, M.; Terrell, L. L.; Gong, H., Jr. (2000) Field evaluation of a modified DataRAM MIE scattering monitor for real-time $PM_{2.5}$ mass concentration measurements. Atmos. Environ. 34: 4829-4838.

Sjögren, B. (1997) Occupational exposure to dust: inflammation and ischaemic heart disease. Occup. Environ. Med. 54: 466-469.

Sjögren, M.; Li, H.; Banner, C.; Rafter, J.; Westerholm, R.; Rannug, U. (1996) Influence of physical and chemical characteristics of diesel fuels and exhaust emissions on biological effects of particle extracts: a multivariate statistical analysis of ten diesel fuels. Chem. Res. Toxicol. 9: 197-207.

Smith, K. R.; Aust, A. E. (1997) Mobilization of iron from urban particulates leads to generation of reactive oxygen species *in vitro* and induction of ferritin synthesis in human lung epithelial cells. Chem. Res. Toxicol. 10: 828-834.

Smith, B. A.; Fullerton, N. F.; Aidoo, A.; Heflich, R. H.; Beland, F. A. (1993) DNA adduct formation in relation to lymphocyte mutations and lung tumor induction in F344 rats treated with the environmental pollutant 1,6-dinitropyrene. Environ. Health Perspect. 99: 277-280.

Smith, K. R.; Veranth, J. M.; Lighty, J. S.; Aust, A. E. (1998) Mobilization of iron from coal fly ash was dependent upon the particle size and the source of coal. Chem. Res. Toxicol. 11: 1494-1500.

Soukup, J. M.; Becker, S. (2001) Human alveolar macrophage responses to air pollution particulates are associated with insoluble components of coarse material, including particulate endotoxin. Toxicol. Appl. Pharmacol. 171: 20-26.

Soukup, J. M.; Ghio, A. J.; Becker, S. (2000) Soluble components of Utah Valley particulate pollution alter alveolar macrophage function in vivo and in vitro. Inhalation Toxicol. 12: 401-414.

Spengler, J. D.; Thurston, G. D. (1983) Mass and elemental composition of fine and coarse particles in six U.S. cities. J. Air Pollut. Control Assoc. 33: 1162-1171.

Śpiewak, R.; Krysińska-Traczyk, E.; Sitkowska, J.; Dutkiewicz, J. (1996a) Microflora of allergenic pollens–a preliminary study. Ann. Agric. Environ. Med. 3: 127-130.

Śpiewak, R.; Skórska, C.; Prażmo, Z.; Dutkiewicz, J. (1996b) Bacterial endotoxin associated with pollen as a potential factor aggravating pollinosis. Ann. Agric. Environ. Med. 3: 57-59.

Steerenberg, P. A.; Zonnenberg, J. A. J.; Dormans, J. A. M. A.; Joon, P. N. T.; Wouters, I. M.; Van Bree, L.; Scheepers, P. T. J.; Van Loveren, H. (1998) Diesel exhaust particles induced release of interleukin 6 and 8 by (primed) human bronchial epithelial cells (BEAS 2B) in vitro. Exp. Lung Res. 24: 85-100.

Steerenberg, P. A.; Dormans, J. A. M. A.; Van Doorn, C. C. M.; Middendorp, S.; Vos, J. G.; Van Loveren, H. (1999) A pollen model in the rat for testing adjuvant activity of air pollution components. Inhalation Toxicol. 11: 1109-1122.

Steerenberg, P. A.; Withagen, C. E.; Dormans, J. A. M. A.; Van Dalen, W. J.; Van Loveren, H.; Casee, F. R. (2003) Adjuvant activity of various diesel exhaust and ambient particle in two allergic models. J. Toxicol. Environ. Health A 66: 1421-1439.

Strandell, M.; Zakrisson, S.; Alsberg, T.; Westerholm, R.; Winquist, L.; Rannug, U. (1994) Chemical analysis and biological testing of a polar fraction of ambient air, diesel engine, and gasoline engine particulate extracts. In: Symposium of risk assessment of urban air: emissions, exposure, risk indentification, and risk quantitation; May-June 1992; Stockholm, Sweden. Environ. Health Perspect. 102(suppl. 4): 85-92.

Stringer, B.; Kobzik, L. (1996) Alveolar macrophage uptake of the environmental particulate titanium dioxide: role of surfactant components. Am. J. Respir. Cell Mol. Biol. 14: 155-160.

Stringer, B.; Kobzik, L. (1998) Environmental particulate-mediated cytokine production in lung epithelial cells (A549): role of preexisting inflammation and oxidant stress. J. Toxicol. Environ. Health Part A 55: 31-44.

Stringer, B.; Imrich, A.; Kobzik, L. (1996) Lung epithelial cell (A549) interaction with unopsonized environmental particulates: quantitation of particle-specific binding and IL-8 production. Exp. Lung Res. 22: 495-508.

Su, W.-Y.; Jaskot, R. H.; Richards, J.; Abramson, S. R.; Woessner, J. F., Jr.; Yu, W.-H.; Dreher, K. L. (2000a) Induction of pulmonary matrilysin expression by combustion and ambient air particles. Am. J. Physiol. 279: L152-L160.

Su, W.-Y.; Jaskot, R. H.; Dreher, K. L. (2000b) Particulate matter induction of pulmonary gelatinase A, gelatinase B, tissue inhibitor of metalloproteinase expression. In: Phalen, R. F., ed. Inhalation Toxicology: proceedings of the third colloquium on particulate air pollution and human health (second special issue); June, 1999; Durham, NC. Inhalation Toxicol. 12(suppl. 2): 105-119.

Sun, G.; Crissman, K.; Norwood, J.; Richards, J.; Slade, R.; Hatch, G. E. (2001) Oxidative interactions of synthetic lung epithelial lining fluid with metal-containing particulate matter. Am. J. Physiol. 281: L807-L815.

Suwa, T.; Hogg, J. C.; Quinlan, K. B.; Ohgami, A.; Vincent, R.; Van Eeden, S. F. (2002) Particulate air pollution induces progression of atherosclerosis. J. Am. Coll. Cardiol. 39: 935-942.

Takano, H.; Yoshikawa, T.; Ichinose, T.; Miyabara, Y.; Imaoka, K.; Sagai, M. (1997) Diesel exhaust particles enhance antigen-induced airway inflammation and local cytokine expression in mice. Am. J. Respir. Crit. Care Med. 156: 36-42.

Takano, H.; Ichinose, T.; Miyabara, Y.; Shibuya, T.; Lim, H.-B.; Yoshikawa, T. Sagai, M. (1998) Inhalation of diesel exhaust enhances allergen-related eosinophil recruitment and airway hyperresponsiveness in mice. Toxicol. Appl. Pharmacol. 150: 328-337.

Tan, W. C.; Qiu, D.; Liam, B. L.; Ng, T. P.; Lee, S. H.; Van Eeden, S. F.; D'Yachkova, Y.; Hogg, J. C. (2000) The human bone marrow response to acute air pollution caused by forest fires. Am. J. Respir. Crit. Care Med. 161: 1213-1217.

Targonski, P. V.; Persky, V. W.; Ramekrishnan, V. (1995) Effect of environmental molds on risk of death from asthma during the pollen season. J. Allergy Clin. Immunol. 95: 955-961.

Taylor, P. E.; Flagan, R. C.; Valenta, R.; Glovsky, M. M. (2002) Release of allergens as respirable aerosols: a link between grass pollen and asthma. J. Allergy Clin. Immunol. 109: 51-56.

Terashima, T.; Wiggs, B.; English, D.; Hogg, J. C.; Van Eeden, S. F. (1997) Phagocytosis of small carbon particles (PM_{10}) by alveolar macrophages stimulates the release of polymorphonuclear leukocytes from bone marrow. Am. J. Respir. Crit. Care Med. 155: 1441-1447.

Terashima, T.; Amakawa, K.; Matsumaru, A.; Van Eeden, S.; Hogg, J. C.; Yamaguchi, K. (2001) BAL induces an increase in peripheral blood neutrophils and cytokine levels in healthy volunteers and patients with pneumonia. Chest 119: 1724-1729.

Thorn, J.; Rylander, R. (1998a) Inflammatory response after inhalation of bacterial endotoxin assessed by the induced sputum technique. Thorax 53: 1047-1052.

Thorn, J.; Rylander, R. (1998b) Airways inflammation and glucan in a rowhouse area. Am. J. Respir. Crit. Care Med. 157: 1798-1803.

Thurston, G. D.; Lippmann, M.; Scott, M. B.; Fine, J. M. (1997) Summertime haze air pollution and children with asthma. Am. J. Respir. Crit. Care Med. 155: 654-660.

Timblin, C.; BeruBe, K.; Chrug, A.; Driscoll, K.; Gordon, T.; Hemenway, D.; Walsh, E.; Cummins, A. B.; Vacek, P.; Mossman, B. (1998) Ambient particulate matter causes activation of the c-*jun* kinase/stress-activated protein kinase cascade and DNA synthesis in lung epithelial cells. Cancer Res. 58: 4543-4547.

Tofler, G. H.; Brezinski, D.; Schafer, A. I.; Czeisler, C. A.; Rutherford, J. D.; Willich, S. N.; Gleason, R. E.; Williams, G. H.; Muller, J. E. (1987) Concurrent morning increase in platelet aggregability and the risk of myocardial infarction and sudden cardiac death. N. Engl. J. Med. 316: 1514-1518.

Tomatis, L. (1990) Air pollution and cancer: an old and new problem. In: Tomatis, L., ed. Air pollution and human cancer. Berlin, Germany: Springer-Verlag; pp. 1-7.

Tsien, A.; Diaz-Sanchez, D.; Ma, J.; Saxon, A. (1997) The organic component of diesel exhaust particles and phenanthrene, a major polyaromatic hydrocarbon constituent, enhances IgE production by IgE-secreting EBV-transformed human B cells *in vitro*. Toxicol. Appl. Pharmacol. 142: 256-263.

Tucker, J. D.; Xu, J.; Stewart, J.; Baciu, P. C.; Ong, T.-M. (1986) Detection of sister chromatid exchanges induced by volatile genotoxicants. Teratog. Carcinog. Mutagen. 6: 15-21.

Tuomi, T.; Engström, B.; Niemelä, R.; Svinhufvud, J.; Reijula, K. (2000) Emission of ozone and organic volatiles from a selection of laser printers and photocopiers. Appl. Occup. Environ. Hyg. 15: 629-634.

Turpin, B. J. (1999) Options for characterizing organic particulate matter. Environ. Sci. Technol. 33: 76A-79A.

Ulrich, M. M. W.; Alink, G. M.; Kumarathasan, P.; Vincent, R.; Boere, A. J.; Cassee, F. R. (2002) Health effects and time course of particulate matter on the cardiopulmonary system in rats with lung inflammation. J. Toxicol. Environ. Health Part A 65: 1571-1595.

U.S. Environmental Protection Agency. (1982) Air quality criteria for particulate matter and sulfur oxides. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; EPA report no. EPA-600/8-82-029aF-cF. 3v. Available from: NTIS, Springfield, VA; PB84-156777.

U.S. Environmental Protection Agency. (1989) An acid aerosols issue paper: health effects and aerometrics. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; EPA report no. EPA-600/8-88-005F. Available from: NTIS, Springfield, VA; PB91-125864.

U.S. Environmental Protection Agency. (1996a) Air quality criteria for particulate matter. Research Triangle Park, NC: National Center for Environmental Assessment-RTP Office; report nos. EPA/600/P-95/001aF-cF. 3v.

U.S. Environmental Protection Agency. (1996b) Ambient levels and noncancer health effects of inhaled crystalline and amorphous silica: health issue assessment. Research Triangle Park, NC: National Center for Environmental Assessment; EPA report no. EPA/600/R-95/115.

U.S. Environmental Protection Agency. (2002) Health assessment document for diesel engine exhaust. Washington, DC: Office of Research and Development, National Center for Environmental Assessment; report no. EPA/600/8-90/057F. Available: http://cfpub.epa.gov/ncea/ [22 May, 2003].

Utell, M. J.; Morrow, P. E.; Hyde, R. W. (1983) Latent development of airway hyperreactivity in human subjects after sulfuric acid aerosol exposure. J. Aerosol Sci. 14: 202-205.

Vallyathan, V.; Shi, X.; Dalal, N. S.; Irr, W.; Castranova, V. (1988) Generation of free radicals from freshly fractured silica dust: potential role in acute silica-induced lung injury. Am. Rev. Respir. Dis. 138: 1213-1219.

Van Eeden, S. F.; Tan, W. C.; Suwa, T.; Mukae, H.; Terashima, T.; Fujii, T.; Qui, D.; Vincent, R.; Hogg, J. C. (2001) Cytokines involved in the systemic inflammatory response induced by exposure to particulate matter air pollutants (PM_{10}). Am. J. Respir. Crit. Care Med. 164: 826-830.

Van Maanen, J. M.; Borm, P. J.; Knaapen, A.; Van Herwijnen, M.; Schilderman, P. A.; Smith, K. R.; Aust, A. E.; Tomatis, M.; Fubini, B. (1999) *in vitro* effects of coal fly ashes: hydroxyl radical generation, iron release, and DNA damage and toxicity in rat lung epithelial cells. Inhalation Toxicol. 11: 1123-1141.

Van Zijverden, M.; Granum, B. (2000) Adjuvant activity of particulate pollutants in different mouse models. Toxicology 152: 69-77.

Van Zijverden, M.; Van der Pijl, A.; Bol, M.; Van Pinxteren, F. A.; De Haar, C.; Penninks, A. H.; Van Loveren, H.; Pieters, R. (2000) Diesel exhaust, carbon black, and silica particles display distinct Th1/Th2 modulating activity. Toxicol. Appl. Pharmacol. 168: 131-139.

Van Zijverden, M.; De Haar, C.; Van Beelen, A.; Van Loveren, H.; Penninks, A.; Pieters, R. (2001) Co-administration of antigen and particles optimally stimulates the immune response in an intranasal administration model in mice. Toxicol. Appl. Pharmacol. 177: 174-178.

Veronesi, B.; Oortgiesen, M. (2001) Neurogenic inflammation and particulate matter (PM) air pollutants. Neurotoxicology 22: 795-810.

Veronesi, B.; Oortgiesen, M.; Carter, J. D.; Devlin, R. B. (1999a) Particulate matter initiates inflammatory cytokine release by activation of capsaicin and acid receptors in a human bronchial epithelial cell line. Toxicol. Appl. Pharmacol. 154: 106-115.

Veronesi, B.; Carter, J. D.; Devlin, R. B.; Simon, S. A.; Oortgiesen, M. (1999b) Neuropeptides and capsaicin stimulate the release of inflammatory cytokines in a human bronchial epithelial cell line. Neuropeptides 33: 447-456.

Veronesi, B.; Oortgiesen, M.; Roy, J.; Carter, J. D.; Simon, S. A.; Gavett, S. H. (2000) Vanilloid (capsaicin) receptors influence inflammatory sensitivity in response to particulate matter. Toxicol. Appl. Pharmacol. 169: 66-76.

Veronesi, B.; De Haar, C.; Roy, J.; Oortgiesen, M. (2002a) Particulate matter inflammation and receptor sensitivity are target cell specific. Inhalation Toxicol. 14: 159-183.

Veronesi, B.; De Haar, C.; Lee, L.; Oortgiesen, M. (2002b) The surface charge of particulate matter related to cytokine release in human bronchial epithelial cells (BEAS-2B). Toxicol. Appl. Pharmacol. 178: 144-154.

Veronesi, B.; Wei, G.; Zeng, J. Q.; Oortgiesen, M. (2003) Electrostatic charge activates inflammatory vanilloid (VR1) receptors. Neurotoxicology 24: 463-473.

Vincent, R.; Bjarnason, S. G.; Adamson, I. Y. R.; Hedgecock, C.; Kumarathasan, P.; Guénette, J.; Potvin, M.; Goegan, P.; Bouthillier, L. (1997) Acute pulmonary toxicity of urban particulate matter and ozone. Am. J. Pathol. 151: 1563-1570.

Vincent, R.; Kumarathasan, P.; Goegan, P.; Bjarnason, S. G.; Guénette, J.; Bérubé, D.; Adamson, I. Y.; Desjardins, S.; Burnett, R. T.; Miller, F. J.; Battistini, B. (2001) Inhalation toxicology of urban ambient particulate matter: acute cardiovascular effect in rats. Boston, MA: Health Effects Institute; research report no. 104. Available: http://www.healtheffects.org/Pubs/Vincent.pdf [29 January 02].

Vinegar, A.; Carson, A. I.; Pepelko, W. E. (1980) Pulmonary function changes in Chinese hamsters exposed six months to diesel exhaust. In: Pepelko, W. E.; Danner, R. M.; Clarke, N. A., eds. Health effects of diesel engine emissions: proceedings of an international symposium, v. 2; December, 1979; Cincinnati, OH. Cincinnati, OH: U.S. Environmental Protection Agency, Health Effects Research Laboratory; pp. 749-756; EPA report no. EPA-600/9-80-057b. Available from: NTIS, Springfield, VA; PB81-173817.

Vinegar, A.; Carson, A.; Pepelko, W. E.; Orthoefer, J. O. (1981a) Effect of six months of exposure to two levels of diesel exhaust on pulmonary function of Chinese hamsters. Fed. Proc. 40: 593.

Vinegar, A.; Carson, A.; Pepelko, W. E. (1981b) Pulmonary function changes in Chinese hamsters exposed six months to diesel exhaust. Environ. Int. 5: 369-371.

Vinitketkumnuen, U.; Kalayanamitra, K.; Chewonarin, T.; Kamens, R. (2002) Particulate matter, PM10 & PM2.5 levels, and airborne mutagenicity in Chiang Mai, Thailand. Mutat. Res. 519: 121-131.

Vogelzang, P. F. J.; Van Der Gulden, J. W. J.; Folgering, H.; Kolk, J. J.; Heederik, D.; Preller, L.; Tielen, M. J. M.; Van Schayck, C. P. (1998) Endotoxin exposure as a major determinant of lung function decline in pig farmers. Am. J. Respir. Crit. Care Med. 157: 15-18.

Wagner, J. G.; Hotchkiss, J. A.; Harkema, J. R. (2001) Effects of ozone and endotoxin coexposure on rat airway epithelium: potentiation of toxicant-induced alterations. Environ. Health Perspect. 109(suppl. 4): 591-598.

Walters, D. M.; Breysse, P. N.; Wills-Karp, M. (2001) Ambient urban Baltimore particulate-induced airway hyperresponsiveness and inflammation in mice. Am. J. Respir. Crit. Care Med. 164: 1438-1443.

Watkinson, W. P.; Campen, M. J.; Costa, D. L. (1998) Cardiac arrhythmia induction after exposure to residual oil fly ash particles in a rodent model of pulmonary hypertension. Toxicol. Sci. 41: 209-216.

Watkinson, W. P.; Campen, M. J.; Nolan, J. P.; Kodavanti, U. P.; Dreher, K. L.; Su, W.-Y.; Highfill, J. W.; Costa, D. L. (2000a) Cardiovascular effects following exposure to particulate matter in healthy and cardiopulmonary-compromised rats. In: Heinrich, U.; Mohr, U., eds. Relationships between acute and chronic effects of air pollution. Washington, DC: ISLI Press, pp. 447-463.

Watkinson, W. P.; Campen, M. J.; Dreher, K. L.; Su, W.-Y.; Kodavanti, U.P.; Highfill, J. W.; Costa, D. L. (2000b) Thermoregulatory effects following exposure to particulate matter in healthy and cardiopulmonary-compromised rats. J. Therm. Biol. 25: 131-137.

Watkinson, W. P.; Campen, M. J.; Nolan, J. P.; Costa, D. L. (2001) Cardiovascular and systemic responses to inhaled pollutants in rodents: effects of ozone and particulate matter. Environ. Health Perspect. 109(suppl. 4): 539-546.

Waxman, M. B.; Cameron, D.; Wald, R. W. (1994) Vagal activity and ventricular tachyarrhythmias. In: Levy, M.; Schwartz, P. Vagal control of the heart: experimental basis and clinical implications. Armonk, NY: Futura Publishing Co.; pp. 579-612.

Wellenius, G. A.; Saldiva, P. H. N.; Batalha, J. R. F.; Murthy, G. G. K.; Coull, B. A.; Verrier, R. L.; Godleski, J. J. (2002) Electrocardiographic changes during exposure to residual oil fly ash (ROFA) particles in a rat model of myocardial infarction. Toxicol. Sci. 66: 327-335.

Wesselkamper, S. C.; Prows, D. R.; Biswas, P.; Willeke, K.; Bingham, E.; Leikauf, G. D. (2000) Genetic susceptibility to irritant-induced acute lung injury in mice. Am. J. Physiol. 279: L575-L582.

Wexler, A. S.; Sarangapani, R. (1998) Particles do not increase vapor deposition in human airways. J. Aerosol Sci. 29: 197-204.

Wheatley, L. M.; Platts-Mills, T. A. E. (1996) Perennial allergens and the asthma epidemic. Sci. Med. 3: 6-13.

Willich, S. N.; Levy, D.; Rocco, M. B.; Tofler, G. H.; Stone, P. H.; Muller, J. E. (1987) Circadian variation in the incidence of sudden cardiac death in the Framingham Heart Study population. Am. J. Cardiol. 60: 801-806.

Wilson, W. E. (1995) Aerosol exposure, physics, and chemistry. Inhalation Toxicol. 7: 769-772.

Wilson, A. F.; Novey, H. S.; Berke, R. A.; Surprenant, E. L. (1973) Deposition of inhaled pollen and pollen extract in human airways. N. Engl. J. Med. 288: 1056-1058.

Wolff, R. K.; Gray, R. L. (1980) Tracheal clearance of particles. In: Diel, J. H.; Bice, D. E.; Martinez, B. S., eds. Inhalation Toxicology Research Institute annual report: 1979-1980. Albuquerque, NM: Lovelace Biomedical and Environmental Research Institute; p. 252; report no. LMF-84.

Wolff, R. K.; Henderson, R. F.; Snipes, M. B.; Griffith, W. C.; Mauderly, J. L.; Cuddihy, R. G.; McClellan, R. O. (1987) Alterations in particle accumulation and clearance in lungs of rats chronically exposed to diesel exhaust. Fundam. Appl. Toxicol. 9: 154-166.

Wong, D.; Mitchell, C. E.; Wolff, R. K.; Mauderly, J. L.; Jeffrey, A. M. (1986) Identification of DNA damage as a result of exposure of rats to diesel engine exhaust. Carcinogenesis 7: 1595-1597.

World Health Organization. (1993) Biomarkers and risk assessment: concepts and principles. Geneva, Switzerland: World Health Organization. (Environmental health criteria: v. 155).

Wu, W.; Samet, J. M.; Ghio, A. J.; Devlin, R. B. (2001) Activation of the EGF receptor signaling pathway in human airway epithelial cells exposed to Utah Valley PM. Am. J. Physiol. 281: L483-L489.

Yang, C. S.; Johanning, E. (2002) Airborne fungi and mycotoxins. In: Hurst, C. J., Crawford, R. L.; Knudsen, G. R.; McInerney, M. J.; Stetzenbach, L. D. eds. Manual of environmental microbiology. 2nd ed. Washington, DC: American Society for Microbiology; pp. 839-852.

Young, R. S.; Jones, A. M.; Nicholls, P. J. (1998) Something in the air: endotoxins and glucans as environmental troublemakers. J. Pharm. Pharmacol. 50: 11-17.

Zelikoff, J. T.; Sisco, M.; Cohen, M. D.; Frampton, M. W.; Utell, M. J; Schlesinger, R. B. (1994) Interspecies comparison of immunotoxicity of inhaled sulfuric acid. II. New Zealand white rabbits. In: 1994 international conference sponsored by the American Lung Association and the American Thoracic Society; May; Boston, MA. Am. J. Respir. Crit. Care Med. 149: A621.

Zelikoff, J. T.; Frampton, M. W.; Cohen, M. D.; Morrow, P. E.; Sisco, M.; Tsai, Y.; Utell, M. J.; Schlesinger, R. B. (1997) Effects of inhaled sulfuric acid aerosols on pulmonary immunocompetence: a comparative study in humans and animals. Inhalation Toxicol. 9: 731-752.

Zelikoff, J. T.; Chen, L. C.; Cohen, M. D.; Fang, K.; Gordon, T.; Li, Y.; Nadziejko, C.; Schlesinger, R. B. (2003) Effects of inhaled ambient particulate matter on pulmonary antimicrobial immune defense. Inhalation Toxicol. 15: 131-150.

Zhang, Z.; Shen, H. M.; Zhang, Q. F.; Ong, C.-N. (2000) Involvement of oxidative stress in crystalline silica-induced cytotoxicity and genotoxicity in rat alveolar macrophages. Environ. Res. 82: 245-252.

Zock, J.-P.; Hollander, A.; Heederik, D.; Douwes, J. (1998) Acute lung function changes and low endotoxin exposures in the potato processing industry. Am. J. Ind. Med. 33: 384-391.

APPENDIX 7A. RAT-TO-HUMAN DOSE EXTRAPOLATION

7A.1 INTRODUCTION

As noted at the outset of Chapter 7, the 1997 revisions to the PM NAAQS (Federal Register, 1997) were largely based on newly emerging epidemiologic evidence that showed associations between (a) ambient PM measured at community monitoring stations and (b) increased risks for mortality and morbidity (especially cardiorespiratory-related) among human populations exposed to contemporary U.S. ambient PM concentrations. However, little experimental toxicology data from controlled laboratory animal or human exposure studies were then available that provided more direct evidence supporting the plausibility of the PM-mortality/morbidity relationships observed at relatively low ambient PM concentrations.

Since completion of the 1996 PM AQCD supporting the 1997 PM NAAQS decisions, numerous hypotheses have been advanced and extensive new toxicologic evidence generated with regard to possible pathophysiologic mechanisms by which PM exposures (even at low ambient concentrations) might induce increased morbidity and/or mortality. Much of the new toxicologic data (as addressed in Chapter 7) has involved either (a) experimental in vivo exposures of human subjects and/or laboratory animals via inhalation exposures and/or instillation of PM materials into the lung or trachea or (b) in vitro exposures of various (mostly respiratory tract) cells or tissues to diverse types of PM. The exposure conditions used in these studies were typically different from those experienced through inhalation of ambient PM. Therefore, the relevance of the effects observed under experimental conditions compared to the effects observed in humans following ambient PM exposures needed evaluation.

To address this issue, the EPA has conducted analyses of relationships between rat and human lung doses predicted for various exposure scenarios ranging from ambient PM exposures to PM instillations into the lung. This appendix begins in Section 7A.2 by presenting basic principles such as the relationship between PM exposure and PM dose in the lung. The section then introduces the concept of determining PM exposures for rats which lead to PM doses in the rat lung equivalent to those received by humans. The mathematical model used herein for

interspecies comparisons is discussed in Section 7A.3. Particle dosimetry in the lung was described in Chapter 6; however, additional details regarding differences in particle dosimetry between rats and humans are discussed in Section 7A.4. Section 7A.5 expands on the equivalent dose concept and illustrates the variability in PM exposure concentrations that could be required for rats to have the same dose as a human as a function of dose metric, normalizing factor, and level of human exertion. Section 7A.5 provides information that can be used to estimate the exposure concentrations required to give a rat a dose equivalent to the dose that would be received by a human exposed to various levels of ambient PM. In Section 7A.7, the dosimetric modeling techniques discussed earlier are used to compare doses received by rats and humans from experimental exposures. That dosimetry alone cannot explain all differences in response between rats and humans is discussed in Section 7A.6 and again in Section 7A.8. Readers not interested in the comprehensive analyses of dosimetric issues presented in Sections 7A.2 through 7A.6 may wish to skip to Section 7A.7, where several specific studies are compared and contrasted and then further discussed in Section 7A.8. Finally, conclusions based on the analyses are presented in Section 7A.9.

7A.2 QUANTITATIVE INTERSPECIES EXTRAPOLATION

Much of the information on the toxicity of PM comes from studies in which laboratory rats were exposed to PM by inhalation or instillation. For optimal use of these toxicologic data, estimates of PM exposures that would result in similar human doses are needed. The premise of such comparisons is that comparable doses should cause comparable effects. It is the tissue dose, rather than exposure per se, that is responsible for observed responses, making it essential to first consider the dose to the lung that might occur during an exposure to PM.

The rate of deposition in a specific region of the respiratory tract resulting from the inhalation of PM may be given as

$$\dot{D}_r(t) = C(t) \times f(t) \times V_T(t) \times DF_r(t) \qquad (7A\text{-}1)$$

where: $\dot{D}_r$ is the rate of deposition per unit time in region r; C is the PM exposure concentration and may be expressed as particle mass, surface area, or number per unit volume; f is breathing frequency in breaths per unit time; V_T is tidal volume, i.e., the volume of air inhaled per breath; and DF_r is the fraction of inhaled particles deposited in region r.

It should be noted that all of the variables in Equation 7A-1 can potentially vary over time. The effect of activity or exertion level on V_T and f was presented in Tables 6-3 and 6-6. Within an individual, the variability in DF_r over time is largely attributable to variations in inhaled particle size, f, V_T, and route of breathing, i.e., mouth versus nose (ICRP, 1994). Intersubject and interspecies variability in DF_r is additionally affected by morphologic differences in the size and structure of the respiratory tract.

Health effects may be due to deposited dose, retained dose, or a combination of both. Some effects associated with acute exposures may simply be a function of the deposited dose in a region (D_r) of the respiratory tract, given by

$$D_r = \int_{\Delta t} \dot{D}_r(t)\, dt \qquad (7A\text{-}2)$$

where Δt is the exposure time interval.

For chronic exposures, it may be useful to consider both the retained dose due to long term exposure and the acute deposited dose. The PM dose retained in a region of the lung is determined by the balance between rate of input and the rate of removal. The PM burden (B_r) in a lung region may be expressed as

$$dB_r(t)/dt = \dot{D}_r(t) - \lambda_r B_r(t) \qquad (7A\text{-}3)$$

where λ_r is the clearance rate constant for region r. It should be noted that transfer into region r from another region may also occur. Such situations in which a region receives a portion of its burden from another region are common in the lung, e.g., the mucus clearance of the segmental bronchi into the lobar bronchi, which clear into the main bronchi, which in turn clear into the

trachea. In addition, the clearance from one region can transfer burden into more than one other compartment, e.g., soluble particles in the airways may be cleared into the blood as well as via the mucus. The discussion herein of retention is mainly limited to poorly soluble particles. However, multiple pathways for clearance of insoluble particles exist such as from the alveoli into the lymph and into the terminal bronchioles via macrophages.

For instillations into the lung, the total instilled dose can be characterized fairly well. For inhalation studies, however, the dose is not always known and must instead be calculated using a dosimetric model that may be based on empirical relationships, theoretical calculations, or a combination. The following discussion is based on the application of dosimetry to interspecies extrapolation as given in the scientific literature (U.S. Environmental Protection Agency 1994, 1996; Jarabek, 1994, 1995).

For dosimetric calculations and comparisons, it is useful to assume that PM concentrations and activity levels are constant over time. Further, it is convenient to separate the deposited dose into one factor that depends on the exposure-related variables and a second factor that depends on species, particle size, and activity level. Exposure, E, can be defined as

$$E = C \times \Delta t \tag{7A-4}$$

where: C is PM exposure concentration and Δt is exposure duration. A dose adjustment factor, DAF, can also be defined as

$$DAF = f \times V_t \times DF \tag{7A-5}$$

where it is understood that DF refers to specific regions of the lung. Retained dose can be expressed similarly except that the DAF would include a retention fraction.

In order to compare a rat dose with a human dose that might have comparable biological effects, it is useful to introduce the concept of dose normalization. Examples of normalized doses are the dose per body mass, per lung mass, per lung area, per macrophage, or per other biological or physiological parameters. A normalized dose (ND) is the dose (D) to the lung or lung region divided by an appropriate normalizing factor (NF):

$$ND = \frac{D}{NF} = \frac{E \times DAF}{NF} \quad (7A\text{-}6)$$

In Equation 7A-6, ND and DAF refer to specific regions of the lung and could apply to either a rat or human. In the extrapolation modeling presented here, normalized doses are calculated for rats and humans. The concept of dose normalization is not new to interspecies extrapolation of toxicologic data. The ingested dose that produces no adverse effect in animals is normalized and used to estimate a comparable human dose. Typically, an uncertainty factor of 10 is applied to the estimated human dose unless a dosimetric adjustment is made, in which case, the uncertainty factor is reduced to 3 (U.S. Environmental Protection Agency, 1994; Jarabek, 1995).

The objective of the analysis set forth here is to specify an exposure for one species and determine an exposure for the second species, such that both species will receive equivalent normalized doses,

$$ND_R = ND_H \quad (7A\text{-}7)$$

where: subscripts refer to rats (R) and humans (H). Substituting in Equation 7A-6 gives

$$E_R \times (DAF_R / NF_R) = E_H \times (DAF_H / NF_H) \quad (7A\text{-}8)$$

For a given human exposure, Equation 7A-8 may be solved to obtain the rat exposure such that both species receive equivalent normalized doses. An equivalent exposure ratio (EqER) represents the ratio of species' exposures that give equivalent doses.

$$EqER = \frac{E_R}{E_H} = \frac{(DAF_H / NF_H)}{(DAF_R / NF_R)} \quad (7A\text{-}9)$$

Thus, EqER is the factor by which a specified human exposure concentration must be multiplied to obtain a rat exposure concentration yielding an equivalent dose. EqER can be calculated

directly from the DAF and NF for the two species provided that the dose is a linear function of time and concentration. If the exposure time is the same for both species, Equation 7A-9 can be reduced to

$$C_R = EqER \times C_H \quad (7A\text{-}10)$$

If EqER is greater than 1, then the rat must receive a greater concentration than the human in order to receive an equivalent dose.

7A.3 THE MULTIPLE PATH PARTICLE DOSIMETRY MODEL (MPPD)

The deposition and clearance of particles in the human and rat respiratory tract was estimated using the publicly available Multiple Path Particle Dosimetry (MPPD) model[1]. The MPPD model was developed by the CIIT Centers for Health Research (CIIT), USA, in collaboration with the National Institute of Public Health and the Environment (RIVM), the Netherlands, and the Ministry of Housing, Spatial Planning and the Environment, the Netherlands. Other models of deposition and clearance, which are not necessarily publicly available nor in a form easily suited for comparisons between particle disposition in rats and humans, were discussed in Chapter 6 (Sections 6.6.1 to 6.6.3). General information about the MPPD model was discussed in Chapter 6, Section 6.6.4.2; additional details relevant to this appendix are provided here. Comparisons between MPPD-predicted deposition fractions of monodisperse particles (0.01 to 10 μm) in humans during light exercise and in rats at rest were provided in Chapter 6, Section 6.6.4.3. Differences between rats and humans in deposition normalized to lung mass and lung surface were also provided. In this appendix, other normalizing parameters are considered as is the clearance of particles from the lung.

The MPPD model may be used to predict the deposition of particles between 0.01 to 20 μm in diameter in humans and rats. In the lung, the model considers deposition by the mechanisms

[1] Some software problems encountered during the dosimetric modeling were fixed by the developers; and a revised MPPD upgrade version is available on request from the CIIT Centers for Health Research (<asgharian@ciit.org>).

of impaction, sedimentation, and diffusion. The model does not consider particle interception, charge, or hygroscopic growth. Although the lung geometries differ between species, the same mathematical formulation may be used to calculate particle deposition in the rat as well as in the human lung (Anjilvel and Asgharian, 1995). The extrathoracic particle deposition efficiencies used in the MPPD model were adopted from the ICRP (1994) for humans and from Zhang and Yu (1993) for rats. Model input parameters include airways morphology, particle properties (size distribution, density, concentration), and breathing conditions (tidal volume, breathing frequency, and mode of breathing). The effects of these parameters on deposition in rats and humans were reported by Winter-Sorkina and Cassee (2002). The MPPD model also contains an optional correction for the inhalability of particles during nasal breathing which may be applied to both humans and rats (Ménache et al., 1995). This correction becomes increasingly important when particle size exceeds 1 μm (MMAD) for rats and 10 μm (MMAD) for humans. With reference to Equation 7A-1, it should be noted that average exposure concentrations and average breathing patterns are used to estimate particle deposition fractions and lung doses over discrete time periods, i.e., the simulations presented herein do not consider temporal variations on a breath-by-breath basis as suggested by Equation 7A-1.

Several types of normalized deposition predictions are available using the MPPD model. Particle deposition fractions normalized to airway surface area provide an index of the average dose of particles to epithelial cells. These data are useful in assessing generation-to-generation variability but do not consider dose variability within a generation, e.g., between the carina and airway wall. For this normalization, the MPPD model calculates the surface area of the airways based on the diameter, length, and number of airways in a generation. These data are most useful for the tracheobronchial airways since alveolar surface area is not included in the model's calculations. For the alveolar region, the MPPD model calculates particle mass and number deposited per alveolus and per macrophage. From Mercer et al. (1994), the model assumes 4.86×10^8 alveoli in humans and 1.97×10^7 alveoli in rats. From Miller (2000), the number of alveolar macrophage (AM) per alveolus assumed in the model is 12.3 in humans and 1.5 in rats. However, an influx of monocytes and macrophages into the alveoli occurs following acute exposures to numerous pollutants, e.g., PM, O_3, and NO (Oberdörster, 1988; Mercer, 1999; Driscoll, 1988). Furthermore, the volume (and capacity) of a human AM is about 1.5 times that

of a rat macrophage (Miller, 2000). Hence, it is difficult to interpret a dose metric like the predicted number of particles deposited per macrophage.

The balance between deposition and clearance affects tissue dose and lung burden. The MPPD model considers the lung clearance of insoluble particles as a two-phase process. The rapid first phase, tracheobronchial clearance, occurs via the action of the mucociliary escalator. The second clearance phase is the slow removal of particles that have deposited in the alveolar region of the lung. The model considers particle clearance from the alveolar surface via macrophages to the distal TB airways and via the lymphatic system. The clearance of soluble particles is not considered by the current MPPD model.

The MPPD model estimates mucus clearance of insoluble particles in the human and rat lung by assuming a mass balance between the volume of mucus produced in the terminal bronchioles and the volume exiting the trachea. By further assuming that the production of mucus is the same in all terminal bronchioles, the mucus velocity in terminal bronchioles may be determined given tracheal mucus velocity, tracheal diameter, and the number and diameter of terminal bronchioles. Moving proximally from the terminal bronchioles, the mucus velocity in each parent airway is based on its diameter and daughter airways' diameters and mucus velocities. The mucus within an airway is assumed to travel at a constant velocity which incorporates any discontinuity in mucus blanket. An implicit assumption in this mucus clearance model is that particles are transported with the mucus blanket, i.e., there is no particle size-dependent slow-cleared fraction from the airways as in the ICRP (1994) model. A more detailed description of the MPPD mucus clearance model appears elsewhere (Asgharian et al., 2001; Hofmann and Asgharian, 2003). Model simulations of tracheobronchial clearance, presented herein, assumed tracheal mucus velocities of 1.9 mm/min in rats (Felicetti et al., 1981) and 5.5 mm/min in humans (ICRP, 1994).

Clearance from the alveolar region of the lung is treated somewhat differently between humans and rats by the MPPD model. For humans, the alveolar clearance model was adopted from the ICRP (1994). In that model, the alveolar region consists of three compartments which clear particles into the bronchioles at the rates of 0.02, 0.001, and 0.0001 day^{-1}. Of the particles deposited in the alveolar region, 30% was assumed in the fast compartment, 60% in the medium rate, and 10% in the slow compartment. The slow compartment also clears via lymphatic

channels at a rate of 0.00002 day^{-1}. In rats, the MPPD model considers the overall alveolar clearance rate as the sum of the transport rates to the terminal bronchioles and to the lymph. The alveolar clearance rate constants are based on the pulmonary retention and lymphatic uptake of titanium dioxide particles (MMAD = 1.44 μm, σ_g = 1.71) following a 13-week exposure (6 h per day, 5 day per week) to 10, 50, or 250 mg/m^3 (Bermudez et al., 2002). Average postexposure alveolar rate constants of 0.00693, 0.00214, and 0.00083 day^{-1} and postexposure pulmonary burdens of approximately 1, 8, and 41 mg were observed for the 10, 50, or 250 mg/m^3 exposures, respectively. The rates of clearance observed by Bermudez et al. (2002), with the fastest reported retention half-time being 100 days for the 10 mg/m^3 exposure, are slow relative to healthy rats which typically have a retention half-time of ~70 days (Oberdörster, 1995). This reduction in alveolar clearance rates suggests that rat's macrophage-mediated clearance was somewhat impaired even at the lowest exposure concentration of 10 mg/m^3 in the Bermudez et al. (2002) study. Translocation into the lymph nodes increased in a concentration dependent manner. Based on these data, the MPPD model assumes that the overall alveolar clearance rate (λ_A) decreases with pulmonary burden (m_A) in rats. Specifically, λ_A for rats equals $[0.03341 \times \exp(-1.7759 m_A^{0.3123}) + 0.00072]$ day^{-1}. Based on this equation, a clearance rate typical of healthy rats ($t_{1/2} \approx 70$ days, $\lambda_A = 0.01$ day^{-1}) occurs at a lung burden of 0.4 mg. The assumed clearance rate from the alveoli to the lymphatic system is 0.00106 day^{-1}. The MPPD model, in effect, treats the clearance of particles from the alveolar surface (via macrophages) to the distal airways as a pathway subject to saturation or overload in rats but not in humans.

The current version of the MPPD model does not offer the option of calculating clearance for exposures to multiple polydisperse aerosol modes or for multiple activity levels. Also, MPPD clearance calculations for rats during chronic exposures are quite computationally intensive, taking approximately 10 minutes on a Pentium computer (2.8 GHz with 512 MB of RAM) to determine retention at 1 year of exposure. For such cases, alveolar clearance was calculated in a spreadsheet, instead of the MPPD model, using the deposition fraction (calculated using the MPPD model) and the same clearance rate constants as used by the model. Based on Equation 7A-3, the alveolar burden in rats was calculated as

$$B_R(t) = \dot{D}_R(t-\Delta t)\Delta t + B_R(t-\Delta t)\exp(-\lambda_A \Delta t) \quad (7A\text{-}11)$$

where: B_R is the alveolar burden in a rat; t is time; $\dot{D}_R$ is the dose rate to the alveolar region of the rat; Δt is the time increment for the calculations and was selected to be ~1% (or less) of the retention half-time (i.e., 0.693 / λ_A); and λ_A is the overall alveolar clearance rate in the rat. Alveolar burden in humans was computed similarly for the three alveolar compartments (see above discussion) in humans as

$$B_H(t) = \sum_{i=1}^{3} \{F_{H_i}\dot{D}_H(t-\Delta t)\Delta t + B_{H_i}(t-\Delta t)\ \exp(-\lambda_{H_i}\Delta t)\} \quad (7A\text{-}12)$$

B_H is the alveolar burden in a human; F_{H_i} is the fraction of alveolar deposition distributed to the *i*th alveolar compartment; $\dot{D}_H$ is the dose rate to the human alveolar region; Δt is the time increment for the calculations and was selected to be ~1% (or less) of the fastest compartment's retention half-time (35 days); B_{H_i} is the burden in the *i*th alveolar compartment; and λ_{H_i} is the clearance rate constant for the *i*th alveolar compartment.

7A.4 RAT AND HUMAN DOSIMETRY: INTERSPECIES DIFFERENCES

Before providing illustrative examples of how a dosimetric model may be used in rat-to-human extrapolation, it is useful to discuss some of the many differences between rat and human exposure and dosimetry.

7A.4.1 Anatomy

The structure and function of the respiratory tract differs in rats and humans in ways that affect the deposition of particles in the lung. Rats are obligate nose breathers whereas most humans are oronasal breathers who breathe through the nose when at rest but who breathe increasingly through the mouth with increasing activity. It has been estimated that 13% of the

human population are "mouth-breathers" (Niinimaa, 1981). This distinction is important because the nose is a more efficient filter than the mouth for preventing the penetration of particles into the lung. Thus, by breathing through the mouth, humans effectively increase the amount of inhaled particles reaching the lung. Even when breathing through the nose, humans have greater TB and A region deposition fractions for coarse particles compared to rats due to the lower inhalability of particles larger than 3 μm in the rat. The structure of the human and rat intrathoracic airways also differs in ways that affect the regional deposition pattern in the lung. The branching structure of the lung is monopodial in rats and symmetrically dichotomous in humans. A monopodial structure has the potential to allow increased penetration of large particles into the A region. Rats also lack respiratory bronchioles, a site of early airway disease in humans.

7A.4.2 Exposure Scenarios

7A.4.2.1 Exertion Level.

The amount of PM inhaled is influenced by exertion level and the related lung ventilation rate. Chapter 6 discussed how increasing exertion leads to greater deposition of PM in the human lung due to changes in the mode of breathing (nasal to oronasal to oral) as well as the inhalation of greater quantities of PM per unit time due to an increase in minute ventilation (breaths per minute times the tidal volume in liters) (Figure 6-18). Humans typically experience a range of breathing patterns during exposure to ambient PM, including those experienced during light and heavy exertion as well as at rest and during sleep. In contrast, laboratory rats are commonly at rest when exposed to PM by inhalation. It is not clear which human breathing pattern is most appropriate for use in an extrapolation. However, just because the rat received its dose while resting does not mean that only the dose received by a resting human should be of interest. The quantity of PM inhaled during a specified time period is given by

$$\text{PM (Inhaled)} = C \times f \times V_t \times t = C \times \text{minute ventilation} \times t \qquad \text{(7A-13)}$$

where C may be given in μg, μm^2, or particle number per m^3.

Breathing patterns used in subsequent dosimetric calculations are given in Table 7A-1. The minute ventilation, and therefore the mass of PM inhaled per unit time, will increase with exertion level.

TABLE 7A-1. HUMAN AND RAT BREATHING PATTERNS USED IN DOSIMETRIC CALCULATIONS

	Human					Rat
Activity	**Awake Rest [a]**	**Slow Walk [a]**	**Light Exertion [a]**	**Moderate Exertion [a]**	**Heavy Exertion [b]**	**Awake Rest [a]**
Breaths/min	12	16	19	28	26	102
Tidal volume, mL	625	813	1000	1429	1923	2.1
Minute ventilation, L/min	7.5	13	19	40	50	0.214

[a] Winter-Sorkina and Cassee (2002), [b] ICRP (1994).

7A.4.2.2 Size Distribution

The atmospheric aerosol to which people are exposed may be thought of in terms of three particle classes: coarse mode particles (greater than about 1 μm in diameter), accumulation mode particles (about 0.1 to 1.0 μm in diameter, although accumulation mode PM may grow into 1 to 2.5 μm diameter size range at very high relative humidities), and ultrafine particles (< 0.1 μm in diameter, including the nucleation and Aitken modes [see Chapter 2]). However, in toxicologic studies, laboratory rats are rarely exposed to all three size classes at the same time. Some experimental studies reported in the literature use diesel exhaust (ultrafine particles but with some coagulation into the accumulation mode size range), concentrated accumulation mode particles (concentrated air particles [CAPs]), or particles with a narrow size range within the accumulation mode size range (e.g., studies of acid aerosol). A more recent development is the ultrafine concentrator in which ultrafine particles are separated from larger particles, grown by humidification, concentrated, and dehydrated to reconstitute ultrafine particles. In other studies, rats have been exposed to particles produced by resuspension of bulk material or resuspension of

particles previously collected from specific sources (e.g., resuspended oil fly ash, ROFA, or from ambient air). Particles produced by resuspension are frequently passed through an inertial separator (cyclone or impactor) to remove particles > 2.5 μm diameter, thus leaving particles with a nominal MMAD between 1 and 2 μm. The particle size distribution is important because the deposition fraction and the pattern of deposition in the lung varies with particle size.

Some studies suggest that particle surface area (Oberdörster et al., 1994, 2000) or possibly particle number (Wichmann and Peters, 2000; Wichmann et al., 2000) may be as (or more) important than mass in determining the extent of health effects. Figure 7A-1a shows the mass size distribution of a representative resuspended dust (MMAD = 2 μm, $\sigma_g = 2$) overlaid on an atmospheric mass size distribution. Figures 7A-1b and 7A-1c show the distribution of particle surface area and number, respectively. The coarse mode and the resuspended PM mode contribute little to the total particle surface area and contribute minimally to the particle number concentration (note the logarithmic scale for number concentration). Particle characteristics used in subsequent dosimetric calculations and some examples of deposition fractions calculated with the MPPD model are given in Table 7A-2.

In many cases, it is difficult to find good quality and precise information on the size distribution of particles used in laboratory exposure studies. Accumulation mode CAPs might be expected to have a size distribution similar to the accumulation mode in the atmosphere. However, most concentrators have an upper cut of 2.5 μm and do not concentrate particles below about 0.1 to 0.15 μm. Hence, the lower tail of the accumulation mode will not be concentrated while the lower tail of the coarse mode will be. Thus, in atmospheres not influenced by fog or clouds, the size distribution of the CAPs might be bimodal or otherwise non-lognormal. In any event, a single MMD and σ_g probably will not be adequate to characterize the size distribution. Values of σ_g in excess of 2.5, for example as reported for some CAPs (Gordon et al., 2000, 2004), suggest a multimodal, rather than a monomodal, distribution. If a combined accumulation/ultrafine concentration technique is used, the resulting CAPs would be expected to contain several modes. Diesel exhaust, as generated for laboratory exposures, probably has a nucleation mode and an Aitken mode, with some particles possibly having grown by coagulation into the lower end of the accumulation mode. Thus, the size distribution of diesel particles

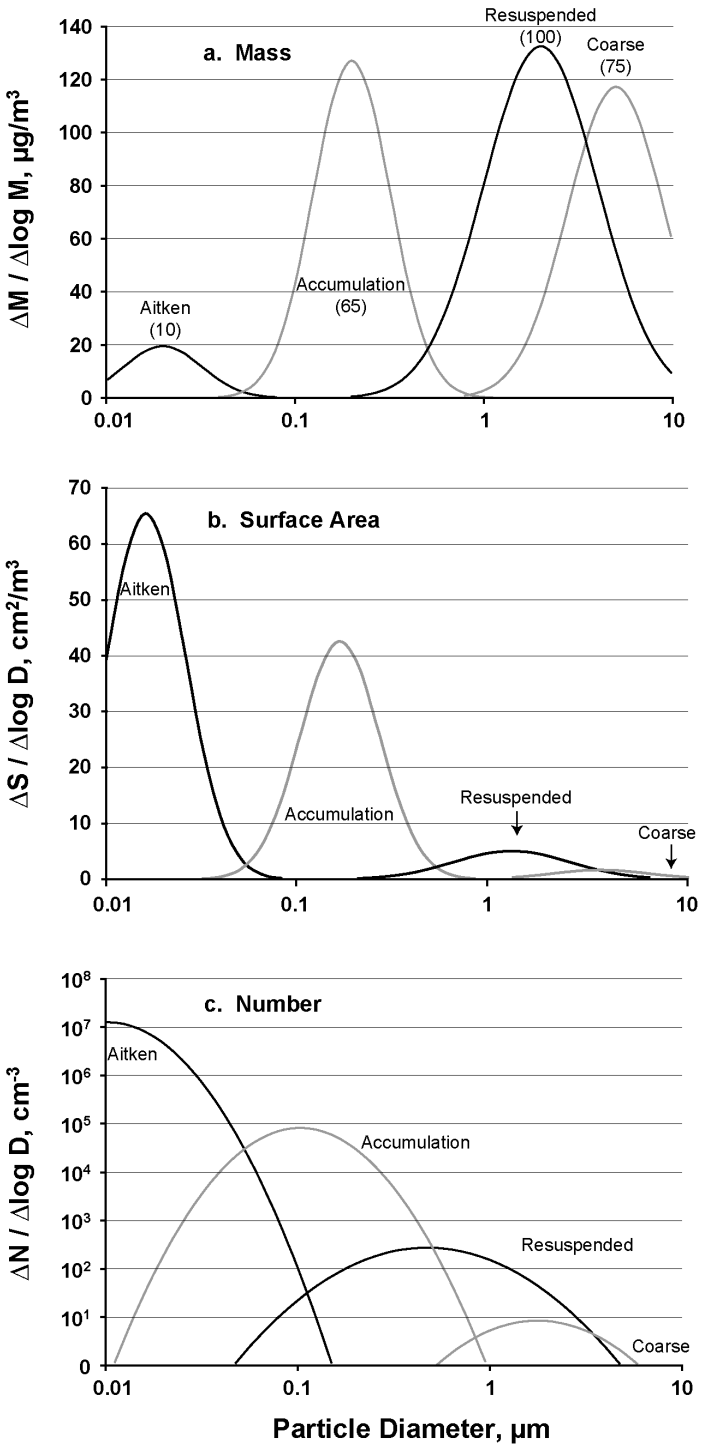

Figure 7A-1a,b,c. **Size distributions of the Aitken, accumulation, and coarse modes of the average urban aerosol (as reported by Whitby [1978]) and a resuspended PM mode: (a) mass distribution, (b) surface area distribution, and (c) number distribution. Concentrations, in µg/cm³, are shown under the name of each mode in (a).**

TABLE 7A-2. PARTICLE CHARACTERISTICS USED BY EPA IN MPPD MODEL CALCULATIONS AND SOME EXAMPLES OF REGIONAL DEPOSITION FRACTIONS

	Human			Rat
Size Distributions	**Aitken [a]**	**Accumulation [a]**	**Coarse [a]**	**Resuspended [b]**
Mass Mean Diameter, μm	0.031	0.31	5.7	2
Surface Mean Diameter, μm	0.023	0.19	3.3	1.2
Number Mean Diameter, μm	0.013	0.069	1.1	0.47
Geometric Standard Deviation, σ_g	1.7	2	2.1	2
Density, g/ml	1	1	1	1
% Mass in Size Range	6.7	43.3	50	100
Fraction Deposited [c]				
TB Region	0.19	0.062	0.024	0.04
A Region	0.32	0.1	0.055	0.058
Thoracic Region	0.51	0.16	0.079	0.098

[a] Size distribution for human calculations from Whitby (1978).
[b] The size distribution for resuspended PM is based on several reported size distributions. To remove larger particles, some studies have used a cyclone (Kodavanti et al., 2002; Dormans et al., 1999) or an impactor (Killingsworth et al., 1997) often with a 50% cut point at 2.5 μm diameter.
[c] Calculated with the MPPD model for activity levels of light exertion for humans and rest for rats.

cannot be adequately modeled as a monomodal distribution. In addition, diesel exhaust contains particles below 0.01 μm in diameter. Since the lower limit of the MPPD model is 0.01 μm, it may underestimate the number of diesel exhaust particles depositing in the lung. The analysis presented here is limited to particles between 0.01 and 20 μm in diameter.

7A.4.3 Quantities Calculated by Dosimetric Models

7A.4.3.1 Deposition Fraction (DF)

The fraction of inhaled particles deposited in various regions of the respiratory tract depends on the particle size and the breathing pattern (breaths per minute, tidal volume, and

whether breathing by nose or mouth). Examples of the ratio, DF_H/DF_R, for a resting rat and a human at various activity levels for nasal and oral breathing are given in Figures 7A-2 and 7A-3.

The ratio increases rapidly for particle diameters above about 5 μm diameter due to differences in inhalability as shown in Figure 7A-4. The DF_H/DF_R for the TB and A region differs only by a small factor in the accumulation size range. Due to the lower inhalability of coarse particles by the rat and differences in the nasal passages of the rat and human, the ratio is quite variable for coarse particles. The ratio is also variable for ultrafine particles due partially to differences in the removal of ultrafine particles in the extrathoracic region.

7A.4.3.2 Clearance

Poorly soluble fine and coarse particles deposited in the lung are cleared by a variety of mechanisms as discussed in Chapter 6. However, the clearance rates from both the TB and A regions are much higher for rats than for humans. Figures 7A-5a and 7A-5b show examples of accumulation and clearance for the TB region for humans and rats. Note the different time scales for the two figures. Because of these species differences in clearance rates, retention half-times also vary by species. Retention half-times in the TB region are highly dependent on the site of deposition, but generally range from 1 to 2 h in rats and 4 to 10 h in healthy humans (Hoffmann and Asgharian, 2003).

Figure 7A-6 compares the longer term clearance of particles initially deposited in the A region for several species (Oberdörster, 1988). A more recent review is given by Kreyling and Scheuch (2000). Clearance from the A region is much slower than clearance from the TB region for both humans and rats, while particles deposited in the A region are cleared more rapidly from the rat than the human. For the A region, retention half-times are 60 to 80 days in rats but up to 2 years in humans.

7A.4.3.3 Retention

Figures 7A-5 and 7A-6 show the clearance of particles after exposure had ceased as a fraction of the particles present in the lung at the time exposure ceased. For chronic exposures, however, it is necessary to consider the retained dose. In comparing retention for rats and humans, how much of the deposited PM remains in the lung after exposures of various

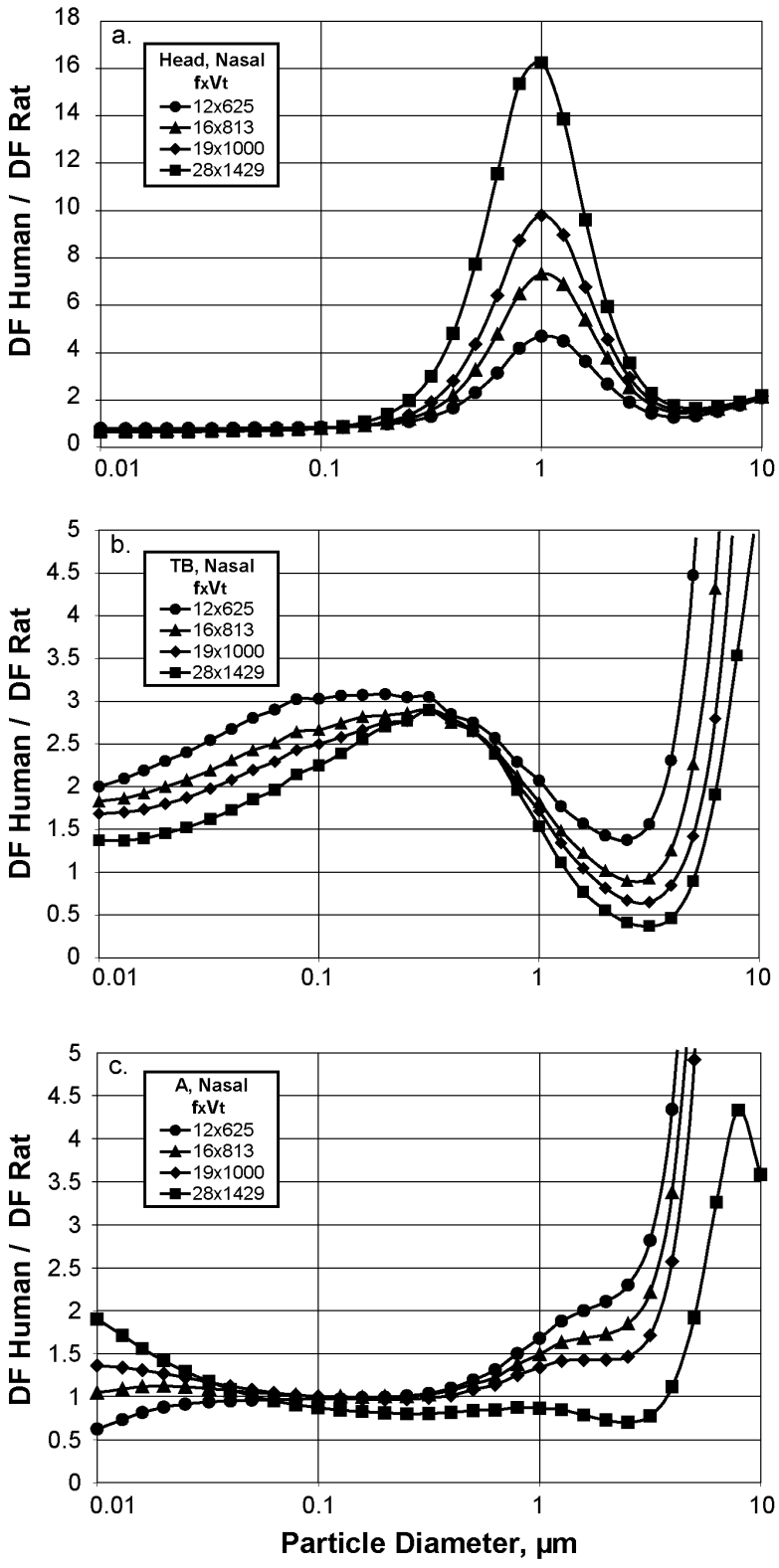

Figure 7A-2a,b,c. The ratio of the predicted deposition fractions for human relative to rat at rest, DF_H/DF_R, (a) the head region, (b) the TB region, and (c) the A region for nasal breathing corrected for particle inhalability.

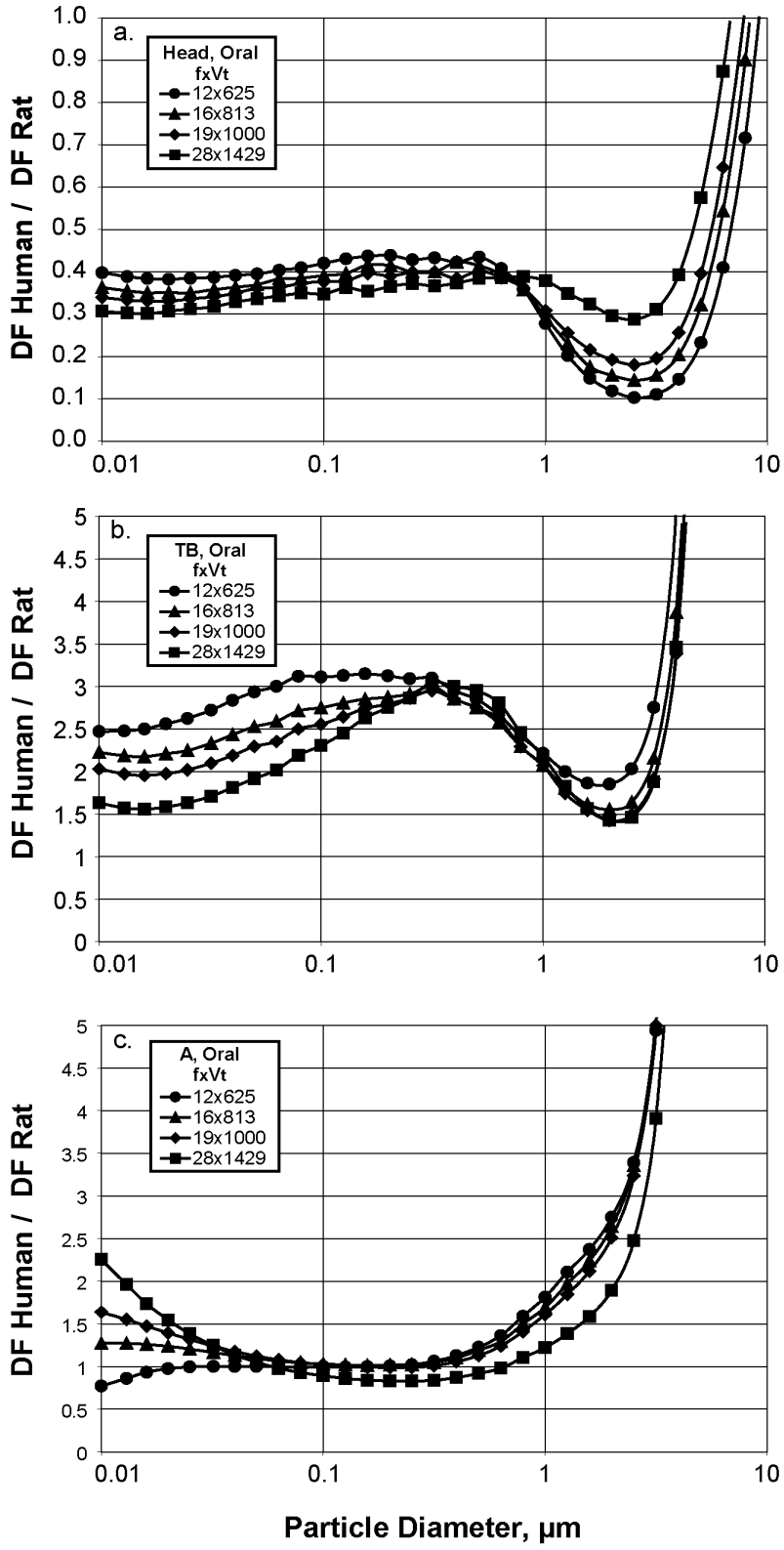

Figure 7A-3a,b,c. **The ratio of the predicted deposition fractions for human relative to rat at rest, DF_H/DF_R, (a) the head region, (b) the TB region, and (c) the A region for oral breathing corrected for particle inhalability.**

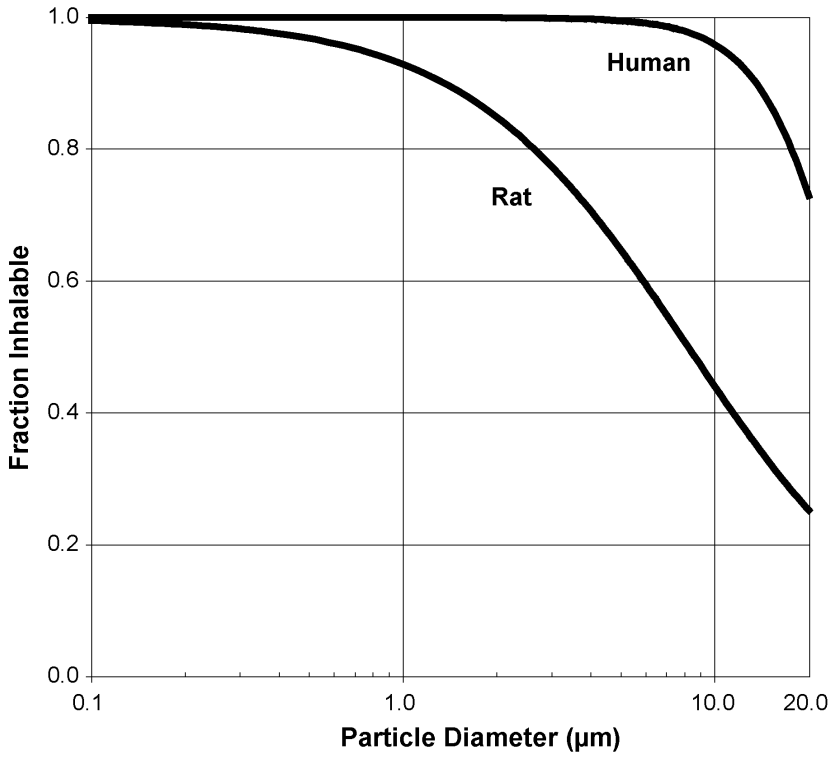

Figure 7A-4. Inhalability curves for human and rat showing the fraction of PM that enters the nose (based on empirical fit to experimental data given in Table 1 from Ménache et al., 1995).

magnitudes and durations is of interest. The PM dose retained in a region of the lung is determined by the balance between the rate of input (deposition) and the rate of removal (clearance) as described by Equation 7A-3. Figure 7A-7a and 7A-7b show how the balance between deposition (for 6 h) followed by clearance (for 18 h) leads to differences in retained burdens between rats and humans and between the TB and A regions. The scenario depicted is for a 6-h-per-day, 3-day exposure to 100 µg/m^3 of 2-µm diameter particles with a σ_g of 2.0. The y-axis on these figures is the fraction of total PM mass (i.e., the total mass that would be deposited in the TB or A region over the 3-day exposure period) that is retained in the TB or A region. As shown in Figure 7A-7a, because of the more rapid clearance of the rat, the fraction of deposited mass retained in the TB region is much smaller for the rat than the human. The maximum retained dose in the rat TB region is never greater than 0.07 of the total deposited

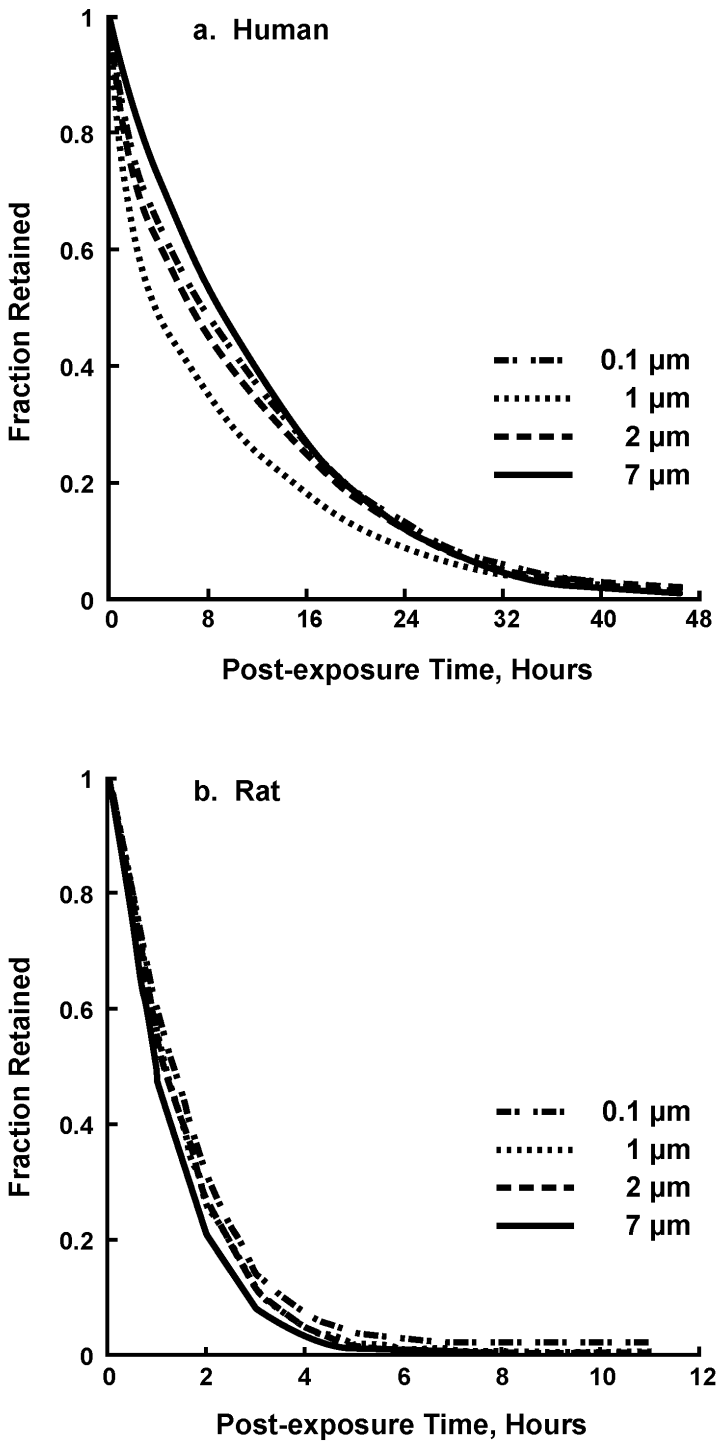

Figure 7A-5. Predicted clearance curves for the TB region for poorly soluble particles for (a) human and (b) rat. Note different time scales. The rat clears PM from the TB region much faster than a human. Fraction of mass retained in the TB region after 1 h of exposure to unit density particles of diameter shown. Adapted from Hofmann and Asgharian (2003).

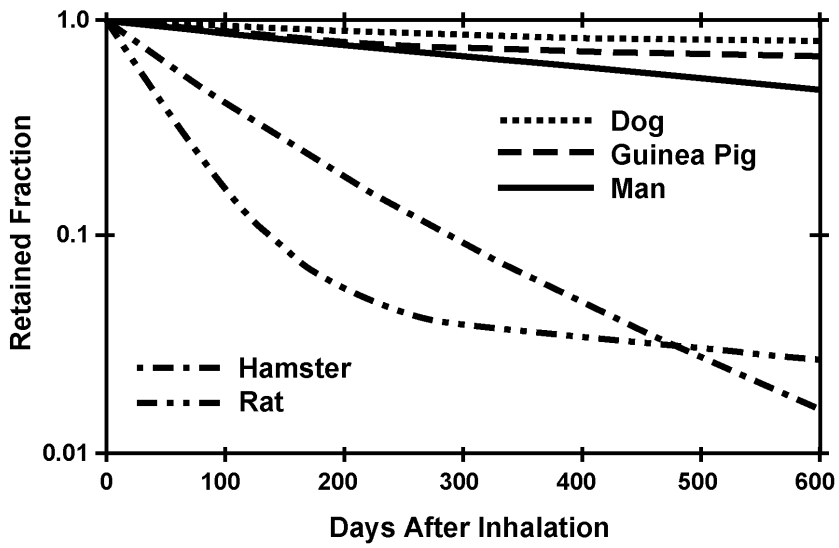

Figure 7A-6. Alveolar region clearance curves for measured poorly soluble particles in several species. Note much higher clearance rate for rat compared to human. From Oberdörster (1988).

dose; whereas, in the case of the human, the maximum retained TB dose reaches as high as 0.30 of the total deposited dose. Figure 7A-7b shows a similar plot for the A region. As shown in Figure 7A-7b, clearance is slower, and retention is greater, in the A region than the TB region for both rats and humans. However, retention in the rat is less than in the human due to the faster clearance in the rat.

7A.4.3.4 Long-Term Burden from Chronic Exposure

PM contains components with various degrees of solubility. Some components of PM deposited in the lung dissolve in seconds to minutes, and others within hours to days. However, there are some PM components that are sufficiently insoluble that they remain in the lung for months to years. If the exposure concentration, breathing rate, tidal volume, and any other dosimetric variables remained constant, then the processes of clearance and removal would eventually approach an equilibrium; and the amount of insoluble PM in the lung would approach a steady-state value. In reality, the exposure concentration and dosimetric parameters will vary

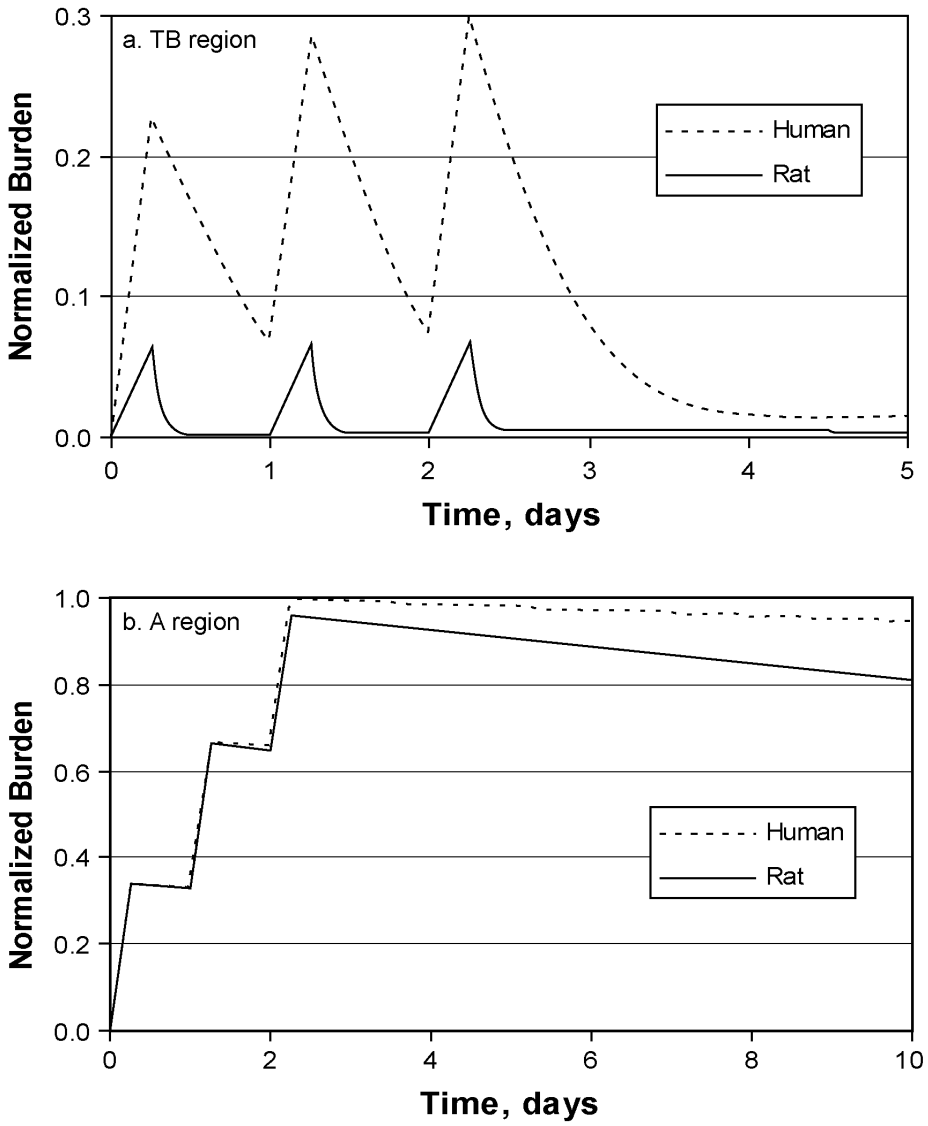

Figure 7A-7a,b. Burden in the (a) TB and (b) A region of the lung normalized to the total particle mass predicted to deposit in these respective regions during a 3-day (6 h/day) exposure. Estimates of deposition and clearance were calculated using the MPPD model for resting breathing patterns (see Table 1) and particles having a MMAD of 2 μg (σ_g = 2).

with time; but after a sufficient length of time, a near steady-state value with small excursions will be achieved. Furthermore, the available model does not allow long-term calculations with variable exposures and dosimetric parameters. Therefore, an average breathing pattern was used in the model.

Rats are usually kept in a laboratory setting and breathe air that has been filtered and conditioned and are, therefore, exposed to relatively clean air for the months prior to their experimental exposure. In addition, rat exposures usually have a daily schedule of 6 h exposure to an experimental atmosphere followed by 18 h exposure to relatively clean air for 5 days a week. On the other hand, people are exposed to ambient and nonambient PM all their lives. Because of its more rapid clearance rate, a rat will reach a near steady state retained dose of poorly soluble particles in the A region in a few months; it will take more than 10 years for a human to do so. Figure 7A-8 shows the accumulation of PM in the lung for chronic exposures for a rat and a human. Exposure parameters and particle sizes used in the MPPD model calculations and the calculated alveolar deposition fractions are given in Table 7A-3.

7A.4.4 Dose Metrics

For inhalation toxicology, several parameters are required to define a dose metric: a PM indicator, a respiratory region, the time over which the dose is integrated, whether the dose is deposited or retained, and whether the dose is incremental or accumulated. Thus, there are many possible dose metrics. It is not clear which dose metric is most appropriate and it may be that different health effects will be associated with different dose metrics. For example, for health effects associated with soluble PM components, mass may be the most appropriate PM indicator and deposited mass more appropriate than retained mass. For health effects associated with poorly soluble ultrafine PM, the particle number or particle surface area might be the more appropriate PM indicator and the retained dose more appropriate than the deposited dose. For acute effects, the maximum deposited incremental dose may be the appropriate type of dose metric. For chronic effects, the total, retained, long-term burden may be more appropriate. For health effects associated with the rupture or inactivation of macrophages, the volume of particles might be an appropriate PM indicator and either total retained incremental dose or long-term burden the appropriate type of dose. Some possible parameters are listed in Table 7A-4.

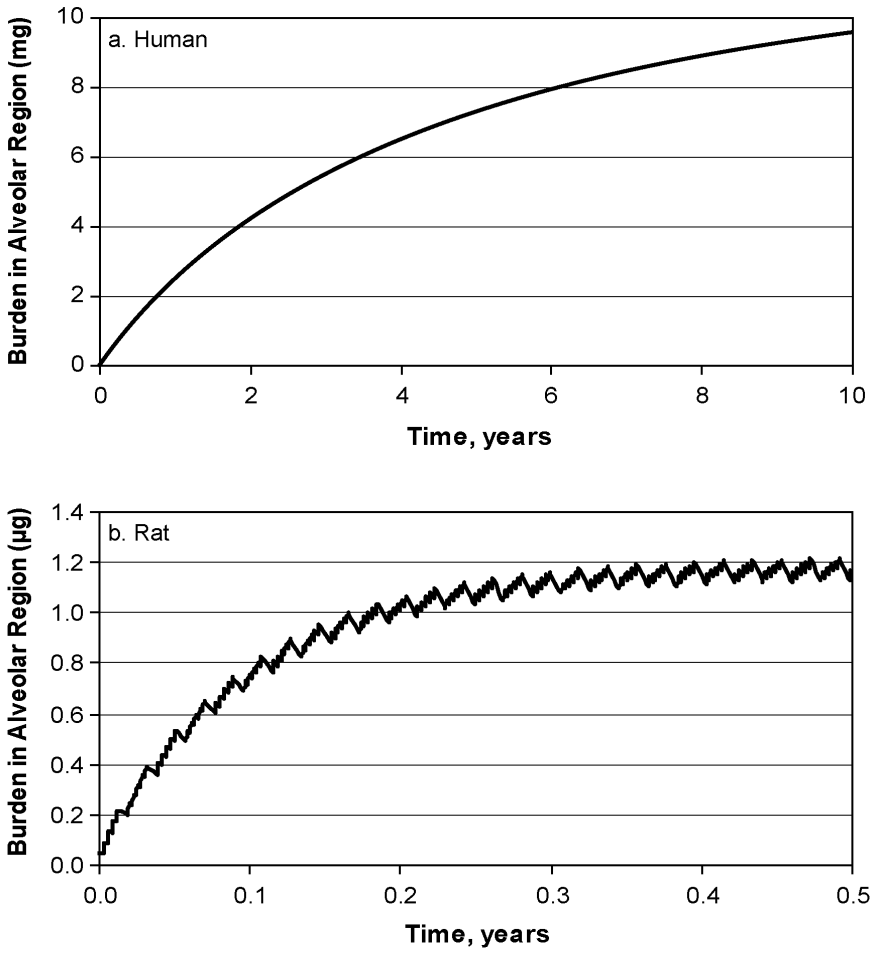

Figure 7A-8. Mass burden of poorly soluble PM predicted for the A region of (a) human and (b) rat. Burdens were calculated by the MPPD model for the exposure scenarios provided in Table 3. The rat reaches a near steady-state burden in 6 months. After 10 years the human is approaching a steady-state burden that is a 1,000 times larger (or approximately 5 times larger when normalized to lung surface area or body mass). Note different time of scales (x-axis) and µg versus mg units (y-axis).

7A.4.5 Normalizing Factors and Other Differences Between Humans and Rats

The human and rat doses may be scaled by a normalizing parameter to better quantify dose to specific target sites of the respiratory tract. If epithelial cells are the target, the tracheobronchial or alveolar surface area would be the most likely normalizing parameter. If the interstitium is the target, then the lung mass or weight may be better parameters. If activation of

TABLE 7A-3. EXPOSURE SCENARIOS FOR ACCUMULATION OF LONG-TERM BURDEN USED BY EPA IN MPPD MODEL CALCULATIONS

Exposure	Human	Rat
Hours a day	24	6
Days a week	7	5
Total time	10 years	6 months
Concentration of insoluble PM	10 $\mu g/m^3$	10 $\mu g/m^3$
Particle Size (MMAD)	1 μm	1 μm
Geometric Standard Deviation (σ_g)	1	1
Density, g/mL	1	1
Breathing pattern	Resting	Resting
Breaths per min	12	102
Tidal volume, mL	625	2.1
Alveolar Deposition Fraction [a]	0.0993	0.0593
Alveolar Surface Dose [b], mg/m^2	0.025 [c] 0.17 [d]	0.0039 [c]

[a] Calculated with MPPD model.
[b] Alveolar burdens from Figure 7A-8 and alveolar surface areas from Table 7A-5.
[c] After 6 months of exposure.
[d] After 10 years of exposure.

TABLE 7A-4. PARAMETERS USED TO DEFINE A DOSE METRIC [a]

PM Indicator	1	Number, surface area, mass, or volume; total PM or of a specific PM component
Respiratory Region	2	Nasal, tracheobronchial (TB), alveolar (A), thoracic (total lower respiratory tract, TB + A), specific TB generation, alveolus, macrophage or other target cells
Type of Dose	3	Total, average, or maximum
	4	Deposited or retained
	5	Incremental dose (over and above long-term burden) or incremental dose plus accumulated, long-term burden

[a] One parameter is chosen from each of the five rows to form a dose metric.

macrophages is a causal process, then the number of macrophages would be an appropriate normalizing parameter. Respiratory parameters for the human and rat that may be used as normalizing factors are shown in Table 7A-5.

TABLE 7A-5. CHARACTERISTICS OF HUMAN AND RAT LUNGS

	Human	Rat	Human/Rat
Functional Residual Capacity, FRC, ml	3300 [a]	4.0 [a]	825
Body Mass, g	73000	330	221
Lung Mass, g	1100 [b]	1.65 [c]	667
TB Area, m^2	0.4419 [d]	0.002346 [e]	188
A Area, m^2	57.22 [d]	0.2972 [e]	193

[a] Winter-Sorkina and Cassee (2002), [b] U.S. EPA (1996), [c] Takezawa (1980) for a 330g rat, [d] Yeh and Schum (1980) scaled to FRC, [e] Yeh et al. (1979) scaled to FRC.

The volume and surface area of the lung are variable. Across various species, lung volume varies with body weight (Weibel, 1972). For humans, lung volume is also a function of age and height (Morris et al., 1984). In addition, the volume and the surface area change as the lung expands and contracts during breathing. The functional residual capacity (FRC), defined as the volume of the lung at the end of a normal expiration during rest, has been chosen as a normalizing parameter. The values of FRC chosen are the default values used in the MPPD model (Winter-Sorkina and Cassee, 2002). The value of 3300 ml for an adult human male is also the default value for the ICRP model (ICRP, 1994). The value of 4 ml for a rat is also the predicted value for a 330 g rat based on data from Takezawa (1980).

Lung surface areas at the FRC were calculated from whole lung anatomic models for a human (Yeh and Schum, 1980) and a rat (Yeh et al., 1979). These models are based on morphometric measurements of silicone rubber casts of the tracheobronchial airways of one human and one rat lung. The models give the number, diameter and length of the airways for

generations 1-24 and the diameter, length (height of a spherical segment) and total number of alveoli. Values for generations distal to the terminal bronchioles were derived by the authors of the references from assumptions and formulae and did not represent direct estimates. The dimensions given correspond to the total lung capacity since the casts were made under a slight positive pressure. Both papers give volume of the ducts and the total number and volume of the alveoli but do not distribute the alveoli to the respiratory bronchioles. For the human, the number of alveoli on each respiratory bronchiole was taken from Weibel (1963). For the rat, the alveoli were distributed to the respiratory bronchiole in proportion to the surface of the respiratory bronchioles. The airway dimensions were then scaled to give the specified FRC and the corresponding surface areas were calculated from the linear dimensions treating the alveoli as segments of a sphere. (The surface areas given in the references are for the cross-sectional areas of the tubes.) A summary of the dosimetric differences between humans and rats is given in Table 7A-6.

7A.5 DOSIMETRIC CALCULATION FOR EXTRAPOLATION MODELING: COMPARING RATS TO HUMANS

7A.5.1 General Exposure Scenarios

7A.5.1.1 Acute Exposures

For the first series of extrapolation modeling, an acute exposure of 6-h in duration for humans and rats is examined. Only an incremental dose is considered, ignoring the burden of PM preexisting in the lung at the time of exposure. Typical of experimental exposure conditions, a resting activity level is used for rats. For humans, three levels of activity are used: resting, light exertion, and moderate exertion. For humans, oronasal (normal augmentor) and oral breathing are considered. Breathing parameters are given in Table 7A-1. For the human exposure, a near-roadway situation with exposure to all three atmospheric modes is used. Dose is calculated for each mode separately and for all three modes together. For the rat, exposure is considered to each of the three atmospheric modes separately. Exposures to resuspended collected particles, e.g., residual oil fly ash (ROFA) or ambient particles collected on a filter,

TABLE 7A-6. DOSIMETRIC DIFFERENCES BETWEEN RATS AND HUMANS

Differences In:	Rats (Experimental Exposures)	Humans (Mainly Ambient Exposure)
Anatomy	Nasal breathers Monopodial branching lung structure	Oronasal breathers Dichotomous branching lung structure
Exertion Level	Usually resting during exposure	Exposure occurs over a range from sleep to heavy exercise or work
Clearance	Fast [a]	Slow
Prior Exposure	Usually kept in clean or relatively clean air in laboratory setting; only a few months of low exposure prior to test exposure	Mature or elderly humans likely will have accumulated larger burdens of PM from prior exposures than will have laboratory rats, on a normalized basis
PM Burden	Retained dose approaches steady state after several months, and at a lower fraction of deposited dose than for a human	On the order of 10 years required for the retained dose to approach steady state
PM Size Distribution	Experimental challenge exposures mostly to particles of limited size distribution. Representative size distributions: Resuspended PM: MMD = 1.2 - 2.5 μm, σ_g = 1.5 -2.5 Diesel exhaust: < 0.2 μm CAPs: usually only the 0.1 to 2.5 μm size range is concentrated	Ambient exposure to all three atmospheric modes: Aitken (0.01-0.1 μm), σ_g = 1.6-1.7 Accumulation (0.1-1 μm), σ_g = 1.6-2.2 Coarse (1-100 μm), σ_g = 1.8-2.4 Experimental CAPs exposures usually to one mode.

[a] Alveolar clearance rates may be a function of retained dose.

impactor, or electronic-air-cleaner plate are also considered for rats. The size distribution and the fraction of particles in each mode used in the model simulations are given in Table 7A-2. Doses were calculated with the MPPD model (described in Section 7A.3). Normalized doses were calculated using several normalizing factors with the values given in Table 7A-5.

Three sets of comparisons are given:

(1) Rat and human each exposed to the same single mode (Aitken, accumulation, or coarse);

(2) Rat exposed to resuspended PM, human exposed to all three modes; and

(3) Rat exposed to each of the three modes separately, human exposed to all three modes together.

The concept of an equivalent exposure ratio (EqER) was discussed in 7A.2. If exposure times are the same, the rat exposure concentration that will give a dose equivalent to that received by a human at a specified concentration can be determined by multiplying the specified human concentration by EqER, i.e.,

$$C_R = EqER \times C_H \qquad (7A–10)$$

In Tables 7A-7a to 7A-9b, values of EqER are reported for some of the dose metrics listed in Table 7A-4. For example, EqER × 100 will yield the rat exposure concentration necessary to produce a dose equivalent to that received by a human at an exposure concentration of 100 $\mu g/m^3$. For clarity, if EqER is greater than 1, the rat must be exposed to a higher concentration than the human for effectively equivalent doses.

It may be worthwhile here to emphasize that dosimetry refers to the deposition of particles in the lung and the removal of deposited particles by a variety of mechanisms. The relationship between exposure and dose for different species, lung sizes, and breathing patterns as well as for a variety of dose metrics and normalizing factors can be characterized. However, this dosimetric analysis provides limited insight into the relative toxicity of particles on a composition or size basis. Toxicologic studies suggest that particle toxicity varies with composition and with size (for particles of the same composition). Particle composition also varies between fine and coarse modes and to a lesser extent within modes. Thus, it is difficult to interpret relative doses in terms of relative toxicity unless the exposures are to particles with identical composition and size. This is especially a problem for coarse mode particles, because differences in inhalability between humans and rats result in greater deposition of the large coarse mode particles in the human than the rat. The subsequent tables report equivalent doses, but equivalent dose does not necessarily mean equivalent toxicity. Dosimetric calculations can be used to predict exposures to give equivalent doses of the same material for the purpose of comparing responses across species. If adequate information were available on size and composition of particles in the exposure mix, and toxicity as a function of size and composition were known, then dosimetry could be used to calculate doses of equivalent toxicity.

7A.5.1.2 Rat and Human Each Exposed to One Mode of the Atmospheric Particle Size Distribution

Tables 7A-7a and 7A-7b give results, in terms of EqER, for a series of simulations in which the rat normalized dose due to exposure to a mode of the atmospheric particle distribution was compared to a human normalized dose due to exposure to the same single mode. The specific particle size and breathing parameters are given in Tables 7A-1 and 7A-2. The rat was assumed to be resting, the usual condition for experimental exposures. Simulations were run for four human breathing patterns: resting, light exertion, moderate exertion (normal augmentor), and moderate exertion (oral breathing). Normalized doses to a specific mode (Aitken [At], accumulation [Ac], and coarse [C] mode particles) were compared over one 6-h exposure period for a variety of dose metrics based on particle mass, surface area, and number for several normalizing parameters. Values of EqER for deposited mass per lung mass, body mass, or lung area range from 0.09 to 5.5 (Table 7A-7a Section I). This means that to provide a normalized dose to a rat equivalent to that a human would receive at an exposure of 100 $\mu g/m^3$, depending on the dose metric chosen, the predicted EqC_R would range from 9 $\mu g/m^3$ (TH deposition per lung mass for a resting human for Aitken particles) to 550 $\mu g/m^3$ (TB deposition per unit TB area for a human undergoing moderate exertion for coarse particles). For short-term retention in the TB region, EqER values are higher, 0.67 to 33, because of the more rapid clearance of PM from the rat TB region. For short-term retention in the A region, EqER values are lower, 0.06 to 4.05.

Dose metrics based on surface area or number are somewhat different from those based on mass due to changes in DF since the median diameter decreases in going from mass to surface area to number. For surface area dose metrics (Table 7A-7b, Sections IV to VI), EqER values range from 0.09 to 4.6 for deposited dose metrics; 1.7 to 47 for short-term (6- or 24-h) retention in TB regions; and 0.16 to 3.7 for short-term retention in the A region. For particle number dose metrics (Table 7A-7b, Sections VII to IX), the EqER range is 0.09 to 2.1 for deposited dose metrics, 1.4 to 15 for short-term retention in the TB region, and 0.14 to 1.8 for short-term retention in the A region. The MPPD model has a lower particle size limit of 0.01 μm. Hence, it could not calculate the DF for the count distribution of the Aitken mode with a σ_g of 1.7, because approximately 30% of the particles are below 0.01. Therefore, the EqER for

TABLE 7A-7a. PREDICTED PARTICLE MASS DOSE METRICS FOR HUMAN AND RAT EACH EXPOSED TO ONE ATMOSPHERIC MODE: EQUIVALENT EXPOSURE RATIO (EqER) FOR PM DOSE AFTER 6-HOUR EXPOSURE FOR SEVERAL BREATHING PATTERNS.*

	Resting			Light			Moderate, Normal Augmentor			Moderate, Oral Breathing		
I. Deposited Mass	**At**	**Ac**	**C**	**At**	**Ac**	**C**	**At**	**Ac**	**C**	**At**	**Ac**	**C**
TH per Lung Mass, µg/g	0.088	0.1	0.18	0.23	0.23	0.24	0.49	0.44	1.2	0.47	0.42	1.7
TH per Body Mass, µg/g	0.21	0.23	0.42	0.55	0.53	0.56	1.1	1.0	2.9	1.1	0.98	4.1
TH per Lung Area, µg/m^2	0.24	0.26	0.48	0.63	0.61	0.64	1.3	1.2	3.3	1.3	1.1	4.7
TB per TB Area, µg/m^2	0.45	0.53	0.42	0.90	1.2	0.42	1.6	2.6	4.1	1.6	2.4	5.5
A per A Area, µg/m^2	0.17	0.20	0.54	0.54	0.47	0.83	1.2	0.86	2.8	1.2	0.82	4.0
µg per Macrophage	0.16	0.19	0.52	0.52	0.46	0.81	1.2	0.83	2.7	1.2	0.79	3.9
II. Retained Mass in TB												
6-h Avg per lung mass, µg/g	0.7	0.7	0.6	1.3	1.4	0.5	2.4	2.7	2.3	2.3	2.6	3.4
24-h Avg per lung mass, µg/g	12	1.8	1.9	3.8	3.5	1.6	6.7	6.3	5.3	6.5	6.0	7.7
6-h Avg per body mass, µg/g	1.6	1.6	1.5	3.1	3.4	1.3	5.6	6.4	5.5	5.4	6.1	7.9
24-h Avg per body mass, µg/g	28	4.2	4.5	9.0	8.1	3.8	16	15	13	15	14	18
6-h Avg per TB area, µg/m^2	1.8	1.9	1.8	3.7	4.0	1.5	6.5	7.5	6.5	6.4	7.1	9.3
24-h Avg per TB area, µg/m^2	33	4.9	5.3	11	9.5	4.4	19	17	15	18	16	21
III. Retained Mass in A												
Maximum per A Area	0.16	0.19	0.54	0.54	0.46	0.83	1.2	0.84	2.7	1.2	0.80	4.0
6-h Avg per lung mass, µg/g	0.060	0.071	0.20	0.20	0.17	0.31	0.45	0.31	1.0	0.44	0.30	1.5
24-h Avg per lung mass, µg/g	0.061	0.072	0.20	0.20	0.17	0.31	0.45	0.32	1.0	0.44	0.30	1.5
6-h Avg per body mass, µg/g	0.14	0.17	0.47	0.47	0.40	0.72	1.0	0.73	2.4	1.0	0.69	3.5
24-h Avg per body mass, µg/g	0.14	0.17	0.48	0.47	0.41	0.74	1.1	0.74	2.4	1.0	0.70	3.5
6-h Avg per A area, µg/m^2	0.16	0.19	0.54	0.54	0.46	0.83	1.2	0.84	2.7	1.2	0.80	4.0
24-h Avg per A area, µg/m^2	0.16	0.19	0.55	0.54	0.47	0.84	1.2	0.85	2.8	1.2	0.81	4

*At, Aitken mode; Ac, accumulation mode; C, coarse mode; TH, thoracic region; TB, tracheobronchial region; A, alveolar region; SA, particle surface area; #, particle number.

TABLE 7A-7b. PREDICTED PARTICLE SURFACE AREA AND NUMBER DOSE METRICS FOR HUMAN AND RAT EACH EXPOSED TO ONE ATMOSPHERIC MODE: EQUIVALENT EXPOSURE RATIO (EqER) FOR PM DOSE AFTER 6-HOUR EXPOSURE FOR SEVERAL BREATHING PATTERNS.*

	Resting			Light			Moderate, Normal Augmentor			Moderate, Oral Breathing		
IV. Surface Area of Particles Deposited	**At**	**Ac**	**C**	**At**	**Ac**	**C**	**At**	**Ac**	**C**	**At**	**Ac**	**C**
TH per Lung Mass, SA /g	0.09	0.09	0.17	0.24	0.22	0.26	0.52	0.42	1.1	0.55	0.43	1.5
TH per Body Mass, SA /g	0.21	0.21	0.41	0.56	0.52	0.60	1.2	0.99	2.5	1.3	.1.0	3.5
TH per Lung Area, SA /m^2	0.24	0.25	0.47	0.65	0.59	0.69	1.4	1.1	2.9	1.5	1.2	4.0
TB per TB Area, SA /m^2	0.43	0.55	0.45	0.86	1.20	0.53	1.5	2.4	3.3	1.6	2.5	4.6
A per A Area, SA /m^2	0.16	0.18	0.49	0.56	0.46	0.82	1.3	0.87	2.6	1.4	0.88	3.7
SA per Macrophage	0.15	0.18	0.47	0.54	0.45	0.79	0.87	0.56	1.7	1.4	0.85	3.6
V. Surface Area of Particles Retained in TB												
6-h Avg per TB area, SA /m^2	1.7	2.3	2.2	3.6	5.1	2.4	4.3	4.9	5.2	7.0	9.8	16
24-h Avg per TB area, SA /m^2	4.9	8.0	8.8	11	16	8.7	13	12	13	20	29	47
VI. Surface Area of Particles Retained in A												
6-h Avg per A area, SA /m^2	0.16	0.18	0.48	0.55	0.46	0.82	0.88	0.57	1.7	1.4	0.87	3.6
24-h Avg A per A area, SA /m^2	0.16	0.18	0.49	0.56	0.46	0.82	0.89	0.58	1.8	1.4	0.88	3.7
VII. Number of Particles Deposited												
TH per Lung Mass, # /g	0.09	0.09	0.12	0.25	0.22	0.23	0.63	0.43	0.53	0.63	0.44	0.64
TH per Body Mass, # /g	0.21	0.20	0.29	0.60	0.51	0.53	1.5	1.0	1.2	1.5	1.0	1.5
TH per Lung Area, # /m^2	0.24	0.23	0.33	0.69	0.59	0.61	1.7	1.2	1.4	1.7	1.2	1.7
TB per TB Area, # /m^2	0.39	0.49	0.36	0.80	1.00	0.65	0.9	1.8	1.8	1.6	1.9	2.1
A per A Area, # /m^2	0.14	0.17	0.32	0.61	0.49	0.60	2.3	1.0	1.3	1.8	1.0	1.6
# per Macrophage	0.13	0.17	0.31	0.59	0.48	0.58	1.1	0.65	0.82	1.8	1.0	1.5
VIII. Number of Particles Retained in TB												
6-h Avg per TB area, # /m^2	1.6	2.0	1.4	3.6	3.8	2.1	4.3	4.3	3.3	6.9	6.7	5.8
24-h Avg per TB area, # /m^2	4.7	5.2	3.8	10.7	10.3	5.6	13	12	8.1	21	18	15
IX. Number of Particles Retained in A												
6-h Avg per A area, # /m^2	0.14	0.17	0.31	0.62	0.49	0.59	1.1	0.66	0.84	1.8	1.0	1.5
24-h Avg per A area, # /m^2	0.14	0.17	0.31	0.62	0.49	0.60	1.1	0.67	0.84	1.8	1.0	1.5

*At, Aitken mode; Ac, accumulation mode; C, coarse mode; TH, thoracic region; TB, tracheobronchial region; A, alveolar region; SA, particle surface area; #, particle number.

number distribution of the Aitken mode is based on monodisperse particles of 0.013 μm diameter, the number mean diameter of the Aitken mode.

7A.5.1.3 Exposure to Resuspended Combustion Particles

Experimental studies with rats have typically used only one particle size range, either Aitken mode particles (exposure to diesel or auto exhaust), accumulation mode particles (CAPs or some acid aerosol exposure studies), or resuspended PM. Resuspended PM, regardless of its initial size distribution, if passed through a 2.5 μm cyclone or impactor, will have a MMAD between 1 and 2 μm and a σ_g between 1.5 and 2.5. One can ask if it is appropriate to compare the rat dose, from only one of the PM size ranges, to the human dose from only that size range when the human is exposed to the entire atmospheric aerosol. The answer to this question may be brought into focus by asking what size particle should be used to calculate the human dose to compare with rat exposures to resuspended combustion particles, such as the stationary source combustion particles (e.g., ROFA) used in many EPA studies. It would not be appropriate to use as a basis for the human dose, or for the equivalent human exposure, an exposure to resuspended particles. People do not typically breath resuspended particles with a MMAD of 2 μm and a σ_g of 2. As shown in Figure 7A-1, resuspended particles have minimal surface area or particle number compared to the PM that a human would be exposed to in an urban atmosphere. Thus, if the health effect of interest were related to particle surface area or particle number, it would require very high doses of a typical resuspended PM to achieve surface area or number doses equivalent to those received by a human. Tables 7A-8a and 7A-8b report calculated values of EqER for the comparison of a rat exposed to resuspended PM (MMAD = 2 μm, σ_g = 2) relative to a human exposed to all three modes of the atmospheric size distribution for four human exposure scenarios.

For a comparison of a rat exposed to resuspended PM for 6 h to a human exposed to ambient PM near a roadway for 6 h, the EqER for mass-based metrics (Table 7A-8a) have a smaller range than for the comparison of individual modes: 0.13 to 2.7 for deposited mass, 0.54 to 16 for mass retained in the TB region, and 0.12 to 2.0 for mass retained in the A region. However, for dose metrics based on surface area or number, EqER values are very high because

TABLE 7A-8a. PREDICTED PARTICLE MASS DOSE METRICS FOR RAT EXPOSED TO RESUSPENDED PM (e.g., ROFA), HUMAN EXPOSED TO ALL THREE ATMOSPHERIC MODES: EQUIVALENT EXPOSURE RATIO (EqER) FOR PM DOSE AFTER A 6-HOUR EXPOSURE FOR SEVERAL BREATHING PATTERNS.*

I. Deposited Mass	**Resting**	**Light**	**Moderate, Normal Augmentor**	**Moderate Oral Breathing**
TH per Lung Mass, μg/g	0.13	0.25	0.72	0.84
TH per Body Mass, μg/g	0.29	0.59	1.7	2.0
TH per Lung Area, $\mu g/m^2$	0.34	0.67	1.9	2.3
TB per TB Area, $\mu g/m^2$	0.35	0.61	2.3	2.7
A per A Area, $\mu g/m^2$	0.33	0.73	1.7	2.0
μg per Macrophage	0.32	0.70	1.7	1.9
II. Retained Mass in TB				
6-h Avg per lung mass, μg/g	0.54	0.84	2.0	2.3
24-h Avg per lung mass, μg/g	3.6	2.4	5.1	5.7
6-h Avg per body mass, μg/g	1.3	2.0	4.7	5.4
24-h Avg per body mass, μg/g	8.4	5.6	12	13
6-h Avg per TB area, $\mu g/m^2$	1.5	2.3	5.5	6.3
24-h Avg per TB area, $\mu g/m^2$	9.9	6.6	14	16
III. Retained Mass in A				
Maximum per A Area	0.33	0.72	1.7	2.0
6-h Avg per lung mass, μg/g	0.12	0.27	0.63	0.73
24-h Avg per lung mass, μg/g	0.12	0.27	0.64	0.74
6-h Avg per body mass, μg/g	0.29	0.62	1.5	1.7
24-h Avg per body mass, μg/g	0.29	0.63	1.5	1.7
6-h Avg per A area, $\mu g/m^2$	0.33	0.72	1.7	2.0
24-h Avg per A area, $\mu g/m^2$	0.33	0.73	1.7	2.0

* At, Aitken mode; Ac, accumulation mode; C, coarse mode; TH, thoracic region; TB, tracheobronchial region; A, alveolar region; SA, particle surface area; #, particle number.

TABLE 7A-8b. PREDICTED PARTICLE SURFACE AREA AND NUMBER DOSE METRICS FOR RAT EXPOSED TO RESUSPENDED PM (e.g., ROFA), HUMAN EXPOSED TO ALL THREE ATMOSPHERIC MODES: EQUIVALENT EXPOSURE RATIO (EqER) FOR PM DOSE AFTER A 6-HOUR EXPOSURE FOR SEVERAL BREATHING PATTERNS.*

IV. Surface Area of Particles Deposited	**Resting**	**Light**	**Moderate, Normal Augmentor**	**Moderate, Oral Breathing**
TH per Lung Mass, SA/g	1.7	4.4	9.4	9.9
TH per Body Mass, SA/g	4.0	10	22	23
TH per Lung Area, SA/m^2	4.6	12	25	27
TB per TB Area, SA/m^2	6.7	14	26	27
A per A, SA/m^2	3.5	11	25	27
SA per Macrophage	27	87	132	208
V. Surface Area of Particles Retained in TB				
6-h Avg per TB area, SA/m^2	31	65	74	125
24-h Avg per TB area, SA/m^2	94	198	218	381
VI. Surface Area of Particles Retained in A				
6-h Avg per A area, SA/m^2	3.4	11	17	26
24-h Avg A per A area, SA/m^2	3.4	11	17	27
VII. Number of Particles Deposited				
TH per Lung Mass, # /g	2.6E + 03	7.3E + 03	1.8E + 04	1.8E + 04
TH per Body Mass, # /g	6.1E + 03	1.7E + 04	4.2E + 04	4.2E + 04
TH per Lung Area, # $/m^2$	7.0E + 03	2.0E + 04	4.8E + 04	4.9E + 04
TB per TB Area, # $/m^2$	2.0E + 04	4.1E + 04	4.5E + 04	8.0E + 04
A per A Area, # $/m^2$	3.0E + 03	1.3E + 04	5.0E + 04	3.9E + 04
# per Macrophage	2.9E + 03	1.3E + 04	2.4E + 04	3.8E + 04
VIII. Number of Particles Retained in TB				
6-h Avg per TB area, # $/m^2$	9.0E + 04	2.0E + 05	2.3E + 05	3.8E + 05
24-h Avg per TB area, # $/m^2$	2.3E + 05	5.3E + 05	6.4E + 05	1.1E + 06
IX. Number of Particles Retained in A				
6-h Avg per A area, # $/m^2$	2.9E + 03	1.3E + 04	2.4E + 04	3.9E + 04
24-h Avg per A area, # $/m^2$	2.9E + 03	1.3E + 04	2.3E + 04	3.9E + 04

* At, Aitken mode; Ac, accumulation mode; C, coarse mode; TH, thoracic region; TB, tracheobronchial region; A, alveolar region; SA, particle surface area; #, particle number.

resuspended PM is lacking in smaller particles. Thus, for particle surface area-based dose metrics (Table 7A-8b, Sections IV to VI), EqER values range from 1.3 to 380. For particle number-based dose metrics (Table 7A-8b, Sections VII to IX), EqER range from 1,100 to 1,100,000.

7A.5.1.4 Rat Exposed to One Fraction, Human Exposed to All Three Modes of the Atmospheric Particle Size Distribution

As suggested in 7A.5.1.2, it may not be appropriate to compare a rat dose from one particle size fraction to a human dose from the same size fraction (as was reported in Tables 7A-7a and 7A-7b) because humans are exposed to the full range of particle sizes. Tables 7A-9a and 7A-9b show EqER values derived from normalized doses calculated from the combined exposure to all three particles size fractions for humans whereas rats were considered to be exposed to only one of the three size fractions in a given individual study. Again, a wide range of EqER values is found: from 0.03 to 4.1 for deposited mass, from 0.19 to 24 for retained mass in the TB region, and from 0.03 to 3.9 for retained mass in the A region. For particle surface area- and particle number-based dose metrics the ranges for EqER values are very high, 0.008 to 1,300 for surface area and 0.01 to 1.3×10^7 for number.

7A.5.1.5 Discussion

Several conclusions can be drawn from the above comparisons. For a specific dose metric, it is possible to calculate a rat exposure that will give a dose equivalent to that received by a human or to calculate a human exposure that would give a dose equivalent to that received by a rat. However, the doses will be equivalent only for the specific dose metric chosen; for other dose metrics, the doses may not be equivalent. If the rat and human are exposed to particles with the same size distributions, or if the comparisons are based only on deposited mass, the variations among dose metrics would be moderate. However, if dose metrics include particle surface area or number, the variations among doses between rats and humans, other than for the specified dose metric, may be very large.

It is especially difficult to determine a human exposure to ambient PM that would yield a human dose equivalent to a rat dose due to exposure to resuspended PM. Toxicity may depend

TABLE 7A-9a. PREDICTED PARTICLE MASS DOSE METRICS FOR RAT EXPOSED TO ONE MODE AT A TIME, HUMAN EXPOSED TO ALL THREE ATMOSPHERIC MODES: EQUIVALENT EXPOSURE RATIO (EqER) FOR PM DOSE AFTER A 6-HOUR EXPOSURE FOR SEVERAL BREATHING PATTERNS.*

	Resting			Light			Moderate, Normal Augmentor			Moderate, Oral Breathing		
I. Deposited Mass	**At**	**Ac**	**C**	**At**	**Ac**	**C**	**At**	**Ac**	**C**	**At**	**Ac**	**C**
TH per Lung Mass, µg/g	0.033	0.10	0.22	0.07	0.20	0.43	0.19	0.58	1.2	0.22	0.68	1.5
TH per Body Mass, µg/g	0.078	0.24	0.51	0.15	0.47	1.0	0.44	1.4	2.9	0.52	1.6	3.4
TH per Lung Area, µg/m^2	0.089	0.27	0.59	0.18	0.54	1.2	0.51	1.6	3.4	0.60	1.8	3.9
TB per TB Area, µg/m^2	0.14	0.57	0.54	0.25	0.98	0.92	0.93	3.7	3.5	1.1	4.4	4.1
A per A Area, µg/m^2	0.071	0.20	0.64	0.16	0.44	1.4	0.37	1.0	3.3	0.43	1.2	3.9
µg Mass per Macrophage	0.069	0.19	0.62	0.15	0.42	1.4	0.36	1.0	3.2	0.42	1.2	3.7
II. Retained Mass in TB												
6-h Avg per lung mass, µg/g	0.19	0.82	0.81	0.30	1.3	1.3	0.71	3.0	3.0	0.8	3.5	3.5
24-h Avg per lung mass, µg/g	1.2	4.8	5.6	0.80	3.2	3.7	1.70	6.8	7.9	1.9	7.7	8.9
6-h Avg per body mass, µg/g	0.45	1.9	1.9	0.70	3.0	3.0	1.66	7.1	7.1	1.9	8.2	8.1
24-h Avg per body mass, µg/g	2.8	11	13	1.9	7.6	8.7	4.00	16	19	4.5	18	21
6-h Avg per TB area, µg/m^2	0.52	2.2	2.2	0.82	3.5	3.5	1.95	8.4	8.4	2.2	9.6	9.5
24-h Avg per TB area, µg/m^2	3.3	13	15	2.2	8.9	10	4.69	19	22	5.3	21	24
III. Retained Mass in A												
Maximum per A Area	0.071	0.20	0.64	0.15	0.43	1.4	0.36	1.0	3.3	0.42	1.2	3.8
6-h Avg per lung mass, µg/g	0.026	0.073	0.24	0.057	0.16	0.51	0.13	0.37	1.2	0.16	0.44	1.4
24-h Avg per lung mass, µg/g	0.026	0.074	0.24	0.057	0.16	0.52	0.14	0.38	1.2	0.16	0.44	1.4
6-h Avg per body mass, µg/g	0.062	0.17	0.56	0.13	0.37	1.2	0.32	0.88	2.9	0.37	1.0	3.3
24-h Avg per body mass, µg/g	0.062	0.17	0.56	0.13	0.38	1.2	0.32	0.89	2.9	0.37	1.0	3.4
6-h Avg per A area, µg/m^2	0.071	0.20	0.64	0.15	0.43	1.4	0.36	1.01	3.3	0.42	1.2	3.8
24-h Avg per A area, µg/m^2	0.071	0.20	0.65	0.16	0.43	1.4	0.37	1.02	3.3	0.43	1.2	3.9

*At, Aitken mode; Ac, accumulation mode; C, coarse mode; TH, thoracic region; TB, tracheobronchial region; A, alveolar region; SA, particle surface area; #, particle number.

TABLE 7A-9b. PREDICTED PARTICLE SURFACE AREA AND NUMBER DOSE METRICS FOR RAT EXPOSED TO ONE MODE AT A TIME, HUMAN EXPOSED TO ALL THREE ATMOSPHERIC MODES: EQUIVALENT EXPOSURE RATIO, EqER, FOR PM DOSE AFTER A 6-HOUR EXPOSURE FOR SEVERAL BREATHING PATTERNS.*

	Resting			Light			Moderate, Normal Augmentor			Moderate, Oral Breathing		
IV. Surface Area of Particles Deposited	**At**	**Ac**	**C**	**At**	**Ac**	**C**	**At**	**Ac**	**C**	**At**	**Ac**	**C**
TH per Lung Mass, SA/g	0.008	0.17	7	0.021	0.44	18	0.04	0.93	37	0.05	1.0	40
TH per Body Mass, SA/g	0.019	0.40	16	0.048	1.04	42	0.10	2.2	88	0.11	2.3	93
TH per Lung Area, SA/m^2	0.021	0.46	18	0.056	1.2	48	0.12	2.5	100	0.12	2.7	110
TB per TB Area, SA/m^2	0.035	1.30	23	0.072	2.7	47	0.13	4.9	87	0.14	5.2	92
A per A Area, SA/m^2	0.015	0.28	15	0.049	0.88	49	0.11	2.0	110	0.12	2.1	120
SA per Macrophage	0.12	2.2	120	0.38	6.9	390	0.58	11	590	0.91	17	920
V. Surface Area of Particles Retained in TB												
6-h Avg per TB area, SA/m^2	0.052	2	38	0.11	4.1	81	0.13	4.7	92	0.21	8.0	160
24-h Avg per TB area, SA/m^2	0.16	5.3	120	0.33	11	250	0.37	12	280	0.64	21.4	490
VI. Surface Area of Particles Retained in A												
6-h Avg per A area, SA/m^2	0.015	0.27	15	0.048	0.87	49	0.07	1.3	74	0.12	2.1	120
24-h Avg A per A area, SA/m^2	0.015	0.27	15	0.049	0.88	50	0.07	1.3	75	0.12	2.1	120
VII. Number of Particles Deposited												
TH per Lung Mass, # /g	0.006	3.2	4.4E + 04	0.017	9.0	1.2E + 05	0.042	22	3.0E + 05	0.043	22	3.1E + 05
(TH per Body Mass, # /g	0.014	7.5	1.0E + 05	0.040	21	2.9E + 05	0.099	52	7.1E + 05	0.10	52	7.2E + 05
TH per Lung Area, # /m^2	0.016	8.6	1.2E + 05	0.046	24	3.3E + 05	0.11	60	8.2E + 05	0.11	60	8.2E + 05
TB per TB Area, # /m^2	0.026	29	2.5E + 05	0.054	60	5.0E + 05	0.06	66	5.5E + 05	0.10	115	9.7E + 05
A per A Area, # /m^2	0.009	3.5	5.7E + 04	0.041	15	2.5E + 05	0.16	59	9.6E + 05	0.12	46	7.6E + 05
per Macrophage	0.009	3	5.5E + 04	0.040	15	2.5E + 05	0.07	28	4.6E + 05	0.12	45	7.4E + 05
VIII. Number of Particles Retained in TB												
6-h Avg per TB area, # /m^2	0.040	42	4.0E + 05	0.086	91	8.7E + 05	0.10	110	1.0E + 06	0.17	180	1.7E + 06
24-h Avg per TB area, # /m^2	0.12	107	1.1E + 06	0.26	240	2.5E + 06	0.32	290	3.1E + 06	0.52	480	5.0E + 06
IX. Number of Particles Retained in A												
6-h Avg per A area, # /m^2	0.009	3.4	5.6E + 04	0.042	16	2.5E + 05	0.076	28	4.6E + 05	0.12	46	7.5E + 05
24-h Avg per A area, # /m^2	0.009	3.5	5.7E + 04	0.042	16	2.6E + 05	0.073	27	4.4E + 05	0.12	46	7.6E + 05

*At, Aitken mode; Ac, accumulation mode; C, coarse mode; TH, thoracic region; TB, tracheobronchial region; A, alveolar region; SA, particle surface area; #, particle number.

on both particle size and composition. In addition, the rat has a much smaller deposition fraction for coarse particles than a human, and particle composition (and probably toxicity) varies with mode (and possibly with size within the coarse mode). Therefore, it is difficult to estimate what tissue doses would yield comparable toxicity in rats and humans for exposures in which rats and humans are exposed to particles with different size distributions or for exposures involving coarse PM.

It is possible to use dosimetric models to predict the tissue doses for specific dose metrics. However, it is difficult to determine what exposures would yield doses of comparable toxicity since toxicity may vary with particle size and composition as well as with the distribution of deposition within the lung.

7A.5.1.6 Rat-to-Human Extrapolation of Long-Term PM Burden in the Alveolar Region

As discussed in 7A.4.3.4, differences in clearance, and resulting differences in the long-term burden of poorly soluble PM retained in the lungs of humans and rats, must be considered in extrapolation of chronic exposures. In the MPPD model, the first order alveolar clearance rate constants for the human (for removal of poorly soluble particles from the A region to the TB region) are independent of PM burden (see Appendix Equations 7A-3 and 7A-12). This is probably a reasonable assumption for humans exposed to ambient PM. However, the first order alveolar clearance rate (for removal of poorly soluble particles from the A region to the TB region) for a rat, exposed to PM levels well in excess of ambient PM, depends on the particle burden in the alveolar region (see Appendix Equations 7A-3 and 7A-11). Thus, the fraction of deposited PM mass retained in the alveolar region, as estimated by the MPPD model, does not depend on the PM burden in humans whereas it increases with increasing exposure concentration and PM burden for rats. This phenomenon of the first order rate constant for alveolar clearance decreasing with increased loading is illustrated in Figure 7A-9 for the exposure parameters and particle size given in Table 7A-3.

For rat to human extrapolation of chronic exposure, we have chosen the dose metric of retained mass of poorly soluble PM per unit lung surface area. Dosimetric modeling enables us to estimate the exposure scenario to yield a retained dose in the rat equivalent to a retained dose

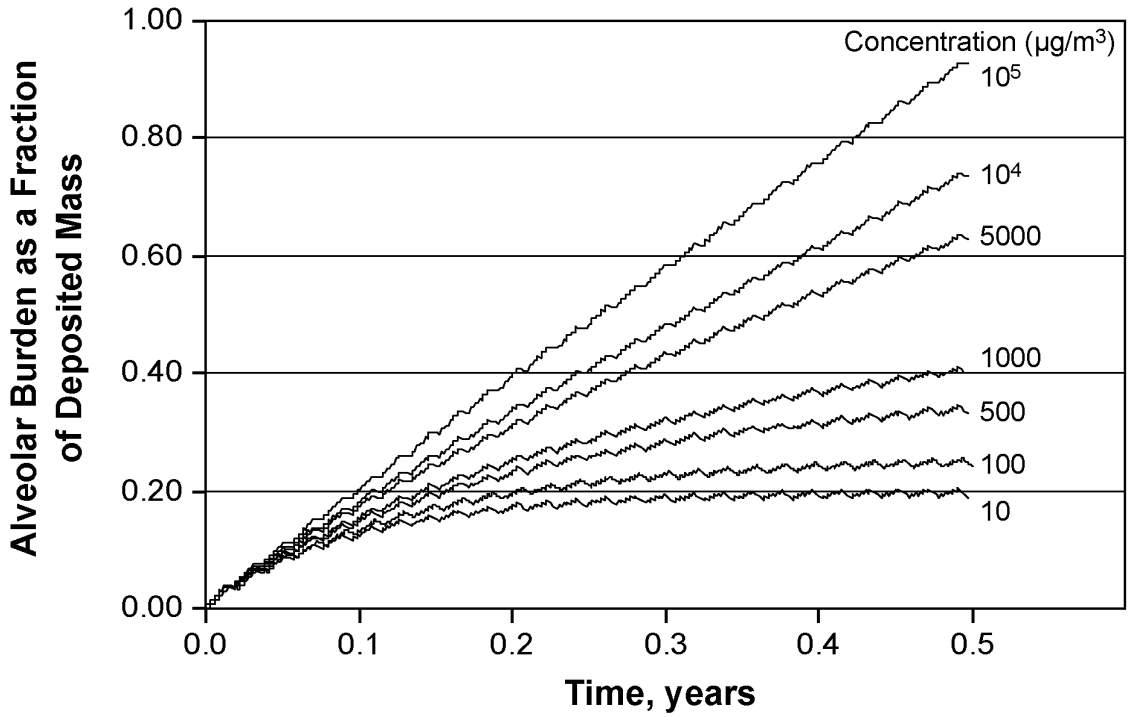

Figure 7A-9. Mass of poorly soluble PM predicted to be retained in the alveolar (A) region of the rat lung as a fraction of the total mass deposited in the A region during a 6-month exposure. The MPPD model estimates illustrated in this figure are for the exposure scenario in Table 3 with the exception of exposure concentrations, which are provided in the figure.

in a human. As illustrated in Figure 7A-10, a rat would require an exposure of 60 µg/m^3 versus a human exposure of only 10 µg/m^3 to have the same retained PM mass per unit alveolar area after 6-months exposure. For shorter exposure times, the rat equivalent dose would be less than 60 µg/m^3.

Suppose that it is necessary to give a rat an exposure such that after 6 months the rat dose (in mass of PM retained per unit alveolar surface area) is the same as a human's steady state dose (0.15 mg/m^2) reached only after about 10-years of exposure. Figure 7A-11 shows the accumulation of PM burden per unit area in a rat for various exposure concentrations. In order to better interpolate the rat 6-month exposure concentration needed to yield the burden in a human at steady state, Figure 7A-12 shows a log log plot of burden versus exposure

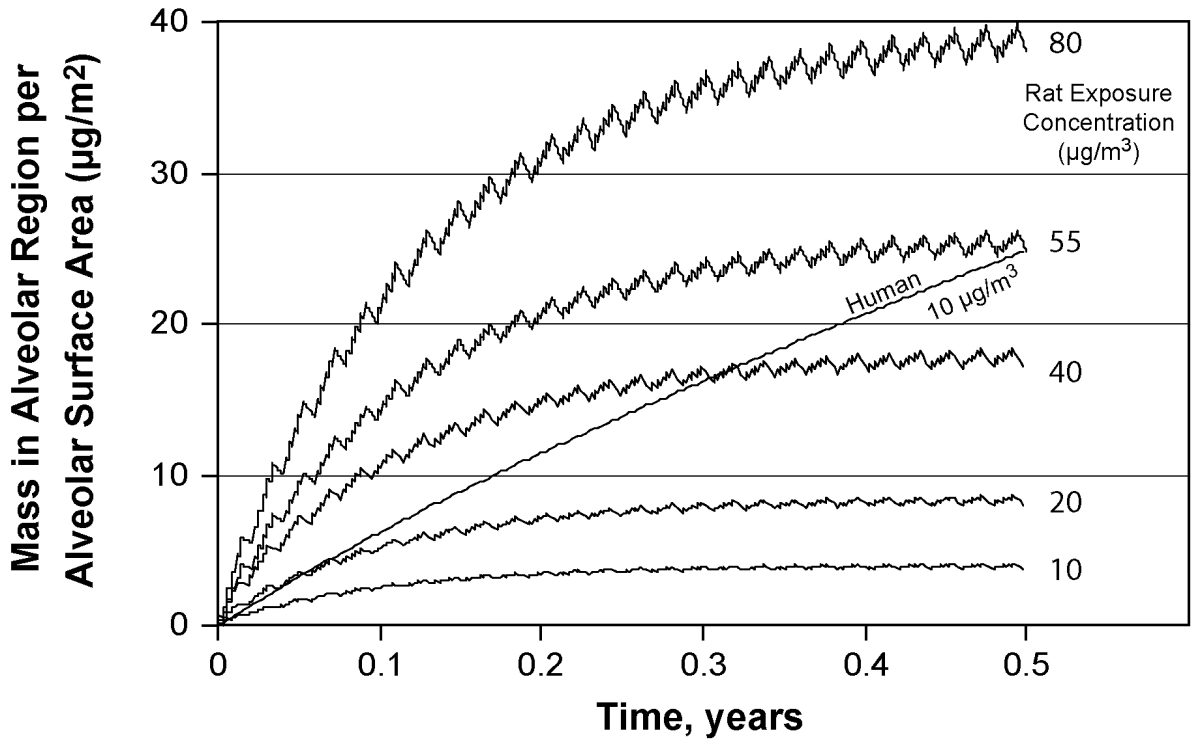

Figure 7A-10. Mass of poorly soluble PM predicted to be retained in the alveolar (A) lung region normalized to A surface area. The MPPD model estimates illustrated in this figure are for the exposure scenarios in Table 3 with the exception of rat exposure concentrations, which are provided in the figure. For the exposure concentration illustrated, the burden in a rat is predicted to reach a plateau or equilibrium during a 6-month exposure, whereas the burden in a human continues to increase montonically with exposure.

concentration and the equation for the regression line. This equation can be used to calculate the rat-equivalent exposure concentration. The equivalent rat exposure concentration is 300 µg/m^3. If one assumes a human exposure to 50 µg/m^3 total PM of which 20% is insoluble, the rat would have to be exposed to the same PM at a concentration of 1,500 µg/m^3 for 6 months (6 h a day, 5 days a week) in order to receive a dose or burden equivalent to the near steady-state dose or burden of a human after exposure to 50 µg/m^3 24 h a day, 7 days a week, for 10 years. The rat would, of course, receive a much greater dose of soluble PM than the human.

The previous discussion applies to obtaining an equivalent lung burden at some instant in time. However, if a health outcome is related to the lung burden that existed over some period

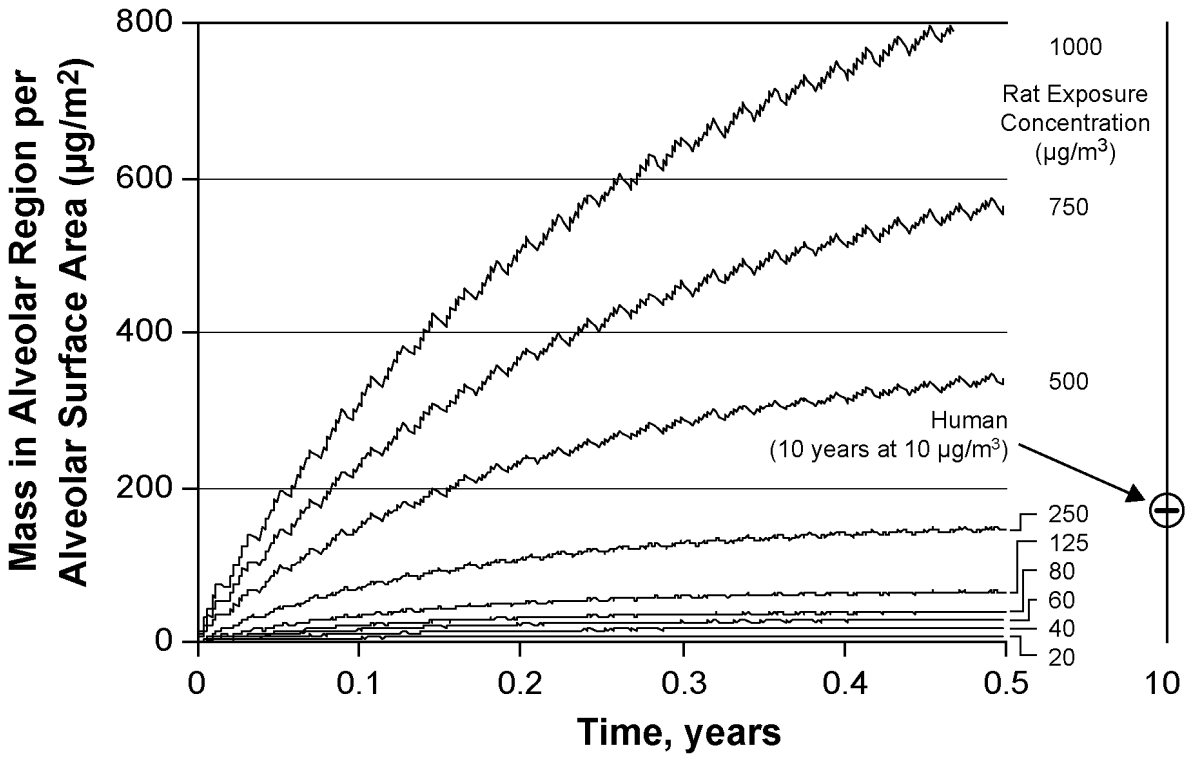

Figure 7A-11. Mass of poorly soluble PM predicted to be retained in the alveolar (A) lung region normalized to A surface area. The MPPD model estimates illustrated in this figure are for the exposure scenarios in Table 3 with the exception of rat exposure concentrations, which are provided in the figure. Due to decreasing clearance rates with increasing burden, it takes longer for the rat to reach equilibrium at the higher exposure concentrations. Illustrated for comparative purposes, humans are predicted to reach a burden of 0.17 mg/m^2 after 10 years of exposure to 10 µg/m^3.

of time, rather than the recent dose, then instantaneous lung burden is less important than the integral of burden over time. Comparing the areas under the rat and human curves in Figure 7A-10 clearly illustrates that the human and rat lung burdens integrated over time (similar to the concept of C × T) are different. In order to mimic the time course of lung burden in a human, it would be necessary to use a constantly, or frequently, changing rat exposure concentration. While it would be possible to obtain an equivalent rat lung burden of very poorly soluble PM, either at a point in time or integrated over time, in either case the rat would receive a much higher dose of soluble PM.

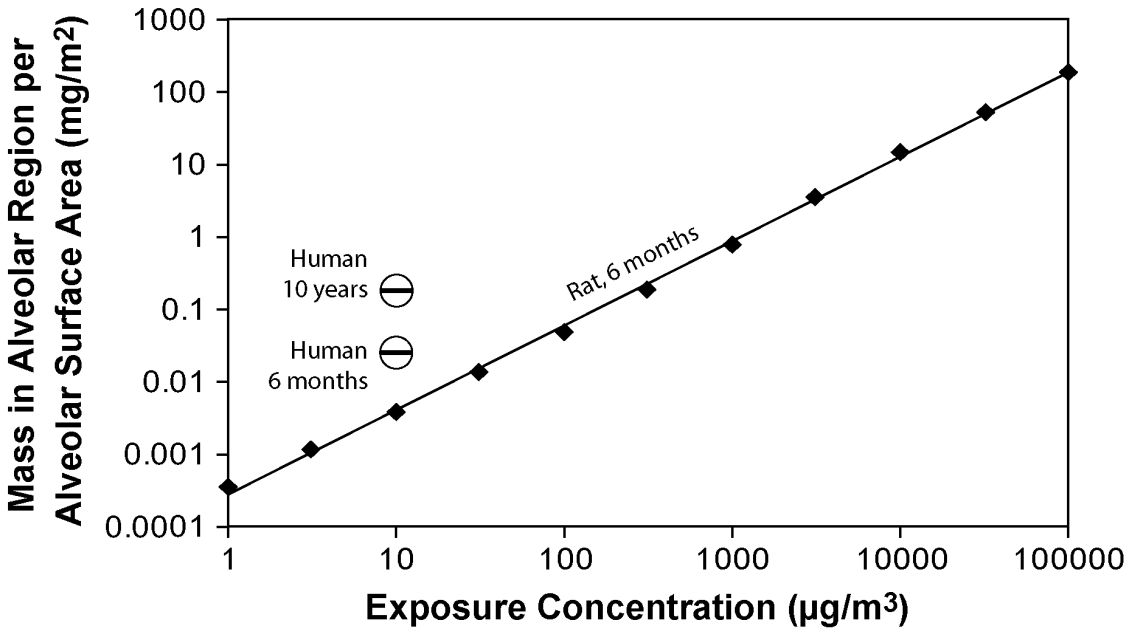

Figure 7A-12. Mass of poorly soluble PM predicted to be retained in the alveolar (A) lung region normalized to A surface area. The MPPD model estimates illustrated in this figure are for the exposure scenarios in Table 3 with the exception of exposure concentrations, which are illustrated. On a log-log plot, particle retention per A surface area in rats after a 6-month exposure is a linear function concentration, i.e, log(Retention [mg/m^2]) = 1.17 × log(Concentration [µg/m^3]) – 3.56, R^2 = 0.999.

7A.5.1.7 Caveats

The simulations are based on a model, and while the model uses similar deposition calculations for humans and rats, the results of the simulations are only considered to be estimates. The particles were assumed to have a density of 1 g/cm^3, making the physical and aerodynamic diameters the same. The calculations for the number dose of At mode particles used a single size, 0.013 µm, rather than a distribution since the MPPD model does not go below 0.01 µm diameter in particle size. No consideration was given to the difference between human PM exposures and ambient PM concentrations nor to exposures to indoor-generated or occupational PM. Thus, while the results may not be quantitatively accurate, the general relationships between human and rat exposure may provide useful information in the attempt to understand rat to human PM dose extrapolation.

7A.6 HEALTH STATUS: A NON-DOSIMETRIC CONSIDERATION

Clearly, many host factors may come into play when considering response to PM. While the mechanistic reasons for enhanced responsiveness are poorly understood, some specific host attributes or health conditions seem to be contributory. Chronic conditions such as diabetes, chronic heart or vascular disease, or chronic lung disease generally have been shown to lead to increased susceptibility. It appears that existent lung conditions which may increase or alter the deposition or retention of PM provide one means (i.e., dose) by which risk is augmented. The very old and the very young may also be more susceptible due to underlying disease, impaired or immature defenses, perhaps exacerbated or associated with other factors such as poor nutrition. Rats normally have higher concentrations of some of the major endogenous antioxidants than people (e.g., ascorbate), and, thereby, may be better able to resist the effects of reactive oxygen species thought to be generated by or in response to PM. However, rats also are subject to "overload," a condition in which sufficiently high doses of PM overwhelm both their clearance and antioxidant defenses. Under these conditions the rat lung is highly sensitive to PM, and fibrosis and tumor formation can occur.

7A.7 COMPARATIVE DOSIMETRY FOR SPECIFIC PUBLISHED STUDY EXAMPLES

This section describes specific human and rat PM exposure studies. The section is divided into three main parts: one examining exposures by intratracheal instillation, a second exposure by inhalation, and a third discussing overload in rats. The MPPD model served as the primary means of estimating regional deposition fractions and retained doses for comparisons. The first part of this section considers ***Utah Valley Dust*** (UVD) instillation studies conducted in humans by Ghio and Devlin (2001) and in rats by Dye et al. (2001). Under the premise that equal tissue doses might produce similar across-species responses, instilled doses are compared across species, and inhalation exposure scenarios leading to comparable tissue doses are presented. The second part examines ***Concentrated Ambient Particles (CAPs)*** inhalation studies conducted in humans by Ghio et al. (2000) and in rats by Kodavanti et al. (2000) and Clarke et al. (1999).

Across-species dose comparisons are made for the same exposure durations and concentrations used in each of the studies. The final part of this section discusses ***Clearance Overload in Rats*** and derives exposure concentrations predicted to achieve varied levels of alveolar loading in subchronically and chronically exposed rats.

7A.7.1 Utah Valley Dust

Table 7A-10a provides assumed exposure scenarios and alveolar doses based on the Utah Valley epidemiology study by Pope (1989) in the context of instillation studies conducted in humans by Ghio and Devlin (2001) and in rats by Dye et al. (2001). The hypothetical exposure scenarios are for humans and rats in the Utah Valley during an "Open-Plant" period (December 1985 to January 1986). On 13 occasions during those 2 months, the 24-h average PM_{10} values exceeded 300 μg/m^3. The 2-month average PM_{10} was 120 μg/m^3 (Pope, 1989). In order to compare instilled doses with a dose received by inhalation, it is necessary to assume a size distribution of the UVD. For this region of the U.S., PM_{10} might typically be expected to be about 50% $PM_{2.5}$ by mass (Chapter 3). However, because the steel mill accounted for the majority of PM_{10}, it was assumed that $PM_{2.5}$ was likely closer to 80% of the mass, such as in a highly polluted industrial area (Pinto et al., 1998).

The activity patterns of the exposed humans and rats are also provided in Table 7A-10a. People were presumed generally sedentary, spending 50% of their time at rest and 50% of their time in an activity similar to a slow walk. Rats were assumed always at rest. Tidal volumes and breathing frequencies associated with these activity levels were provided earlier in Table 7A-1. Based on these exposure conditions, people are predicted to deposit between 176 μg (nasal breather) and 222 μg (oral breather) in the A region of the lung on a daily basis, whereas rats are predicted to deposit 2 μg. Only the alveolar region of the lung was considered for comparison to the instilled doses, because most material depositing in the tracheobronchial airways is rapidly cleared.

Ghio and Devlin (2001) tested the hypothesis that the soluble components (~20% of particle mass on average for 1986 - 1987 UVD) of UVD might differ between years when the Geneva Steel Mill was open (1986 and 1988) versus when it was closed (1987) and that these

TABLE 7A-10a. UTAH VALLEY DUST: EXPOSURE SCENARIO

Utah Valley Dust, ambient exposures (December 1985-January 1986)	
– 120 μg/m^3 PM_{10} (2-month average)	
Assumed characteristics of Utah Valley Dust	
– 80% Fine mode (MMAD = 0.31 μm; σ_g = 2.03)	
– 20% Coarse mode (MMAD = 5.7 μm; σ_g = 2.1)	
Activity level and route of breathing	
Human	Rat
– 12 h rest, 12 h slow walk [a]	– 24 h rest
– nasal and oral breathing	– nasal breathing
Predicted Daily Mass Depositing in A region	
Human	Rat
– 176 μg (nasal breathing)	– 2.0 μg
– 222 μg (oral breathing)	

[a] These values represent the presumed average amount of time over the course a day that a person might spend either at rest (sitting or sleeping) or engaged in an activity similar in exertion to a slow walk.

differences might affect biological response. In their study of 24 healthy adults, UVD extracts (500 μg) from either 1986 (n = 8), 1987 (n = 8), or 1988 (n = 8) were instilled into the lingula of the lung. As a control, saline was instilled into a subsegment of the right middle lobe of each study participant. Extracts of UVD were prepared by agitating filter samples in deionized water for 24 h. Following centrifugation, supernatants were removed and lyophilized. The desired amounts of the resulting dry but soluble extracts for each year were then placed in sterile saline for instillations. The estimated surface dose of the instilled material is ~170 μg per m^2 of alveolar surface area (see Table 7A-10b). At 24-h postinstillation and relative to a saline control, lavage fluid from subjects instilled with the 1986 and 1988 extracts contained significantly increased total cells, neutrophils, protein, fibronectin, albumin, and cytokines. The extracts of UVD from 1987 (the year the steel mill was closed) did not elicit a response different from the saline control. Considering the inflammatory response, neutrophil levels were increased

TABLE 7A-10b. UTAH VALLEY DUST: HUMAN INSTILLATION STUDY

Instilled Mass and Surface Dose	
Human	Rat {Similarly exposed}
– 500 μg to lingula[a] (Ghio and Devlin, 2001)	– 50 μg to entire lung
– 170 μg/m^2 (lingular surface dose)	– 170 μg/m^2 (whole lung surface dose)
Predicted Time to Achieve Instilled Surface Dose by Inhalation (assuming no A clearance)[b]	
Human	Rat {Similarly exposed}
– 55 days (nasal breathing)	– 25 days
– 44 days (oral breathing)	
Predicted Time to Achieve Instilled Surface Dose by Inhalation (adjusted for A clearance)[b]	
Human	Rat {Similarly exposed}
– 65 days (nasal breathing)	– 32 days
– 50 days (oral breathing)	

[a] The lingula is the lower anterior portion of the left upper lobe and is the left lung's homologue of the right middle lobe. The volume of lobes relative to total lung capacity is 15.4% for the left upper lobe, 15.4% for the right upper lobe, and 7.7% for the right middle lobe (Yeh and Schum, 1980). Based on the ratio of right middle lobe to right upper lobe volume, the lingula was assumed one-third the volume of the left upper lobe or 5.1% of total lung volume and lung surface area.

[b] Exposure scenario provided in Table 7A-10a.

3.5- and 2.9-fold by the 1986 and 1988 UVD extracts, respectively, but only 1.2-fold by the 1987 UVD extract.

Ghio and Devlin (2001) provided an estimate of the time it might take for their instilled dose to occur by inhalation. They assumed a hypothetical ambient UVD exposure level of PM_{10} (100 μg/m^3). The computations described in their discussion were based on a total lung DF of 0.42. They concluded that the dose instilled (500 μg) into the lingula of human volunteers was roughly comparable to the PM deposited as the result of living about 5 days in the Utah Valley. Strictly speaking, the Ghio and Devlin (2001) analysis is flawed in that they only instilled the soluble fraction of UVD (~20% of particle mass on average for 1986-1988 UVD), whereas their estimates of dose by inhalation are based on total PM_{10}, which contains both soluble and insoluble components. For simplicity, the analysis presented here also considered PM_{10} as

insoluble. The results of this analysis are provided in Table 7A-10b. It was estimated that between 44 and 65 days would be required for a person to deposit the instilled dose on the basis of mass per surface area. A comparable surface dose would occur in a rat after a month of exposure.

The human dose estimate provided in Table 7A-10b differs from that of Ghio and Devlin (2001) for a number of reasons. First, their DF included the nasal, TB, and A regions of the lung. In contrast, the estimate provided here considered only the A region and had an average DF of only 0.1. Second, the lingula is only about 5% of total lung volume, whereas the authors assumed the lingula represented 10% of lung volume. This difference effectively doubled the estimated surface dose from the instillation. Based on the present analysis, it appears possible to achieve the instilled surface dose at the relatively high ambient PM_{10} concentrations. However, this instilled dose would be achieved only from a subchronic exposure and not in the acute manner in which it was delivered by instillation. Considered from the perspective of a *single exposure day*, the corresponding estimated *24-h average* PM exposure would need to be between 5.2 mg/m^3 (oral breather) and 6.6 mg/m^3 (nasal breather) for humans and 3.0 mg/m^3 for rats.

In the study by Dye et al. (2001), rats received intratracheal instillations of soluble extracts from UVD collected in 1986, 1987, and 1988. UVD extracts were prepared by agitating filter samples in deionized water for 96 h. Following centrifugation, supernatants were removed and lyophilized. The desired amounts of the resulting dry but soluble extracts for each year were then placed in sterile saline for instillations. The 1986 UVD extracts were instilled at the doses of 250, 1000, and 2500 µg. Largely driven by an influx of neutrophils, the BAL fluid collected at 24 h postinstillation showed a dose dependent increase in total cell counts (see Figure 4 in Dye et al., 2001). Neutrophil cell counts (BAL fluid cell counts × 10^3/mL) were 105, 245, and 370 for the 250-, 1000-, and 2500-µg doses, respectively. These increases in neutrophils are 10-, 22-, and 34-fold [for the doses of 250, 1000, and 2500 µg, respectively] relative to an average neutrophil level of 11 (BAL fluid cell counts × 10^3/mL) in the saline controls (n = 22). The 1987 UVD (collected the year the Geneva Steel Mill was closed) extract instilled at the dose of 5000 µg only increased neutrophil levels to 61 (BAL fluid cell counts × 10^3/mL). These findings are generally consistent with Ghio and Devlin (2001) in that the 1987 dust extracts were far less potent producers of an inflammatory response relative to 1986 and 1988 extracts.

Considering the 250-μg dose instilled by Dye et al. (2001), the surface dose to the entire rat lung was computed to be 840 μg per m^2 alveolar surface area and used as the dose-equivalent parameter for comparison to humans. These data appear in Table 7A-10c (1). By inhalation and ignoring particle clearance, an 840 μg per m^2 alveolar surface area dose of PM could occur in 124 days for rats and between 215 and 272 days for humans at an ambient PM concentration of 120 $\mu g/m^3$ (see Table 7A-10a for exposure scenarios). When clearance is considered, however, a lung burden equal to the instilled dose is not achievable in rats by inhalation, given the exposure conditions provided in Table 7A-10a. Other exposure conditions in which the rat would receive the instilled dose are provided in Table 7A-10c (2). One finds that the rat instillation of 250 μg corresponded to a *single 24-h* exposure by inhalation to a concentration of 15 mg/m^3 in the rats or roughly double this concentration for humans. A 30-day (24 h per day) exposure would still require PM concentrations of 0.6 mg/m^3 in the rats or about 1 mg/m^3 in humans.

The simulations presented here show that ambient PM_{10} exposure periods on the order of months in the Utah Valley (winter 1986) would be required for poorly soluble PM to reach alveolar surface doses equivalent to those instilled by Ghio and Devlin (2001) and by Dye et al. (2001). For a sedentary person, 24 h exposures of at least 5.2 mg/m^3 would be required to reach the doses instilled by Ghio and Devlin (2001). For resting rats, a 24 h exposure to 15 mg/m^3 was predicted to achieve the lowest dose instilled by Dye et al. (2001). However, only the soluble extracts of UVD (~20% of total PM) were instilled in these studies. Approximately 5-fold greater exposures, i.e. 26 mg/m^3 instead of 5.2 mg/m^3 for humans, would be required to reach the instilled surface doses of soluble extracts. It appears very unlikely that a person in the Utah Valley could have received the instilled doses via inhalation in an acute ambient exposure. The dose rates for instillation versus inhalation are also quite obviously different. Thus, the health effects from acute ambient exposures to soluble PM are difficult to predict based on these instillation studies. This, however, does not imply that these studies are without merit. In both the human and rat study, the 1987 dust extracts were far less potent producers of an inflammatory response relative to 1986 and 1988 extracts. Although the pulmonary doses used in these instillation studies may not be achieved via inhalation, these studies suggest that PM composition can affect response.

TABLE 7A-10c(1). UTAH VALLEY DUST: RAT INSTILLATION STUDY

Instilled Mass and Surface Dose

Rat	Human {Similarly exposed}
– 250 μg to whole lung (Dye et al., 2001)	– 48,000 μg to whole lung
– 840 $\mu g/m^2$ (whole lung surface dose)	– 840 $\mu g/m^2$ (whole lung surface dose)

Predicted Time to Achieve Instilled Surface Dose by Inhalation (assuming no A clearance)[b]

Rat	Human {Similarly exposed}
– 124 days	– 272 days (nasal breathing)
	– 215 days (oral breathing)

Predicted Time to Achieve Instilled Surface Dose by Inhalation (adjusted for A clearance)[b]

Rat	Human {Similarly exposed}
– indefinite time[a]	– 3.0 years (nasal breathing)
	– 2.0 years (oral breathing)

[a] The equilibrium lung burden for the exposure conditions is only 160 μg. After one year of exposure, the burden is within 2.5% of this equilibrium.
[b] Exposure scenario provided in Table 7A-10a.

TABLE 7A-10c(2). UTAH VALLEY DUST: RAT INSTILLATION STUDY EXPOSURE SCENARIOS ACHIEVING INSTILLED DOSE

Predicted 24-h Exposure Concentration to Achieve Instilled Surface Dose by Inhalation[a]

Rat	Human {Similarly exposed}
– 15,000 $\mu g/m^3$	– 32,500 $\mu g/m^3$ (nasal breathing)
	– 26,000 $\mu g/m^3$ (oral breathing)

Predicted 30-day Exposure Concentration to Achieve Instilled Surface Dose by Inhalation[a]

Rat	Human {Similarly exposed}
– 590 $\mu g/m^3$	– 1,200 $\mu g/m^3$ (nasal breathing)
	– 950 $\mu g/m^3$ (oral breathing)

[a] With the exception of exposure concentrations, the exposure scenario is provided in Table 7A-10a.

7A.7.2 Concentrated Ambient Particles (CAPs)

In this section, tissue doses predicted to occur in a human and two rat CAPs exposure studies are determined. Ghio et al. (2000) exposed healthy young adult human subjects (n = 38) in Chapel Hill, NC to an average 120 μg/m^3 CAPs for 2 h. Table 7A-11a provides the predicted tissue doses to the subjects that participated in this study as well as the doses that would be predicted to occur in rats for similar exposure conditions (time and concentration). For this particle size and exposure conditions, the dose to the A region of the lung is quite similar between species. This dose elicited a mild inflammatory response but did not affect the pulmonary function of the exposed subjects.

TABLE 7A-11a. CAPs: HUMAN INHALATION STUDY (Ghio et al., 2000)

	Human CAPs Ghio et al. (2000) [a]	Rat {Similarly exposed} [b]
MMAD (μm)	0.65	0.65
σ_g	2.35	2.35
Concentration (μg/m^3)	120	120
Deposited TB Dose per SA [c] (μg/m^2)	64	37
Deposited A Dose per SA (μg/m^2)	0.7	0.78

[a] Two-hour protocol with 15-min periods of heavy exercise ($\dot{V}_E$ = 50 L/min) followed by 15-min of recovery ($\dot{V}_E$ = 13 L/min) repeated four times. Subjects were presumed to breathe as normal oronasal augmenters.
[b] Rats were presumed exposed at rest.
[c] Surface area of lung region.

Kodavanti et al. (2000) exposed healthy (n = 5) and bronchitic (n = 4) rats in Research Triangle Park, NC to 590 μg/m^3 CAPs, 6 h per day, for 3 days. Table 7A-11b provides the predicted tissue doses in the rats and predicted doses for similarly exposed humans. As a control, healthy (n = 4) rats were exposed 6 h per day for 3 days to filtered air. At 18 h after the third exposure, the CAPs-exposed rats showed no significant inflammatory response despite the high delivered and retained doses relative to controls. For clarification, in two of four additional CAPs exposure protocols, Kodavanti et al. (2000) observed a significant neutrophil influx in

TABLE 7A-11b. CAPs: RAT INHALATION STUDY (Kodavanti et al., 2000)

	Rat CAPs Kodavanti et al. (2000) [a]	Human {Similarly exposed} [a]
MMAD (μm)	0.98 [b]	0.98
σ_g	1.41 [b]	1.41
Concentration ($\mu g/m^3$)	590	590
Deposited TB Dose per SA [c] ($\mu g/m^2$)	1740	642
Deposited A Dose per SA ($\mu g/m^2$)	29	8.8
Retained TB Dose per SA ($\mu g/m^2$)	11 [d]	43 [d]
Retained A Dose per SA ($\mu g/m^2$)	28 [d]	8.6 [d]

[a] Exposure was for 6 h/day for 3 days, both rats and humans were presumed exposed at rest.
[b] Personal communication by study authors.
[c] Surface area of lung region.
[d] Retained dose at 18 h following the 3rd exposure.

bronchitic rats when lavaged within 3 h postexposure. However, data from the rats lavaged at 18 h postexposure are used here for comparison to the Ghio et al. (2000) and Clarke et al. (1999) studies where lavages were performed at 18 and 24 h postexposure, respectively.

Clarke et al. (1999) exposed healthy (n = 12) and bronchitic (n = 12) rats in Boston, MA to 515 $\mu g/m^3$ of CAPs, 5 h per day, for 3 days. Table 7A-11c provides the predicted tissue doses for rats in the Clarke et al. (1999) study and the predicted doses for similarly exposed humans. Note that due to differences in the inhaled particle size, the rats in the Clarke et al. (1999) study were predicted to receive a greater dose than the rats in the Kodavanti et al. (2000) study despite a shorter exposure time and lower CAPs concentration. The dose of CAPs per alveolar surface area was about 67 times greater in the rats (Clark et al., 1999) relative to the humans (Ghio et al., 2001). The inflammatory response observed in healthy rats by Clarke et al. (1999), however, was quantitatively similar to that observed by Ghio et al. (2000) in healthy humans.

TABLE 7A-11c. CAPs: RAT INHALATION STUDY (Clarke et al., 1999)

	Rat CAPs Clarke et al. (1999) [a]	Human {Similarly exposed} [a]
MMAD (μm)	0.18 [b]	0.18
σ_g	2.9 [b]	2.9
Concentration ($\mu g/m^3$)	515	515
Deposited TB Dose per SA [c] ($\mu g/m^2$)	1580	802
Deposited A Dose per SA ($\mu g/m^2$)	48	8.9
Retained TB Dose per SA ($\mu g/m^2$) [b]	16 [d]	36 [d]
Retained A Dose per SA ($\mu g/m^2$) [b]	47 [d]	8.8 [d]

[a] Exposure was for 5 h/day for 3 days, both rats and humans were presumed exposed at rest.
[b] This is the size distribution of the ambient particles and may differ from the concentrated aerosol to which the rats were exposed.
[c] Surface area of lung region.
[d] Retained dose at 24 h following the 3rd exposure.

7A.7.3 Clearance Overload in Rats

Unlike other laboratory animals and humans, rats appear susceptible to "overload"-related effects due to impaired macrophage-mediated alveolar clearance. Numerous reviews have discussed this phenomenon and the difficulties it poses for the extrapolation of chronic effects in rats to humans (ILSI, 2000; Miller, 2000; Oberdörster, 1995, 2002; Morrow, 1994). In brief, rats chronically exposed to high concentrations of insoluble particles, even those which may generally be considered as nuisance or low toxicity dusts, experience a reduction in their alveolar clearance rates. With continued exposure, some rats eventually develop pulmonary fibrosis and both benign and malignant tumors. These high-dose effects are not observed at lower doses in rats. Oberdörster (2002) proposed that high-dose effects observed in rats may be associated with two thresholds. The first threshold is the pulmonary dose that results in a reduction in macrophage-mediated clearance. The second threshold, occurring at a higher dose than the first, is the dose at which antioxidant defenses are overwhelmed and pulmonary tumors develop. In chronic exposure studies, maintaining pulmonary doses below these thresholds should lessen

the uncertainty in the extrapolation of effects observed in rats to those expected in humans. Here the focus will be on the lower threshold, i.e., the dose capable of overwhelming macrophage-mediated alveolar clearance in rats, and derive concentrations for chronic exposures below which overload might be avoided.

Overload has been loosely defined as the alveolar burden causing a 2- to 4-fold reduction in alveolar clearance rates relative to normal clearance rates (ILSI, 2000; Oberdörster, 1995). There is some discrepancy between whether overload is related to deposited particle volume or surface area (Miller, 2000; Oberdörster, 2002). Here, only the relationship between volume loading and overload is considered. To be consistent with Morrow's (1988, 1994) analyses in this discussion of overload, the following values are assumed for rats: lung weight, 1.5 grams; displaced volume of an AM, 1000 μm^3; number of AM, 2.5×10^7. Morrow (1988) suggested a rat's macrophage-mediated clearance was impaired at a volumetric loading of 60 μm^3 per AM and that macrophage stasis occurred at a loading of 600 μm^3. These volumes represent 6 and 60% of the AM's displaced volume and correspond to the volumetric loadings of 1,000 and 10,000 nL/g-lung, respectively. Clearance rates do not differ from control at the volume loading of 100 nL/g-lung or 6 μm^3 per AM (Morrow, 1994). Morrow (1994) described the relationship between alveolar clearance rates (k, day^{-1}) in rats and the particle volume loading (V_a, nL/g-lung) as $k = 0.021 - 0.0052 \times \log(V_a)$ for $100 < V_a < 10{,}000$ nL/g-lung. Based on this equation and consistent with Morrow (1988), the loading that would cause a doubling of the retention half-time (a loose definition of overload) can be determined to occur at 1,000 nL/g-lung or 60 μm^3 per AM. For comparison, from Table 2 in Oberdörster (1995), a loading of 1,400 nL/g-lung can be inferred as doubling retention half-times, fairly consistent with Morrow (1994).

Based on the work of Morrow (1988, 1994), estimates of the volumetric loadings associated with no effect on clearance (100 nL/g-lung), the onset of overload (1,000 nL/g-lung), and AM stasis (10,000 nL/g-lung) can be determined. The goal here was to derive concentrations for chronic exposures below which overload might be avoided. Miller (2000) estimated the amount of time that it would take for a rat (F344) exposed to 10 mg/m^3 for 24 h per day to reach clearance stasis on the basis of volumetric loading. For monodisperse 1 µm particles (DF = 0.04, V_T = 2.1ml, f = 102 min^{-1}), Miller estimated it would take about 80 days

(ignoring clearance) for the AM to become filled and reach stasis. Within the macrophage, particles were assumed to be tightly packed spheres occupying a volume of 1.43 times greater than the volume of the particles themselves, i.e., the porosity or void space between spheres is 0.3. Using the clearance kinetics from the MPPD model, an additional 10 days (90 days total) would be required to reach stasis. This approach can also be used to determine the amount of time required to reach lower levels of AM loading, or conversely, the exposure concentration achieving a level of loading in a given period of time.

In Table 7A-12, particle concentrations for rat exposures predicted to cause various levels of alveolar loading are shown. Alveolar loadings in this table refer to the volumes occupied by unit density spheres. However, particle density cannot be ignored, because for a constant MMAD, the physical size and volume of particles decreases with increasing density. Hence, despite having the same MMAD, dense particles would achieve a lower volumetric loading than unit density spheres for the same exposure concentration. The loading achieving stasis has been reduced from 10 μL/g-lung to 7 μL/g-lung as an adjustment for the void space between packed particles within macrophages. The onset of overload may also be considered as adjusted for void space based on a reduction from 1.4 μL/g-lung (Oberdörster, 1995) to1 μL/g-lung. Although, this difference (1 versus 1.4 μL/g-lung) may be due to variability between experiments.

The volumetric loadings in the Table 7A-13 were estimated for an exposure scenario of 6 h per days, 5 days per week. However, other exposure scenarios can easily be considered by maintaining a constant weekly exposure. For instance, in rats exposed 6 h per day, 1 day per week for 1 year to an aerosol (MMAD = 2μm, σ_g = 1.5), a loading of 1 μL/g-lung is predicted for an exposure concentration of 12.5 mg/m^3. This exposure concentration of 12.5 mg/m^3 is calculated as 2.5 mg/m^3 (from table) × 30 h (used for table estimates) ÷ 6 h (the desired weekly exposure time).

The analysis of particle overload in rats presented here is somewhat simplistic in that it only considered the accumulated volumetric burden of particles in the lung. More sophisticated multicompartment models of AM-mediated clearance, based on particle volume (Stöber, 1994) and particle surface area (Tran, 2000), exist. An important consideration addressed by Stöber et al. (1994) is that not all AM carry the same burden. Another important AM-related

TABLE 7A-12. ESTIMATED EXPOSURE CONCENTRATIONS (mg/m^3) LEADING TO VARIED LEVELS OF ALVEOLAR LOADING AS A FUNCTION OF PARTICLE SIZE AND EXPOSURE DURATION

		Alveolar Volume Loading[c] (µL/g-lung)				
		0.1 *No effect*	0.3	1 *Overload*	3	7 *Stasis*
Exposure Time[a]	**MMAD[b] (µm)**	**Exposure Concentration (mg/m^3) to Achieve Above Alveolar Loadings**				
2 months	1	1.1	3	9.1	25	57
	2	1	2.7	8.1	22	50
	3	1.3	3.4	10	29	64
	4	1.8	4.8	15	40	90
3 months	1	0.8	2.2	6.2	16	36
	2	0.8	1.9	5.5	15	32
	3	1	2.5	7	19	41
	4	1.3	3.5	10	26	58
6 months	1	0.6	1.5	3.9	9.5	20
	2	0.6	1.4	3.5	8.4	18
	3	0.7	1.7	4.4	11	22
	4	1	2.4	6.2	15	32
1 year	1	0.6	1.3	2.8	6.1	12
	2	0.5	1.1	2.5	5.4	10
	3	0.7	1.4	3.2	6.9	13
	4	0.9	2	4.5	9.7	19
2 years	1	0.6	1.2	2.4	4.4	7.6
	2	0.5	1	2.1	3.9	6.8
	3	0.6	1.3	2.7	5	8.6
	4	0.9	1.9	3.8	7.1	12

[a] Rats presumed exposed at rest for 6 h per day, 5 days per week.
[b] Geometric standard deviation of 1.5.
[c] Effects of alveolar loading on macrophage-mediated clearance range from no effect at 0.1 µL/g-lung, to overload at 1 µL/g-lung, to stasis at 7 µL/g-lung.

consideration is that particle uptake by AM depends on particle size. The efficiency of phagocytosis by AM appears to be greatest for particles between 1.5 and 3 µm in diameter (Oberdörster, 1988). Adamson and Bowden (1981) reported less phagocytic activity in rats following instillation of 0.1 µm versus 1.0 µm latex spheres. In addition, Adamson and Bowden (1981) identified 0.1 µm spheres in Type 1 epithelial cells, free in the interstitium, and in

interstitial macrophages — all of which were rarely seen for the larger 1.0 μm spheres. Recognizing the importance of particle size on AM-mediated clearance, only values of MMAD between 1 and 4 μm were included in the analysis of overload discussed here.

Particles formed by the aggregation of smaller particles also warrant special consideration with regard to alveolar clearance kinetics. Ferin et al. (1992) conducted an inhalation study using particle aggregates having MMAD of 0.78 and 0.71 μm, which were composed of 0.021 and 0.25 μm TiO_2 primary particles, respectively. Rats were exposed to an aerosol concentration of 23 to 23.5 mg/m^3 (6 h/day, 5 days/week, 12 weeks). Postexposure retention half-times were 174 days for fine primary particles (0.25 μm diameter) versus 501 days for the ultrafine primary particles (0.021 μm diameter). With primary particle size affecting clearance kinetics, this study supports the supposition that TiO_2 particles may disaggregate following deposition in the lung. Particle disaggregation following deposition in the lung appears to be specific to TiO_2 aerosols (Takenaka et al., 1986). Contrary to the analysis of overload as a function of volume loading as presented in Table 7A-12, ultrafine TiO_2 particles have a longer retention than fine TiO_2 particles, despite having the same alveolar loading on the basis of particle volume. The overload of ultrafine particles might be function of particle surface area rather than volume. Hence, depending on material from which an aggregate is composed, it may be inappropriate to assess alveolar loading on the basis of particle volume.

7A.8 SUMMARY

The MPPD model was used to calculate concentrations of atmospheric and resuspended PM that would be necessary to achieve doses in the rat comparable to those in humans breathing ambient PM, as measured by a variety of dose metrics. The same model was then used to estimate the differences in doses in rats and humans exposed to comparable types of ambient or emission PM in salient published studies. Complementary approaches were used to analyze the relationship between PM doses resulting from inhalation exposures or intratracheal instillation in rats and PM doses in humans resulting from exposures during a variety of activities.

The MPPD model estimates in Table 7A-8a suggest that, depending on the activity level and breathing pattern of the human, a rat may need to be exposed to between 33 and 200 $\mu g/m^3$ of resuspended PM over 6 h to receive an incremental dose in the A region per surface area (measured as deposited mass) comparable to that of a healthy human working for 6 h near a busy road and exposed to 100 $\mu g/m^3$ ambient PM_{10}. To achieve an incremental dose retained in the rat TB region per TB surface area (averaged over 6 h) comparable to that in the human, the rat would need to be exposed to between 150 and 630 $\mu g/m^3$ (depending on the activity level and breathing pattern of the human) of resuspended PM for 6 h. However, because of the more rapid clearance in the rat, a higher exposure concentration of between 0.7 and 1.6 mg/m^3 would be required for the rat to achieve a retained TB dose per TB surface area (averaged over 24 h) comparable to that in the human.

The chronic retention of PM in the A region of the human cannot be simulated in the rat except under conditions in which the normal clearance process of the rat is inhibited. However, giving high doses of PM to healthy mature rats will likely not simulate the response of humans who are vulnerable because of heart or vascular disease, infectious diseases of the lung, conditions such as diabetes, or acute or chronic stress. Therefore, development of rat models of human vulnerabilities would enhance the value of using the rat in inhalation toxicology studies. Understanding the interplay of dose and responsiveness in animal models as well as in the human will substantially advance the ability to predict adverse health outcomes in the human population.

In daily life, humans are exposed to PM in the atmosphere and inhale a complex profile of Aitken, accumulation, and coarse mode particles covering a size range from below 0.1 to over 10 μm diameter. On the other hand, laboratory inhalation studies do not simulate the full size distribution to which humans are exposed and in some cases do not simulate the chemical composition or physical structure of atmospheric particles. Resuspended PM (e.g., ROFA-like material or other bulk material) has a particle size intermediate between coarse and accumulation modes but does not have the smaller sizes of the accumulation or Aitken modes. CAPs give a better simulation of the chemical composition of atmospheric particles but typically concentrate only one mode. For ultrafine particles, the physical structure and possibly the chemical composition may be changed by going through growth and shrinkage during the concentration

process. Fresh diesel exhaust particles, especially if more concentrated than in a roadway, will have a larger particle size than when diluted by vehicle turbulence. They will also differ in physical structure and chemical composition from aged diesel particles. Acid aerosol studies may also use particle sizes in the accumulation mode size range but usually do not contain the metals and organic components found in atmospheric aerosols. Laboratory exposures of rats to resuspended dust can simulate the dose of particle mass to the alveolar region but not dose metrics based on particle surface area or number unless very high concentrations are used.

While the calculation of EqER for various dose metrics and normalizing factors is simple, the interpretation of the resulting EqERs can be somewhat more ambiguous. Optimally, the choice of dose metrics and normalizing factors should be based on the biological mechanisms mediating an effect. For soluble compounds, the mass of PM depositing in a region of the lung may be the most appropriate dose metric. For poorly soluble particles depositing in the A region, particle surface area (for ultrafine PM) or particle volume (for coarse PM) may be more appropriate dose metrics. The appropriateness of a normalizing factor is, in part, determined by the site most affected by PM. For soluble compounds, an appropriate normalizing factor could be the surface area of the airways for irritants whereas body mass would be more logical when considering systemic effects. For insoluble compounds retained in the lung, normalizing factors can range from the number of macrophages in an alveolus to the mass of the lung. Due to the more rapid clearance in rats, larger rat exposure doses will be required to simulate retained doses in humans than would be the case for deposited doses. If dose metrics based on surface area or particle number are appropriate, rat exposure concentrations using resuspended PM must be very high because resuspended PM contains few accumulation mode or ultrafine particles.

It appears that no single dose metric nor normalizing factor is appropriate for all situations. As illustrated in Tables 7A-7a through 7A-9b, the parameters chosen can drastically affect the rat exposure concentration required to provide a normalized dose equivalent to that occurring in a human. A rat exposure which simulates a human dose for one specific dose metric or normalizing factor may provide a higher or lower dose as measured by a different dose metric or normalizing factor. In addition, regardless of the dose metric and normalizing factor chosen, the exposure concentration required for a rat to achieve an equivalent human dose increases with the

level of activity of the human being considered. From a purely dosimetric standpoint, the complexity of interspecies extrapolation is obvious but not necessarily insurmountable. Conclusions regarding rat to human comparisons may require the use of a variety of dose metrics and normalizing factors depending on the degree to which biological mechanisms mediating an effect are understood.

Instillation studies in both animals and humans have been criticized for lack of relevance related to dose and means of administration. Ghio and Devlin (2001) instilled 500 μg of Utah Valley Dust (UVD) extracts into the lingula of human volunteers (healthy young adults). This instilled dose (about 170 μg per m^2 alveolar surface area) elicited a robust inflammatory response for the 1986 and 1988 extracts, but not the 1987 extract, suggesting that extract composition is important. In a complementary animal study, the intratracheal instillation of rats with 250 μg (840 μg per m^2 alveolar surface area) of 1986 UVD extracts also caused an inflammatory response (Dye et al., 2001). The neutrophilic response elicited by the 1986 UVD extract instillations was about 3 times greater in the rats (10-fold PMN increase) than in humans (3.5-fold PMN increase). On the basis of mass per alveolar surface area, however, the dose delivered to the rats was about 5 times greater than delivered to the humans. This disparity (3 times the response at 5 times the dose) is suggestive of a decreased susceptibility for an inflammatory response in the rats relative to humans. However, baseline levels of PMN may differ between studies and might account for some of the differences described here.

For comparison to delivery by inhalation, it was estimated that 44-65 days of exposure in the Utah Valley during the winter 1985-1986 would have been required for a person to have received a PM dose per alveolar surface area equivalent to that of instillations in the study by Ghio and Devlin (2001) (see Table 7A-10b). However, it was estimated that a rat lung burden of 250 μg, the mass instilled by Dye et al. (2001), could not be achieved by inhalation at the assumed ambient exposure scenario due to the rapid clearance in the rat (Table 7A-10c [1]). Toxicologically, it is obvious that a different response might be expected between an instilled dose (delivered as a bolus) versus the a subchronic delivery by inhalation. For a more acute (24-h period) delivery by inhalation, humans would need to be exposed to ~6 mg/m^3 and rats to 15 mg/m^3 in order to reach the instilled doses used in the Ghio and Devlin (2001) and Dye et al. (2001) studies, respectively. Dosimetrically, the relevance of both the human and the rat

instillation studies to exposure by inhalation are difficult to judge and it should again be noted that the extracts contained only the soluble fraction of the UVD. However, both rat and human instillation studies showed that the 1987 UVD (collected while the Gevena Steel Mill was closed) extract was relatively less potent compared to the 1986 and 1988 extracts.

Several studies (one human and two rat) involving exposure by inhalation to CAPs provide a seemingly more useful basis for comparing dose and response. Tables 7A-11a, -11b, and -11c provided exposure conditions and estimated doses for the human study by Ghio et al. (2000), the rat study by Kodavanti et al. (2000), and the rat study by Clarke et al. (1999), respectively. Bronchial lavages were performed at 18 h postexposure in both the Ghio et al. (2000) and Kodavanti et al. (2000) studies and at 24 h postexposure in the Clarke et al. (1999) study. At the time of bronchial lavage, the estimated alveolar dose in the human study was 0.7 $\mu g/m^2$. This dose produced a mild inflammatory response in young healthy human subjects. In the Clarke et al. (1999) study, an increase in neutrophils in response to CAPs exposure was found in healthy rats (air, ~1%; CAPs, ~7%) that was very similar to that observed in healthy humans (air, 2.7%; CAPs, 8.1%) by Ghio et al. (2000). However, the alveolar tissue doses (mass per surface area) are estimated to be 67 times greater in the rats than in the humans. The similarity in the response, but disparity in dose, suggests that healthy rats may be less susceptible to inflammatory effects of CAPs than healthy humans. In the Kodavanti et al. (2000) study, rats were predicted to have 40 times the human dose in the Ghio et al. (2000) study but only 60% of the dose delivered to the rats in the Clarke et al. (1999) study. Interestingly, neither the healthy nor bronchitic rats in the Kodavanti et al. (2000) study showed a consistent inflammatory response, again suggesting that rats are less susceptible to CAPs effects than healthy humans. The composition, size distribution, and concentration of CAPs varies temporally and spatially. Thus, some of the above-described differences between studies may be attributable to the toxicity of the CAPs itself.

A key premise for the dosimetric analysis presented here is that comparable tissue doses should cause comparable effects. From the preceding discussion of CAPs studies, however, it appears that rats (whether healthy or compromised) may have a decreased inflammatory response (indexed by PMN levels) relative to healthy humans at comparable tissue doses. Decreased sensitivity of rats relative to humans may only occur in studies of several days

duration. For longer subchronic and chronic studies, rats appear susceptible to an overload of their macrophage-mediated alveolar clearance. Under conditions of overload, rats may indeed be more susceptible than humans, having decreased rates of alveolar clearance and antioxidant defenses. Table 7A-12 provided exposure concentrations for chronic exposures below which overload might be avoided.

7A.9 CONCLUSIONS

- Exposure concentrations can be estimated that give a rat the same dose as received by a human exposed to various levels of ambient PM as a function of dose metric, normalizing factor, and level of human exertion. The estimated concentrations will vary widely depending on the selection of these parameters. While human and rat doses may be matched for a specific dose metric, normalizing factor, and level of human exertion, the dose estimated for other dose metrics and normalizing factors may be quite different. Thus, it may not be possible to match all relevant dose metrics.

- The dosimetric calculations indicate that PM concentration exposures in rats, somewhat higher than in humans, would be justified in certain conditions to achieve nominally similar acute doses per surface area relative to the humans undergoing moderate to high exertion. However, for resting or light exertions, lower rat exposure concentrations are adequate to produce equivalent doses.

- Given that rats clear PM much faster than humans, the MPPD model results show that much higher exposure concentrations in the rat are required to simulate the retained burden of poorly soluble particles which builds up over years of human exposure.

- In resuspended PM, used in some inhalation studies, the smaller particles found in the accumulation and Aitken modes of the atmospheric aerosol are aggregated onto (or into) larger particles. Thus, for dose metrics based on particle surface area or number very high exposure concentrations of resuspended PM for rats would be required to provide a dose equivalent to that received by humans exposed to atmospheric aerosol.

- The biological mechanisms of PM toxicity are uncertain, as are the dose metrics most appropriate for establishing human-rat equivalent doses. The concept of using dosimetric calculations to provide a quantitative rat to human extrapolation depends on the assumption that an equal dose to target cells or tissues will produce a similar response in each species. At sufficiently high doses, however, the rat is subject to an overload phenomenon. When this occurs in the rat, clearance slows and anti-inflammatory defenses become depleted. Under these conditions, rats are more sensitive to PM than humans and tumor formation and fibrosis may occur. At lower doses, healthy rats clear PM faster than healthy humans and appear less sensitive to PM-induced inflammatory responses than humans. Thus, it is essential for toxicological studies to characterize dose

to the fullest extent possible and to carefully consider dose-response relationships in both rats and humans.

- Particle characteristics and biological normalizing factors which mediate effects should be carefully considered in study design. It is important that investigators provide accurate and complete information regarding exposure conditions (PM concentration, exposure duration, and particle size distribution) so that respiratory doses can be calculated for comparisons between studies.

- It is difficult to judge the relevance of human and rat instillation studies to ambient exposures via inhalation dosimetrically. The UVD instillation studies discussed herein used extracts containing only the soluble fraction of the UVD. The estimated alveolar surface doses from UVD extract instillations are likely far greater than would have occurred in residents of the Utah Valley during the winters of 1986-1988. However, both rat and human instillation studies showed that the 1987 UVD (collected while the Geneva Steel Mill was closed) extract was relatively less potent compared to the 1986 and 1988 extracts.

- Inflammatory responses were compared between several CAPs inhalation studies (one human and two rat). Exposure concentration data did not provide a useful means for comparing studies even when considering only the two rat studies. An analysis of inflammatory response as a function of PM dose showed rats to be less sensitive than humans in short duration studies of 3 days or less, although some of the variability between studies may be attributable to differences in the CAPs itself.

- Calculation of PM dose to the lung requires data on exposure concentration, exposure duration, and particle characteristics (solubility, hygroscopicity, size distribution, etc.) as well as information about the exposed individual or animal (age, gender, respiratory health, lung size, breathing conditions, etc.). Erroneous estimates of dose can occur from missing or faulty data, e.g., a multimodal particle size distribution being characterized as if unimodal. In order to examine the PM dose-response relationship across studies, complete and accurate information about the exposure and the exposed subjects need to be provided in the published literature.

REFERENCES

Adamson, I. Y. R.; Bowden, D. H. (1981) Dose response of the pulmonary macrophagic system to various particulates and its relationship to transepithelial passage of free particles. Exp. Lung Res. 2: 165-175.

Anjilvel, S.; Asgharian, B. (1995) A multiple-path model of particle deposition in the rat lung. Fundam. Appl. Toxicol. 28: 41-50.

Asgharian, B.; Hofmann, W.; Miller, F. J. (2001) Mucociliary clearance of insoluble particles from the tracheobronchial airways of the human lung. J. Aerosol Sci. 32: 817-832.

Bermudez, E.; Mangum, J. B.; Asgharian, B.; Wong, B. A.; Reverdy, E. E.; Janszen, D. B.; Hext, P. M.; Warheit, D. B.; Everitt, J. I. (2002) Long-term pulmonary responses of three laboratory rodent species to subchronic inhalation of pigmentary titanium dioxide particles. Toxicol. Sci. 70: 86-97.

Clarke, R. W.; Catalano, P. J.; Koutrakis, P.; Krishna Murthy, G. G.; Sioutas, C.; Paulauskis, J.; Coull, B.; Ferguson, S.; Godleski, J. J. (1999) Urban air particulate inhalation alters pulmonary function and induces pulmonary inflammation in a rodent model of chronic bronchitis. Inhalation Toxicol. 11: 637-656.

Dormans, J. A. M. A.; Steerenberg, P. A.; Arts, J. H. E.; Van Bree, L.; De Klerk, A.; Verlaan, A. P. J.; Bruijntjes, J. P.; Beekhof, P.; Van Soolingen, D.; Van Loveren, H. (1999) Pathological and immunological effects of respirable coal fly ash in male wistar rats. Inhalation Toxicol. 11: 51-69.

Driscoll, K. E.; Schlesinger, R. B. (1988) Alveolar macrophage-stimulated neutrophil and monocyte migration: effects of in vitro ozone exposure. Toxicol. Appl. Pharmacol. 93: 312-318.

Dye, J. A.; Lehmann, J. R.; McGee, J. K.; Winsett, D. W.; Ledbetter, A. D.; Everitt, J. I.; Ghio, A. J.; Costa, D. L. (2001) Acute pulmonary toxicity of particulate matter filter extracts in rats: coherence with epidemiological studies in Utah Valley residents. Environ. Health Perspect. Suppl. 109(3): 395-403.

Federal Register. (1997) National ambient air quality standards for particulate matter; final rule. F. R. (July 18) 62: 38,652-38,752.

Felicetti, S. A.; Wolff, R. K.; Muggenburg, B. A. (1981) Comparison of tracheal mucous transport in rats, guinea pigs, rabbits, and dogs. J. Appl. Physiol.: Respir. Environ. Exercise Physiol. 51: 1612-1617.

Ferin, J.; Oberdörster, G.; Penney, D. P. (1992) Pulmonary retention of ultrafine and fine particles in rats. Am. J. Respir. Cell Mol. Biol. 6: 535-542.

Ghio, A. J.; Devlin, R. B. (2001) Inflammatory lung injury after bronchial instillation of air pollution particles. Am. J. Respir. Crit. Care Med. 164: 704-708.

Ghio, A. J.; Kim, C.; Devlin, R. B. (2000) Concentrated ambient air particles induce mild pulmonary inflammation in healthy human volunteers. Am. J. Respir. Crit. Care Med. 162: 981-988.

Gordon, T.; Nadziejko, C.; Chen, L. C.; Schlesinger, R. (2000) Effects of concentrated ambient particles in rats and hamsters: an exploratory study. Cambridge, MA: Health Effects Institute; research report no. 93.

Gordon, T.; Nadziejko, C.; Lung, C. C.; Schlesinger, R. (2004) Effects of concentrated ambient particles in rats and hamsters: an exploratory study [erratum]. Boston, MA: Health Effects Institute; research report no. 93; p. 15. Available: http://www.healtheffects.org/Pubs/Gordon-Table2.pdf (15 July, 2004).

Hofmann, W.; Asgharian, B. (2003) The effect of lung structure on mucociliary clearance and particle retention in human and rat lungs. Toxicol. Sci. 73: 448-456.

International Commission on Radiological Protection (ICRP). (1994) Human respiratory tract model for radiological protection: a report of a task group of the International Commission on Radiological Protection. Oxford, United Kingdom: Elsevier Science Ltd. (ICRP publication 66; Annals of the ICRP: v. 24, pp. 1-482).

International Life Sciences Institute (ILSI) Risk Science Institute Workshop Participants. (2000) The relevance of the rat lung response to particle overload for human risk assessment: a workshop consensus report. In: Gardner, D. E., ed. ILSI Risk Science Institute Workshop: The Relevance of the Rat Lung Response to Particle Overload for Human Risk Assessment; March, 1998. Inhalation Toxicol. 12: 1-17.

Jarabek, A. M. (1994) Inhalation RfC methodology: dosimetric adjustments and dose-response estimation of noncancer toxicity in the upper respiratory tract. Inhalation Toxicol. 6(suppl.): 301-325.

Jarabek, A. M. (1995) Interspecies extrapolation based on mechanistic determinants of chemical disposition. Hum. Ecol. Risk Assess. 1: 641-662.

Killingsworth, C. R.; Alessandrini, F.; Krishna Murthy, G. G.; Catalano, P. J.; Paulauskis, J. D.; Godleski, J. J. (1997) Inflammation, chemokine expression, and death in monocrotaline-treated rats following fuel oil fly ash inhalation. Inhalation Toxicol. 9: 541-565.

Kodavanti, U. P.; Mebane, R.; Ledbetter, A.; Krantz, T.; McGee, J.; Jackson, M. C.; Walsh, L.; Hilliard, H.; Chen, B. Y.; Richards, J.; Costa, D. L. (2000) Variable pulmonary responses from exposure to concentrated ambient air particles in a rat model of bronchitis. Toxicol. Sci. 54: 441-451.

Kodavanti, U. P.; Schladweiler, M. C.; Ledbetter, A. D.; Hauser, R.; Christiani, D. C.; McGee, J.; Richards, J. R.; Costa, D. L. (2002) Temporal association between pulmonary and systemic effects of particulate matter in healthy and cardiovascular compromised rats. J. Toxicol. Environ. Health Part A 65: 1545-1569.

Kreyling, W. G.; Scheuch, G. (2000) Clearance of particles deposited in the lungs. In: Gehr, P.; Heyder, J.; eds. Particle-lung interactions. New York, NY: Marcel Dekker, Inc.; pp. 323-376. (Lung Biology in Health and Disease, v. 143.)

Ménache, M. G.; Miller, F. J.; Raabe, O. G. (1995) Particle inhalability curves for humans and small laboratory animals. Ann. Occup. Hyg. 39: 317-328.

Mercer, R. R. (1999) Morphometric analysis of alveolar responses of F344 rats to subchronic inhalation of nitric oxide. Cambridge, MA: Health Effects Institute; research report no. 88.

Mercer, R. R.; Russell, M. L.; Crapo, J. D. (1994) Alveolar septal structure in different species. J. Appl. Physiol. 77: 1060-1066.

Miller, F. J. (2000) Dosimetry of particles in laboratory animals and humans in relationship to issues surrounding lung overload and human health risk assessment: a critical review. Inhalation Toxicol. 12: 19-57.

Morris, A. H.; Kanner, R. E.; Crapo, R. O.; Gardner, R. M. (1984) Clinical pulmonary function testing: a manual of uniform laboratory procedures. 2nd ed. Salt Lake City, UT: Intermountain Thoracic Society.

Morrow, P. E. (1988) Possible mechanisms to explain dust overloading of the lungs. Fundam. Appl. Toxicol. 10: 369-384.

Morrow, P. E. (1994) Mechanisms and significance of "particle overload." In: Mohr, U.; Dungworth, D. L.; Mauderly, J. L.; Oberdörster, G., eds. Toxic and carcinogenic effects of solid particles in the respiratory tract: [proceedings of the 4th international inhalation symposium]; March 1993; Hannover, Germany. Washington, DC: International Life Sciences Institute Press; pp. 17-25.

Niinimaa, V.; Cole, P.; Mintz, S.; Shephard, R. J. (1981) Oronasal distribution of respiratory airflow. Respir. Physiol. 43: 69-75.

Oberdörster, G. (1988) Lung clearance of inhaled insoluble and soluble particles. J. Aerosol Med. 1: 289-330.

Oberdörster, G.; Ferin, J.; Lehnert, B. E. (1994) Correlation between particle size, *in vivo* particle persistence, and lung injury. Environ. Health Perspect. 102(suppl. 5): 173-179.

Oberdörster, G. (1995) Lung particle overload: implications for occupational exposures to particles. Regul. Toxicol. Pharmacol. 27: 123-135.

Oberdörster, G.; Finkelstein, J. N.; Johnston, C.; Gelein, R.; Cox, C.; Baggs, R.; Elder, A. C. P. (2000) Acute pulmonary effects of ultrafine particles in rats and mice. Cambridge, MA: Health Effects Institute; research report no. 96.

Oberdörster, G. (2002) Toxicokinetics and effects of fibrous and nonfibrous particles. Inhalation Toxicol. 14: 29-56.

Pinto, J. P.; Stevens, R. K.; Willis, R. D.; Kellogg, R.; Mamane, Y.; Novak, J.; Šantroch, J.; Beneš, I.; Leníček, J.; Bureš, V. (1998) Czech air quality monitoring and receptor modeling study. Environ. Sci. Technol. 32: 843-854.

Pope, C. A., III. (1989) Respiratory disease associated with community air pollution and a steel mill, Utah Valley. Am. J. Public Health 79: 623-628.

Stöber, W.; Morrow, P. E.; Koch, W.; Morawietz, G. (1994) Alveolar clearance and retention of inhaled insoluble particles in rats simulated by a model inferring macrophage particle load distributions. J. Aerosol Sci. 25: 975-1002.

Takenaka, S.; Dornhöfer-Takenaka, H.; Muhle, H. (1986) Alveolar distribution of fly ash and of titanium dioxide after long-term inhalation by Wistar rats. J. Aerosol Sci. 17: 361-364.

Takezawa, J.; Miller, F. J.; O'Neil, J. J. (1980) Single-breath diffusing capacity and lung volumes in small laboratory mammals. J. Appl. Physiol.: Respir. Environ. Exercise Physiol. 48: 1052-1059.

Tran, C. L.; Buchanan, D.; Miller, B. G.; Jones, A. D. (2000) Mathematical modeling to predict the responses to poorly soluble particles in rat lungs. Inhalation Toxicol. 12(suppl. 3): 403-409.

U.S. Environmental Protection Agency. (1994) Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; report no. EPA/600/8-88/066F. Available: http://cfpub1.epa.gov/ncea/cfm/recordisplay.cfm?deid=71993 (15 June, 2004).

U.S. Environmental Protection Agency. (1996) Air quality criteria for particulate matter. Research Triangle Park, NC: National Center for Environmental Assessment-RTP Office; report nos. EPA/600/P-95/001aF-cF. 3v.

Weibel, E. R. (1963) Morphometry of the human lung. New York, NY: Academic Press Inc.

Weibel, E. R. (1972) Morphometric estimation of pulmonary diffusion capacity: V. comparative morphometry of alveolar lungs. Respir. Physiol. 14: 26-43.

Whitby, K. T. (1978) The physical characteristics of sulfur aerosols. Atmos. Environ. 12: 135-159.
Wichmann, H.-E.; Peters, A. (2000) Epidemiological evidence of the effects of ultrafine particle exposure. Philos. Trans. R. Soc. London, Ser. A 358: 2751-2768.
Wichmann, H.-E.; Spix, C.; Tuch, T.; Wölke, G.; Peters, A.; Heinrich, J.; Kreyling, W. G.; Heyder, J. (2000) Daily mortality and fine and ultrafine particles in Erfurt, Germany. Part I: role of particle number and particle mass. Cambridge, MA: Health Effects Institute; research report no. 98.
Winter-Sorkina, R. de; Cassee, F. R. (2002) From concentration to dose: factors influencing airborne particulate matter deposition in humans and rats. Bilthoven, The Netherlands: National Institute of Public Health and the Environment (RIVM); report no. 650010031/2002. Available: http://www.rivm.nl/bibliotheek/rapporten/650010031.html (13 June 2003).
Yeh, H. C.; Schum, G. M. (1980) Models of human lung airways and their application to inhaled particle deposition. Bull. Math. Biol. 42: 461-480.
Yeh, H. C.; Schum, G. M.; Duggan, M. T. (1979) Anatomic models of the tracheobronchial and pulmonary regions of the rat. Anat. Rec. 195: 483-492.
Zhang, L.; Yu, C. P. (1993) Empirical equations for nasal deposition of inhaled particles in small laboratory animals and humans. Aerosol Sci. Technol. 19: 51-56.

APPENDIX 7B. AMBIENT BIOAEROSOLS

7B.1 INTRODUCTION AND BACKGROUND INFORMATION ON AMBIENT BIOAEROSOLS

The American Conference of Industrial Hygienists defines bioaerosols as airborne particles, large molecules or volatile compounds that are living, contain living organisms, or originate from living organisms. Such particles may be suspended in the air adhered to dust particles or tiny droplets of water. Bioaerosols include fungal materials, pollen, bacteria, viruses, endotoxins, and plant and animal debris, and range in size from 0.01 μm (viruses) to well over 20 μm (pollen). They are naturally present in the environment and can pose a threat to human health, especially for sensitive individuals for whom some bioaerosols, when inhaled, may cause diseases such as asthma, allergic rhinitis, and respiratory infections. The 1996 PM AQCD (U.S. Environmental Protection Agency, 1996), highlighted several examples of common bioaerosol sources, particles, and agents, as listed in Table 7B-1 and discussed in several earlier bioaerosols reviews, e.g., Cox (1987), Pope et al. (1993), Lighthart and Mohr (1994), and Cox and Wathes (1995).

TABLE 7B-1. EXAMPLES OF MAJOR SOURCES, TYPES OF PARTICLES, AND DISEASE AGENTS ASSOCIATED WITH BIOAEROSOLS

Sources	Aerosol Particles	Disease Agents
Plants	Pollen and pollen fragments, fragments of other plant parts, spores (ferns, mosses), algal cells	Glycoprotein allergens
Animals	Skin scales, secretions (saliva, skin secretions), excreta, body parts (arthropods)	Glycoprotein allergens
Fungi	Spores, hyphae, yeast cells, metabolites (toxins, digested substrate material)	Glycoprotein allergens, infectious units, glucans, mycotoxins
Bacteria	Cells, fragments, metabolites (toxins, digested substrate material)	Infectious units, allergens, endotoxin, exotoxins
Viruses	Viral particles	Infectious units

Source: Modified from 1996 PM AQCD (U.S. EPA, 1996).

7B.1.1 Plant Aerosols

Pollen. Among the best known plant aerosols are pollens produced by flowering plants, including trees (e.g., pines, cedars, birch, elm, maple, oak, etc.), weeds (e.g., ragweed, sage, etc.), and grasses (e.g., rye grass, Bermuda grass, etc.). Within these groupings, specific types are regionally more common, e.g., ragweed more so in the eastern United States, birch during the spring pollen season in New England, mountain cedar early in the year in the southwest, etc. (Lewis et al., 1983). Outdoor pollen levels are determined by numbers of plants available for pollen release, the amount of pollen produced per plant, factors controlling pollen release and dispersion from the plant, and factors directly affecting the aerosols (Edmonds, 1979). Plant numbers depend on many environmental factors (some human) that control plant prevalence, e.g., numbers of plants that produced seed in the past year, disturbed ground available for seed germination and growth, growing season, and other meteorological factors (temperature, rainfall, day length, etc.). Pollen shed is controlled by temperature, humidity, wind, and rain. Air pollen levels depend on all of these factors, as well as wind and rain conditions after release and on surfaces available for impaction. Pollen grains are large complex particles that consist of cellular material surrounded by a cell membrane and a complex wall. Pollen allergens are water-soluble glycoproteins that rapidly diffuse from the grain when it contacts a wet surface and are generally specific to the type of pollen, although large groups include a single allergen (e.g., many different kinds of grasses have similar allergens in their pollen grains). Several pollen allergens have been characterized: *Amb a* I (ragweed), *Bet v* I (birch), *Par j* I (parietaria).

Other Natural Plant Aerosols. Other plant-derived particles naturally occurring in outdoor air include algal cells; spores of mosses, liverworts, club mosses, and ferns; and fragments of all kinds of plants. Very little has been reported about the prevalence or human impact of any of these aerosol particles, but they are presumed to carry allergens.

Plant-Related Bioaerosols Generated by Human Activities (Grain Dust, Latex, etc.). Human activities that accumulate plant materials, e.g., storage, handling, and transport of farm products (hay, straw, grain), composting, produce bioaerosols. Grain dusts that include respirable-size particles (< 10 μm) are of particular interest. Soybean dust aerosols released from freighters unloading the beans in port have been blamed for epidemics of asthma. Also, human uses of some plant products can result in disease-causing aerosols (Alberts and Brooks, 1992), e.g., wood trimmer's disease (from inhalation of wood dust particles released during

high-speed wood cutting); sewage composting involving use of wood chips which can release allergenic aerosols, and latex particles from automobile tires that can contaminate reentrained roadway dust.

7B.1.2 Animal Aerosols

Mammalian Aerosols. All mammals produce aerosols. Human aerosols (skin scales, respiratory secretions) generally do not cause disease except for agents of infection (see below). Other mammals release aerosols that cause hypersensitivity diseases, the most common sources being cats, dogs, farm animals, laboratory animals, and house mice — although all animals release aerosols that could be sensitizing under appropriate conditions (Burge, 1995). Mammals only cause human disease under appropriate exposure conditions, e.g., having a cat in a house or handling of any animal. Cat allergens apparently become aerosolized on very small particles (< 1 μm) shed from skin and saliva. Dog, mouse, and other rodent allergens may be borne on dried urine particles, having sizes similar to those of cat allergen. Little is known about other mammalian aerosols. Cat and dog allergens (*Fel d* I, *Can f* I) have been characterized.

Avian Aerosols. Examples of wild and domesticated birds associated with disease-causing aerosols include: starlings (histoplasmosis); pigeons (histoplasmosis, pigeon-breeders disease); parrots (psittacosis); poultry (poultry-handlers disease); etc. Only the hypersensitivity diseases (e.g., pigeon breeders and poultry handlers disease) are caused by "bird" aerosols per se. The others are infectious diseases caused by agents inhabiting the birds (see below). The avian aerosol-hypersensitivity diseases are almost exclusively confined to sites where birds are bred and handled extensively, especially in indoor environments; and birds that release antigens observed to cause human disease are those that congregate or are typically confined close to people. Relatively little is known about avian aerosols. Probably skin scales, feather particles, and fecal material are all released as antigen-containing aerosols. The antigens (allergens) responsible for avian-related hypersensitivity diseases have yet to be well characterized.

Insect Aerosols. Dust mites are arthropods (family Pyrogliphidae) that include two common species in temperate climates: *Dermatophagoides farinae*, which proliferates under relatively dry conditions; and *D. pteronyssinus*, which dominates in more humid environments (Arlian, 1989). Dust mites thrive where relative humidity consistently exceeds 60% and where skin scales and fungal spores are available as food. Bedding and carpet dust are prime exposure

reservoirs. The mite itself is about 100 μm long, but excretes 20 μm membrane-bound fecal particles that contain allergens that are a major cause of sensitization in children. The allergens are digestive enzymes that gradually diffuse from fecal particles after deposition on mucous membranes. Several dust mite allergens have been characterized, including: *Der f* I and II; and *Der p* I and II (Platts-Mills and Chapman, 1987). Cockroaches are nocturnal insects belonging to the Orthoptera (Mathews, 1989) that inhabit dark environments where food and water are available. Cockroaches are very prolific, given favorable environmental conditions, and population pressure eventually drives them into daylight in search of food. They shed body parts, egg cases, and fecal particles (all of which probably carry allergens), but little is known about the particles that actually carry the allergens. Two cockroach allergens have been characterized: *Bla g* I, and *Bla g* II; and they are likely a major cause of asthma for some populations of children. Fragments of gypsy moths and other insects that undergo massive migrations can also become abundant in ambient air. Sizes, nature, and allergen content of such particles have not been well studied; but cases of occupational asthma from exposure to insects (e.g., sewer flies) have been reported.

Other Animal Allergens. It is likely that proteinaceous particles shed from any animal could cause sensitization if exposure conditions are appropriate. For example, exposure to proteins aerosolized during seafood processing have caused epidemics of asthma.

7B.1.3 Fungal Aerosols

Fungi are primarily filamentous microorganisms that reproduce and colonize new areas by airborne spores. Most use complex nonliving organic material for food, require oxygen, and have temperature optima within the human comfort range. The major structural component of the cell wall is acetyl-glucosamine polymers (chitin). Cell walls also may contain β-glucans, waxes, mucopolysaccharides, and many other substances. In the process of degrading organic material, fungi produce CO_2, ethanol, other volatile organic compounds, water, organic acids, ergosterol, and other metabolites that include many antibiotics and mycotoxins.

Fungi colonize dead organic materials in both indoor and outdoor environments. Some invade living plant tissue and cause many important plant diseases; some invade living animal hosts, including people. Fungi are universally present in indoor environments unless specific efforts are made for their exclusion (i.e., as in clean rooms). Kinds of fungi able to colonize

indoor materials are generally those with broad nutritional requirements (e.g., *Cladosporium sphaerospermum*), those that can colonize dry environments (e.g., members of the *Aspergillus glaucus* group), or organisms that readily degrade cellulose and lignin present in many indoor materials (e.g., *Chaetomium globosum*, *Stachybotrys atra*, *Merulius lacrymans*). Yeasts (which are unicellular fungi) and other hydrophilic taxa (e.g., *Fusarium*, *Phialophora*) are able to colonize air/water interfaces. Moisture, in fact, is the most important factor determining indoor fungal growth, since food sources are ubiquitous (Kendrick, 1992).

Particles that become airborne from fungal growth include spores (the unit of most fungal exposure); fragments of the filamentous body of the fungus; and fragments of decomposed substrate material. Fungal spores range from about 1.5 μm to > 100 μm in size and come in many different shapes, the simplest being smooth spheres and the most complex large multicellular branching structures. Most fungal spores are near unit density or less. Some include large air-filled vacuoles. Fungal spores form the largest and most consistently present component of outdoor bioaerosols. Levels vary seasonally, with lowest levels occurring during periods of snow. While rain may initially wash large dry spores from the air, these are immediately replaced by wet (hydrophilic) spores that are released in response to the rain.

Some kinds of spores are widespread in outdoor air (e.g., *Cladosporium herbarum*, *Alternaria tenuissima*). Others produced by fungi with more fastidious nutritional requirements are only locally abundant. Typical indoor fungal aerosols are composed of particles penetrating from outdoors, particles released from active growth on indoor substrates, and reaerosolized particles that had settled into dust reservoirs. Indoor fungal aerosols are produced by active forcible discharge of spores; by mechanisms intrinsic to the fungus that "shake" spores from the growth surface; and, most commonly, by mechanical disturbance (e.g., air movement, vibration).

Allergic rhinitis and asthma are the only commonly reported diseases resulting from fungal exposures outdoors, and which also commonly occur indoors. The allergens of fungi are probably digestive enzymes that are released as the spore germinates. Other spore components (of unknown function) may also be allergenic. Only very few fungal allergens (e.g., *Alt a* I, *Cla h* I, and *Asp f* I), out of possibly hundreds of thousands, have been characterized.

Allergic fungal sinusitis and allergic bronchopulmonary mycoses occur when fungi colonize thick mucous in the sinuses or lungs of allergic people. The patterns of incidence of allergic fungal sinusitis may be explained in part by geographic variability in ambient fungal

exposures. This disease is most commonly caused by *Bispora*, *Curvularia*, and other dark-spored fungi. Exposure patterns required for allergic bronchopulmonary mycoses are unknown. This disease is usually caused by *Aspergillus fumigatus*. Coccidioidomycoses and Histoplasmosis are infectious fungal diseases that result from outdoor exposures to *Histoplasma capsulatum* (a fungus that contaminates damp soil enriched with bird droppings) and *Coccidioides immitis* (a fungus that grows in desert soils). Indoor aerosol-acquired fungal infections are rare and mostly restricted to immunocompromised people (Rippon, 1988).

Toxic agents produced by fungi include antibiotics, mycotoxins, and some cell-wall components that have irritant or toxic properties. The antibiotics and mycotoxins are secondary metabolites produced during fungal digestion of substrate materials, and their presence depends, in part, on the nature of the substrate. The locations of the toxins in spores or other mycelial fragments are unknown, as are the dynamics of release in the respiratory tract. Aerosol exposure to fungal antibiotics in levels sufficient to cause disease is unlikely. Mycotoxicoses have been reported as case studies from exposure to spores of *Stachybotrys atra* (Croft et al., 1986), and epidemiologically for *Aspergillus flavus* (Baxter et al., 1981).

7B.1.4 Bacterial Aerosols

Most bacteria are unicellular, although some form "pseudo" filaments when cells remain attached following cell division. The actinomycetes are bacteria that do form filaments and, in some cases, dry spores designed for aerosol dispersal. Bacteria can be broadly categorized into two groups based on a response to the Gram stain procedure. The cell walls of Gram positive (Gram+) bacteria are able to absorb a purple stain; the cell walls of Gram negative (Gram−) bacteria resist staining and contain endotoxin consisting of proteins, lipids, and polysaccharides.

Most infectious agents are maintained in diseased hosts. A few, including *Legionella pneumophila*, reside in water-filled environmental reservoirs such as water delivery systems, cooling towers, air conditioners, and lakes, streams, oceans, etc. Infectious agents are often released from hosts in droplets exhaled from the respiratory tract. Each droplet contains one or more of the infectious agent, possibly other organisms, and respiratory secretions. Most droplets are very large and fall quickly. Smaller droplets dry quickly to droplet nuclei, which range from

the size of the individual organism (< 1 μm for the smallest bacteria) to clumps of larger organisms (> 10 μm for larger bacteria).

Environmental-source aerosols are produced by mechanical disturbances that include wind, rain splash, wave action, and as occurs in air recirculation, in sprays of washes and coolants, and in humidifiers. Particle sizes from all of these activity cover a wide range from well below 1 μm to > 50 μm. The thermophilic actinomycetes produce dry aerial spores that require only slight air movements to stimulate release. Each spore is about 1 μm in diameter.

Whole living bacteria are agents of infectious disease (e.g., tuberculosis, Legionnaires' disease, etc.). For tuberculosis, a single virulent bacterial cell deposited in the appropriate part of the lung can cause disease in a host without specific immunity. For Legionnaires' disease, the number of organisms needed for disease development likely depends on how well the host's general protective immune system is operating. Some bacteria release antigens that cause hypersensitivity pneumonitis. The antigens may be enzymes (e.g., *Bacillus subtilis* enzymes used in the detergent industry) or may be cell wall components (e.g., endotoxin or glucans).

7B.1.5 Viral Aerosols

Viruses are either RNA or DNA units surrounded by a protein coat that have no intrinsic mechanism for reproduction, but rather require living cells (whose enzyme systems they utilize to make new viral particles). Viruses can be crystallized and yet remain able to reproduce and are often considered intermediates between nonlife and life. Because viruses require living cells to reproduce, reservoirs for them are almost exclusively living organisms. Viruses, in rare cases, even survive (but do not reproduce) in environmental reservoirs from which they are re-aerosolized to cause disease. Hanta virus that causes severe respiratory disease in people exposed to intense aerosols of infected mouse urine is an example of this. Viral aerosols are produced when the infected organism coughs, sneezes, or otherwise forces respiratory or other secretions into the air. The viral particles are coated with secretions from the host and, as in the case for bacteria, there may be one to many in a single droplet. The size of a single viral particle is very small (a small fraction of a μm), but infectious droplets more usually occur within a larger size range (1 to 10 μm). Each kind of virus produces a specific disease, although some of the diseases present with similar symptoms. Thus, the measles virus produces measles, the chicken pox viruses produces chicken pox and shingles, etc. Influenza and common colds are

produced by a variety of viruses, all of which produce similar (but not necessarily identical) symptoms.

7B.2 NEWLY AVAILABLE BIOAEROSOLS RESEARCH

Since the 1996 PM AQCD, a number of newly available studies provide interesting new information pertinent to evaluating potential involvement of bioaerosols in contributing to health effects associated with exposures to ambient PM. Of much interest are newly published findings which (a) indicate greater contributions (than previously thought) of bioaerosols to airborne ambient PM concentrations; (b) improve our understanding of factors and mechanisms affecting release of some bioaerosol materials into ambient air; and (c) provide evidence indicative of bioaerosols contributing to ambient PM-related health effects, including contributions made in combination with other, nonbiological, PM components.

The fate of bioaerosols is dependent on a number of variables: geography, time of day, moisture levels, air temperature/humidity, wind speed and direction, and seasonal variations in the latter variables. Once airborne, depending on the particle size, bioaerosols may travel great distances. As discussed in more detail below, bioaerosols generally represent a rather small fraction of the measured urban ambient PM mass and are typically present at even lower concentrations outdoors during cold seasons, when notable ambient PM effects have been demonstrated (Ren et al., 1999; Kuhn and Ghannoum, 2003). Bioaerosols tend to be in the coarser fraction of PM; but some bioaerosols (e.g., fungal spores, fragmented pollens, nonagglomerated bacteria) are found in the fine fraction as well (Meklin et al., 2002a; Schäppi, 1999), possibly due to reactions of the biological agents with ambient particles (Schäppi et al., 1999; Oikonen et al., 2003; Behrendt et al., 2001; Ormstad et al., 1998).

For the sake of bringing together information regarding bioaerosols, the following discussions include new information on bioaerosol sources and factors affecting their dispersal in ambient air as well as new studies on their health effects. The latter include not only toxicology studies, but also some studies conducted in occupational settings or results from epidemiology studies assessing health responses to airborne allergens or biological material. To the extent that other aspects of air pollution evaluated in these epidemiology studies are deemed pertinent and important, the results are discussed in Chapter 8. Tables 7B-2 and 7B-3

TABLE 7B-2. RESPIRATORY EFFECTS OF POLLEN/FUNGI AND PM EXPOSURES

Species, Gender, Strain, Age, etc.	Particle	Exposure Technique	Concentration	Particle Size	Exposure Duration	Particle Effects/Comments	Reference
Humans	Pollen	Ambient, London	Pollen count increased from 37 to 130 grains/L 3 h after thunderstorm	Not characterized	2 month study period	ER visits increases from 2.25 patients/day to 40 patients/day following thunderstorm. Peak in pollen levels about 9 h before peak in ER visits.	Celenza et al. (1996)
Human, Netherlands	Ambient PM Pollens: grass; sorrel; birch; dock	Ambient (Leiden and Helmond)	*Poaceae* (grass) 78 pol. grains/m^3 *Betula* (birch) 69 pol. grains/m^3 *Quercus* (oak) 13 pol. grains/m^3		Deaths from 1986 to 1994 evaluated	Pollen concentrations only weakly associated with air pollution. Grass pollen levels were associated with daily deaths from pneumonia and COPD. Other pollens (birch, sorrel, dock) were also positively correlated with mortality.	Brunekreef et al. (2000)
Human, male and female, normal and allergic, ages 26-29	Ragweed	Bronchoscopic challenge	Not characterized	Not characterized	3 h	*Nonallergic subjects:* ragweed had little effect on ciliary activity; acid reduced activity *Allergic subjects:* slight increase in albumen and 2-fold increase in BAL cell number. Allergic subjects with severe inflammatory changes had a 12-fold increase in albumin and 9-fold increase in BAL cell number	Hastie and Peters (2001)
Human, male and female, 21-49, with allergic rhinitis, nonsmoking	DPM ragweed	Intranasal spray	0.3 mg in 200 µl saline		1,4,8 days	Combined DEP/ragweed challenge induced ragweed-specific IgE, but not total IgE or IgE-secreting cell numbers. Also caused a decrease in IFNγ and IL-2 and an increase in IL-4, IL-5, IL-6, IL-10, and IL-13.	Diaz-Sanchez et al. (1997)

TABLE 7B-2 (cont'd). RESPIRATORY EFFECTS OF POLLEN/FUNGI AND PM EXPOSURES

Species, Gender, Strain, Age, etc.	Particle	Exposure Technique	Concentration	Particle Size	Exposure Duration	Particle Effects/Comments	Reference
Mice, Male, BALB/c, 7 weeks old	DPM Japanese cedar pollen OVA	Intratracheal Instillation	0.3 mg/mouse 1 mg 10 µg	0.4 µm	3 times with an interval of 3 weeks	IgE antibody and IL-4 production increased. Slight increase in IL-3 output. DEP affects antigen-specific IgE antibody response by enhanced IL-4 production.	Fujimaki et al. (1994)
Mice, Female, BALB/c, 6-8 weeks old	SPM DPM (SRM1650)	Injection into mouse footpad		< 2.5 µm	20-26 days	Adjuvant activity noted on the production of IgE antibodies to OA.	Ormstad et al. (1998); Ormstad (2000)
Human, asthmatic, 9-16 years old	PM fungal spores	Ambient, (San Diego, CA area)	24.8 ± 11.1 µg/m^3 2461 ± 1307/m^3	2.5 µm 10 µm	12 h	Inhaler puffs increased by 1.2 per 1000 fungal spores/m^3. Positive association between asthma severity and PEFR and total fungal spores. No significant relationship between asthma severity and PM_{10} or pollen exposure.	Delfino et al. (1996, 1997)
Human, children < 15, adults, adults > 59	*Ascomycetes* basidiospore content in ambient TSP and PM_{10}	Ambient (Mexico City)	56-98 78-156 100-207 100-1000 spores/m^3	10 µm	1 year analysis	Statistically significant increase in fungal spore exposure-related asthma hospital admissions in children (but not adults and seniors) in Mexico City.	Rosas et al. (1998)
Human	Mold spores; tree, grass, and ragweed pollen	Ambient (Chicago)	Variable		7-month periods from 1985 through 1989	On days that mold spores were > 1000 spores/m^3, death caused by asthma were 2.16 times greater than days with spores < 1000; but no increase in death seen with tree, grass, or ragweed pollen.	Targonski et al. (1995)
Chicken tracheal rings	Filamentous fungi	in vitro	N/A	N/A	24, 48, 96 h	Chloroform-extractable endo- and exometabolites stopped tracheal ciliary movement.	Piecková and Kunová (2002)

SPM = suspended particulate matter DPM = diesel particulate matter OVA = ovalbumin

TABLE 7B-3. RESPIRATORY EFFECTS OF INHALED ENDOTOXIN-LADEN AMBIENT BIOAEROSOLS

Species, Gender, Strain, Age, etc.	Particle	Exposure Technique	Concentration	Particle Size	Exposure Duration	Particle Effects/Comments	Reference
Humans (pig farmers), 82 symptomatic and 89 asymptomatic n = 171	Dust Endotoxin	Inhalation	2.63 mg/m^3 σg = 1.3 105 ng/m^3 σg = 1.5	N/A	5 h/day average lifetime exposure	Large decline in FEV_1 (73 mL/year) and FVC (55 mL/year) was significantly associated with estimated long-term average exposure to endotoxin at 105 ng/m^3.	Vogelzang et al. (1998)
Humans (healthy); 32 male, 32 female, 16 to 50 years old	Indoor pool water spray Endotoxin	Inhalation	N/A	0.1-7.5 µm	N/A	Recurring outbreaks of pool-associated granulomatous pneumonitis (n = 33); case patients had higher cumulative work hours. Analysis indicated increased levels of endotoxin in pool air and water.	Rose et al. (1998)
Humans (potato plant workers), low (37 male) and high (20 male) exposures	Endotoxin	Inhalation	low: 21.2 EU/m^3 σg = 1.6 high: 55.7 EU/m^3 σg = 2.1	N/A	8 h	Concentration-related decreased FEV_1, FVC, and MMEF over the work shift; endotoxin effects on lung function can be expected above 53 EU/m^3 (≈ 4.5 ng/m^3) over 8 h.	Zock et al. (1998)
Humans (healthy); 5 male, 4 female, 24 to 50 years old	LPS [1] (endotoxin)	Inhalation	0.5 µg 5.0 µg 50 µg	1 - 4 µm MMAD	30 min	Significant decrease in PMN luminal-enhanced chemiluminescence with 0.5 µg LPS; increase in blood CRP and PMNs, and increase in sputum PMNs, monocytes, and MPO with 5.0 µg LPS; increase in body blood PMNs, temperature, blood and urine CRP, sputum PMNs, lymphocytes, monocytes, TNFα, and ECP with 50 µg LPS.	Michel et al. (1997)
Rats (Fischer 344), 8 wks to 22 mo old, n = 3/group	LPS [1] (endotoxin)	Inhalation	70 EU/m^3	0.72 µm σg = 1.6	12 min	Significant increase in PMNs in bronchoalveolar lavage (BAL) in LPS exposed animals. LPS significantly affected the reactive oxygen species activity in BAL. Effects were age-dependent.	Elder et al. (2000a,b)

[1] LPS = lipopoly saccharide.

summarize salient features of newly available studies of respiratory effects of pollens/fungi and endotoxins, respectively.

7B.2.1 Atmospheric Levels of Cellulose/Other Plant Debris Markers

Puxbaum and Tenze-Kunit (2003) investigated seasonal variations in atmospheric cellulose levels (as a "microtracer" for airborne plant debris) in and around Vienna, Austria. The 9-month average of "free" cellulose concentrations at the downtown site was 0.374 $\mu g/m^3$ (reflective of 0.75 $\mu g/m^3$ plant debris). Given an annual average for organic carbon (OC) at the downtown site of 5.7 $\mu g/m^3$, plant debris appears to be more than a minor contributor to ambient organic aerosol at that site. Unexpectedly, size distribution determinations via impactor measurements indicated that the "free cellulose" (on a mass basis) comprised ~ 0.7% of ambient fine PM (0.1 - 1.5 μm), forming a "wetable but insoluble part of the accumulation mode aerosol," as noted by Puxbaum and Tenze-Kunit (2003). They further noted that the cellulose levels at the downtown site showed maximum concentrations during the fall (probably due to increased biological activity involving seed production and entrainment of other plant cellulose materials into the air). Comparison of simultaneous measurements of cellulose at the downtown site to those from a suburban site indicated that the ambient PM cellulose did not originate in notable amounts from within the city.

The Puxbaum and Tenze-Kunit (2003) study adds further to a growing database which points toward plant debris being a significant contributor to organic aerosols present at continental sites. As discussed by Puxbaum and Tenze-Kunit, Rogge et al. (1993) and Zappoli et al. (1999) have shown a considerable portion of the organic aerosols not to be soluble in water or organic solvents, suggesting larger molecular sizes of the insoluble compounds. Also, Matthias-Maser and Jaenicke (1995) found up to 40% of the number of particles > 0.2 μm (AD) at a continental site to be of primary "biological origin". Puxbaum and Tenze-Kunit further noted that Bauer et al. (2002) found fungal spores in the 2.15 to 10 μm fraction of organic background aerosol at a mountain site to comprise on average, about 6% of the OC mass in the coarse PM fraction. Also, they noted that the main constituents of the organic aerosol appear to be humic-like substances (HULIS) that are present in continental aerosol samples at concentrations (HULIS-carbon) that range from 7 to 24% of the OC mass (Havers et al., 1998; Zappoli, et al., 1999; Facchini et al., 1999). The macromolecular HULIS materials likely have

many origins, e.g., from biomass fires (Facchini et al., 1999) or secondary atmospheric reactions (Gelencsér et al., 2003). It was further noted by Puxbaum and Tenze-Kunit that cellulose is also contained in pollen at 3 to 7% dry mass (Stanley and Linskens, 1985).

Other new studies evaluated atmospheric levels of levoglucosan (LVG) and other markers (e.g., palmitic acid, stearic acid) of biomass burning so as to investigate potential inputs of materials from that source category to ambient PM. One study (Fraser and Lakshaman, 2000), measuring effects in Texas of biomass fires in Mexico/Central America, found 0.2 to 1.2 $\mu g/m^3$ of LVG during episodes resulting from long-range transport of smoke haze. In another study, Poore (2002) reported on LVG concentrations in $PM_{2.5}$ samples taken at the Fresno, California supersite during the year 2000. Highest levels of LVG (up to 4.05 $\mu g/m^3$) were found during late fall/winter months (November-January), whereas LVG concentrations during spring/summer months were near or below the detection limit of 0.01 $\mu g/m^3$. Analogous seasonal patterns of variations in concentrations of palmitic and stearic acid were also seen for the Fresno supersite $PM_{2.5}$ samples. Given that agriculturally-related biomass burning in the Fresno area is typically completed by the end of October, the elevated LVG levels during fall/winter months were most likely derived from residential woodsmoke emissions. The same may also be true for fall/winter increases in palmitic and stearic acid levels, although as noted by Poore (2002), both of these acids are emitted from a variety of sources, including food production. In any case, these results appear to be indicative of episodic or more prolonged seasonal increases in plant-derived bioaerosol materials contributing to ambient PM levels in Texas and California, and by analogy, other areas of the western United States where air quality is affected by biomass burning emissions (e.g., from controlled burns on agricultural land, forest fires, or residential fireplaces/woodstoves).

However, a comprehensive review (Anderson et al., 1992) of a number of studies of rodents exposed to dry cellulose has shown that exposures in the range of mg/m^3 do not cause adverse effects on reproduction or development, nor do they increase in the incidence of cancer. Also, one more recent study (Cullen et al., 2000) has demonstrated that inhalation of 1,000 ml ($^{-1}$) cellulose fibers in rats for 5 d/week for 3 weeks created only an early inflammatory response which peaked at day 1 following the start of inhalation. The inflammation, including levels of BAL TNFα, declined over the next 18 days. Thus, ambient exposures to dry cellulose materials, per se, would appear to pose relatively low risk for health effects. It remains to be

more clearly delineated as the extent to which ambient airborne cellulose materials (especially under wet conditions) may act as effective carriers of other bioaerosol (e.g., fungi, bacteria, viruses) or nonbiologic materials and thereby serve to increase health risks associated with them.

7B.2.2 Pollen

With regard to pollen, important new insights are emerging with regard to: (a) factors influencing the occurrence of asthmatic or other allergic responses to certain types of common, widespread pollens; and (b) the likelihood that such bioaerosol-related asthma events are enhanced by the presence in ambient air of other types of non-bioaerosol airborne particles. More specifically, researchers in several countries have demonstrated links between epidemics of "thunderstorm asthma" (characterized by notable increases in asthma attacks and upsurges in hospital visits/admissions for asthma within hours after such storms) and increased levels of grass pollen allergens among respirable airborne bioaerosol components (Bellomo et al., 1992; Ong, 1994; Venables et al., 1997; Rosas et al., 1998; Newson et al., 1997; Schäppi et al., 1999; Girgis, et al., 2000).

Anemophilous plants (wind-pollinated plants) produce copious amounts of pollen, making pollen from these plants the most abundant in the atmosphere and the most important in terms of human exposure. Typically, exposure to pollen has been thought to only play a role in allergic rhinitis because they are too large to penetrate into the lower airways. However, in more recent years, there is evidence which indicates that pollen may in fact be associated with exacerbation of asthma through the release of pollen allergens small enough in size to penetrate into lower respiratory airways and/or via the binding of these allergens to other respirable size particles (Suphioglu et al., 1992; Burge and Rogers, 2000; Knox et al., 1997; Schäppi et al., 1999). More specifically, although intact (unruptured) pollen grains are typically so large (often > 10 to 20 μm) that, when inhaled, they mainly deposit in upper airways (nasopharyngeal areas), grass pollen allergens are found in the cytoplasm of the pollen grains (Taylor et al., 1994); and, upon the rupture of mature pollen grains, they are released as cytoplasmic fragments that comprise respirable (~0.1 to 5.0 μm) particles (Schäppi et al., 1999; Grote et al., 2000; Taylor et al., 2002).

The release of allergens from the pollen grains is moisture dependent (Suphioglu et al., 1992; Schäppi et al., 1997, 1999). Suphioglu et al. (1992) reported the release of a major allergen (*Lol plX*) from the intracellular starch granules of rye grass when pollen grains were ruptured during a rain storm. The allergen was small enough (< 3 μm) to penetrate to the lower airways. The atmospheric concentration of the allergen showed a 50% increase on days following a rain event. Asthmatic volunteers were exposed by aerosol mask to the starch granules (volume of 1 mL nebulized, of a 0.34 $\mu g/m^3$ solution) or the pollen grain extracts. Asthmatic volunteers (n = 4) that underwent inhalation challenge showed a typical early response, described by the authors as a striking bronchial constriction following exposure to the starch granules. The effect was not noted in volunteers exposed to pollen grain extracts.

Taylor and colleagues (2002) confirmed that the key trigger for rupture of rye grass and Bermuda grass pollen is pollen grain contact with water, e.g., with the moistening of such pollen by dew, fog, rainfall, or lawn watering. They also further provided evidence on the specific sequence of events (and time periods) leading to appearance of the allergen-containing cytoplasmic material in airborne respirable aerosols. Taylor et al. (2002) reported that, upon drying within 1 to 6 h after rye grass or Bermuda grass pollen were moistened with water and grain rupture occurred, allergen-containing cytoplasmic fragment particles were entrained into the air by blowing air across the grass flowers or shaking them, with many thousands of such fragments in the 0.1 to 4.7 μm size range (most below 0.4 μm) being collected by a Cascade impactor. The dispersal of such allergen-laden particles following cycles of wetting and drying of grass pollen, it was noted by Taylor et al. (a) may occur in response to such disturbances as wind, lawn mowing, and recreational activities; (b) likely account for marked increases in asthma attacks after thunderstorms; and (c) may also account for increased asthmatic symptoms during grass flowering season after any moist weather conditions. Also, more recently, Taylor et al. (2003) employed analogous experimental wetting/drying procedures, collection and measurement of wind-released cytoplasmic fragments of birch tree pollen in the 0.03 to 4 μm size range, and found them to contain *Bet v* 1 allergens.

Taylor et al. (2002) also highlighted possible bases for interactions between aerosolized allergen-laden pollen debris and other types of ambient airborne particles. They noted, for example, that diesel emission particles are a major contributor to urban respirable aerosols mass, e.g., 18% in Pasadena, CA (Schauer et al., 1996), and have been implicated as a cause of allergic

rhinitis and asthma in mice and humans (Nel et al., 1998; Bayram et al., 1998; and Diaz-Sanchez, et al., 2000). Taylor et al. further noted (a) that fine combustion particles and aerosols of pollen allergens, because of their small size, may deposit in similar respiratory tract regions; and (b) that synergistic combinations of allergen-laden pollen debris and PAHs found in fine combustion aerosols may explain the notable increased prevalence of pollen-induced asthma during the past 50 years.

Further possibilities exist with regard to possible ways that the copresence of grass pollens and diesel particulate matter (or perhaps other airborne particles) may contribute jointly to enhanced probability of asthma symptoms occurring in susceptible human population groups. More specifically, the EPA Health Assessment Document for Diesel Engine Exhaust (U.S. Environmental Protection Agency, 2002) noted that Ormstad et al. (1998) investigated the potential for DPM (as well as other suspended PM) to act as a carrier for allergens into the airways and found both *Can f* 1 (dog) and *Bet v* 1 (birch pollen) on the surface of airborne PM collected inside homes. They also found that DPM adhered to polycarbonate filters could bind both of these allergens as well as *Fel d* 1 (cat) and *Der p* 1 (house mite) allergens. The authors concluded that soot particles in indoor air house dust may act as a carrier for several allergens in indoor air. The EPA Diesel Document (2002) also noted that Knox et al. (1997) investigated whether free grass pollen allergen molecules, released from pollen grains by osmotic shock (Suphioglu et al., 1992) and dispersed in microdroplets of water in aerosols, can bind to DPM mounted on copper grids in air. Using natural highly purified *Lol p* 1 (the major grass pollen allergen), immunogold labeling with specific monoclonal antibodies, and a high-voltage transmission electron-microscopic imaging technique, Knox et al. found binding of *Lol p* 1 to DPM in vitro. They concluded that binding of *Lol p* 1 with DPM might be a mechanism by which allergens can become concentrated in air and trigger asthma attacks.

In addition to suggesting that airborne diesel exhaust particles can act as carriers of biological aerosols producing an enhanced allergic response (Knox et al., 1997; Diaz-Sanchez et al., 1997; Fujimaki et al., 1994), some studies suggest that allergen carriers (e.g., pollen grains) may incorporate other atmospheric pollutants that alter the pollen surface, leading to altered protein and allergen release (Behrendt et al., 1992, 1995, 1997, 2001). Pollen grains from an industrial region with high PAHs were shown to be agglomerated with airborne particles. In vitro exposure of grass pollen to particles demonstrated ultrastructural changes at

the surface of the pollen and within the protoplasm, such as exocytosis of granular proteinaceous material and increased allergen release (Behrendt et al., 1997).

Fujimaki et al. (1994) examined the effect of intratracheal instillation of a mixture of diesel exhaust particles and Japanese cedar pollen on IgE antibody production and lymphokine production in mice. IgE antibody production and IL-4 production in mediastinal lymph nodes were significantly increased in mice instilled with the diesel exhaust particles and the cedar pollen compared with the cedar pollen alone. There was a slight increase seen in IL-2 output. Measurable levels of birch pollen-specific human IgE were noted in hu-PBL-SCID mice previously stimulated with birch pollen. When the mice were exposed i.p. to the 25 μg birch pollen plus 500 μg of diesel exhaust particles, IgE levels were twice as high as those for birch pollen exposure only. Ormstad et al. (1998) found that *Fel d* 1 (cat), *Can f* 1 (dog), *Der p* 1 (house dust mite) and *Bet v* 1 (birch pollen) allergens bind with soot particles from diesel exhaust in the < 2.5 μm size range. When the particle mixture was injected in the footpad of mice, adjuvant activity was noted on the production of IgE antibodies to ovalbumin (Ormstad, 2000). The authors suggested that it is likely that the soot particles alone were responsible for some of the adjuvant activity. However, the particles may increase the IgE production to allergens by modulating the immune response.

Diaz-Sanchez et al. (1997) studied possible synergistic relationships between diesel exhaust particles (DPM) and ragweed allergen. Inconsistent and low levels of mucosal cytokine mRNAs were found in ragweed sensitized subjects following intranasal challenge with ragweed allergen alone. When the subjects were challenged with ragweed allergen and DPM there was a decrease in Th1-type cytokines (IFN-γ and IL-2) expression but an elevated expression of mRNA for other cytokines (IL-4, IL-5, IL-6, IL-10, IL-13). Ragweed allergen and DPM also produced a 16-fold increase in ragweed-specific IgE but not total IgE levels or IgE-secreting cell numbers. Total and specific IgG-4 levels were enhanced , while total IgG levels were not. Subject were given short ragweed *Amb a* I allergen, starting at 10 allergen units and increasing in 10-fold units until symptoms were noted. The diesel particles were administered for a total of 0.3 mg in 200 μL of saline. Clones of deleted switch circular DNA (Sε/Sμ), representing switching from μ to ε from the nasal lavage cells, also were detected (Fujieda et al., 1998).

Brunekreef et al. (2000) suggested that airborne pollen associated with allergic responses may pose more serious effects than previously thought. They evaluated the relationship between

the daily number of deaths in the Netherlands for the period of 1986 to 1994 and air pollution, meteorological factors, and airborne pollen concentrations (analyzed as categorical variables). The relationship between mortality and airborne pollen concentration was modeled using Poisson regression with generalized additive models. The pollen mortality associations were adjusted for long-term and seasonal trend, influenza morbidity, ambient temperature, humidity, and indicators for the day of the week and holidays. The average number of daily deaths for the study period was 332.5 (total), including 141.8 cardiovascular related deaths, 15.8 COPD related deaths, and 9.8 pneumonia related deaths. Pollen concentrations were only weakly associated with air pollution and there was no confounding by PM_{10}, black smoke, sulphate and nitrate aerosols, NO_2, SO_2, or O^3. *Poaceae* (grass) pollens were associated with daily deaths due to COPD and pneumonia. Other pollens, especially *Betula* (birch) and *Rumex* (sorrel, dock) were also positively correlated with mortality. Information was not included on whether this association was with daily deaths due to cardiovascular disease, COPD, and/or pneumonia. The authors suggested that acute exacerbations of allergic inflammation associated with high pollen exposures may also precipitate death due to cardiovascular disease, COPD, or pneumonia in individuals suffering from these disorders.

Rosas et al. (1998) reported an association between asthma hospital admissions and grass pollen exposure for children, adults, and seniors in Mexico City. The effects were noted for both the wet (May through October) and dry (November through April) seasons. The number of hospital admissions increased by a factor of 2 to 3 for children and adults on day when the grass pollen concentrations were above 20 grains/m^3. There was no association between asthma exacerbation and tree pollen.

An association between asthma and emergency room (ER) visits was reported by Celenza et al. (1996). During a 2-mo study period, the daily average number of emergency room visits was 2.25 patients; but, following a thunderstorm, such visits increased to 40. There was a peak in pollen levels about 9 h before the peak in asthma ER visits. Three hours after the storm, the pollen count increased from 37 to 130 grains/L. There was no evidence that vehicle exhaust pollutants were related to the increase in asthma ER visits.

Hastie and Peters (2001) studied the effect of in vivo ragweed allergen exposure (via bronchoscopic segmented ragweed challenge) on ciliary activity of bronchial epithelial cells harvested 24 h after challenge in human volunteers and allergic subjects with severe

inflammatory response. Nonallergic subjects with mild inflammatory response showed a minimal ragweed allergen effect on ciliary activity, a slight increase in bronchoalveolar cells, and a nonsignificant increase in albumin concentration. Allergic subjects with mild inflammatory changes showed slight but significant increase in albumin concentration and a 2-fold increase in bronchoalveolar cell concentration. The allergic subjects with severe inflammatory changes had a 12-fold increase in albumin concentration and a 9-fold increase in bronchoalveolar cell concentration.

Delfino et al. (1997,1996) conducted several studies evaluating the association between asthma incidence and exposure to various air pollutants and fungal spores and pollen. There was an association between exposure to air pollutants and fungal spores and symptom severity as measured by inhaler usage. Inhaler puffs increased by 1.1/100 ppb O_3 (14 to 87 ppb; 12-h daytime average) and by up to 1.2/1,000 fungal spores/m^3 (648 to 7,512 spores/m^3) depending on the species. Delfino et al. (1997) found an association between asthma severity (asthma symptom scores and inhaler use) and peak expiratory flow rate (PEFR) and total fungal spores. Symptom severity was more strongly associated with basidiospore concentrations, especially during the period of sporulation. There was no detected association between O_3 exposure and asthma severity in the Delfino et al. (1996) study, possibly due to O^3 measurement problems (as suggested by the authors). There was also no significant relationship between asthma severity and PM_{10} or pollen exposure, but, their concentrations during the study period were low, 26 µg/m^3 and 216 grains/m^3, respectively.

In summary, newly available information indicates release of allergen-laden material from pollen-spores in respirable-sized aerosols and suggests possible ways by which binding of such material to other airborne particles (e.g., DPM) may concentrate such allergens in ambient air or, once inhaled, jointly exacerbate allergic reactions in susceptible human populations. It should also be noted that pollen itself may act as a carrier for other allergenic materials. Spiewak et al. (1996a) found Gram-bacteria and endotoxin on the surface of pollens; and Spiewak et al. (1996b) found concentrations of several immunotoxicant allergens (Gram+ and Gram– bacteria, thermophilic actinomycetes, fungi) to range from 0 to 10,000 cfu/g of pollen from several grasses or trees in Poland.

7B.2.3 Fungi and Their Byproducts

Fungal spores are known to cause allergic diseases. All fungi may be allergenic depending on the dose. Once an individual is sensitized to a given fungus, small concentrations can trigger an asthma attack or some other allergic response (Yang and Johanning, 2002). Unlike fungal-induced allergic responses, fungal toxic inflammatory responses depend on concentrations of airborne fungi or fungal fragments and are similar for most individuals. Fungi concentrations are usually higher in the indoor environment; but, as noted earlier, outdoor airborne spores are often the source of indoor fungal contamination (Koch et al., 2000).

Fungi produce a variety of byproducts, including mycotoxins and volatile organic compounds. Mycotoxins have low volatility, making inhalation of volatile mycotoxins unlikely. However, mycotoxins are an integral part of the fungus. Volatile organic compounds or VOCs (derivatives of alcohols, ketones, hydrocarbons, and aromatics) are produced when the fungi are actively growing. Concentrations of these VOCs are generally quite low and relationships between exposure and health effects are unclear (Yang and Johanning, 2002).

A number of studies have suggested a relationship between exposure to fungi and their byproducts in respiratory illnesses and immune pathology (Hodgson et al., 1998; Tuomi et al., 2000; Yang and Johanning, 2002). Some fungal byproducts have been shown to stop ciliary activity in vitro and may act to produce general intoxication of macroorganisms through the lung tissue or to enhance bacterial or viral infection (Piecková and Kunová, 2002; Yang and Johanning, 2002). Larsen et al. (1996) showed nonimmunological histamine release from leukocytes exposed to a suspension of fungal spores and hyphal fragments and suggested that the fungal suspension possessed at least two histamine releasing components; an energy-dependent release process and a cytotoxic release process.

Exposures to airborne fungal spores have been shown to be associated with increased asthma attacks and asthma-related deaths. For example, airborne fungal concentrations of $\geq$ 1000 spores/m^3 were reportedly associated with asthma deaths among 5 to 34 year olds in Chicago between 1985 and 1989 (Targonski et al., 1995). The odds of death occurring on days with airborne fungal concentrations of $\geq$ 1000 spores/m^3 were 2.16 times higher than other days. Logistic regression analysis was used to compare the probability of deaths caused by asthma as the result of tree, grass, and ragweed pollen and fungal spores. Fungal spores were

counted as a single group. Asthma deaths were obtained from death certificates. The deaths were also related to personal, social, and medical access factors.

In a study by Rosas et al. (1998), there was a statistically significant increase in fungal spore exposure-related asthma hospital admissions in children in Mexico City that was not seen in adults and seniors. The highest spore (ascomycetes and basidiospore) levels were associated with a 2- to 3-fold increase in hospital admissions per day. Ascomycetes and basidiospore concentrations ranged from < 100 to 207 spores/m^3 and from < 100 to > 1000 spores/m^3, respectively. There was an association with hospital admissions during both the wet and dry season. There was no strong statistical association between asthma admissions and NO_2 (mean: 0.102 and 0.164 ppm),O_3 (mean: 0.204 and 0.187 ppm), SO_2 (mean: 0.074 and 0.081 ppm), TSP (mean: 78 and 156 μg/m^3) and PM_{10} (mean: 56 and 98 μg/m^3) concentrations during either the wet or dry seasons, respectively.

Another example of serious health effects associated with exposures to ambient airborne fungal material is the occurrence of coccidioidomycosis (or "Valley Fever") caused specifically by the fungus *Coccidioides immitis* — a fungus which grows in soils in areas of low rainfall, high summer temperatures, moderate winter temperatures, and which is emitted with the airborne suspension or resuspension of the soil that supports it (i.e., in the southwestern USA, parts of California, and parts of Mexico, Central and South America). At least 50,000 new coccidioidal infections are estimated to occur each year in endemic areas of the United States, many producing subclinical infections typified by lower respiratory tract signs and symptoms largely indistinguishable from flu-like illnesses or other types of infections due to other etiologies (Galgiani and Appel, 1990). However, in some patients, especially those > 65 years old or immune-suppressed (e.g., due to HIV), more protracted serious outcomes can occur, e.g., chronic pneumonia or, rarely, more widespread systemic infection in lymph nodes, skin, bones, meninges, etc., and can be life-threatening (Galgiani and Appel, 1990). Outbreaks of "Valley Fever" due to exposure to airborne dust containing large amounts of *Coccidioides*-contaminated soil materials have been documented both in Arizona during 1990 to 1995 (Morbidity and Mortality Weekly Report, 1996) and among individuals exposed to dust clouds raised by landslides in the San Joaquin Valley set off by the January 1994 Northridge, California earthquake (Schneider et al., 1997). During dry conditions encountered in desert or other endemic areas during drought periods, both natural dust storms and dust-generating human

agricultural activities and off-road vehicle use that disturbs the soil can reasonably be projected as being likely to increase *Coccidioides immitis* infection risk.

Several newly-published studies have evaluated levels of fungi or their viable propagules in ambient (outdoor) and/or indoor air in various areas of the U.S. or other countries in Europe or East Asia. In an extensive 22-month study, Cooley et al. (1998) investigated the types of fungi found in indoor and outdoor air at 48 schools in U.S. areas located along the Atlantic seaboard and Gulf of Mexico. Five fungal genera consistently found in outdoor air comprised > 95% of the outdoor air fungi detected: *Cladosporium* (81.5%); *Penicillium* (5.2%); *Chrysosporium* (4.9%); *Alternaria* (2.8%); and *Aspergillus* (1.1%). An average of ~700 colony-forming units (CFU)/m^3 of *Cladosporium* fungi were found in outdoor air (about 3 times that found indoors); whereas relatively low concentrations of *Penicillium* (~30 CFU/m^3) and the other species (ranging from < 5 to ~40 CFU/m^3) were found in ambient air (compared to indoors). *Penicillium* was most consistently found to be elevated in indoor "complaint areas", the growth of this rather ubiquitous species being optimized between 10 to 25 °C and it predominating in complaint areas with a wide range (23 to 67%) of relative humidity. Cooley et al. noted: (a) that *Penicillium* spores are small (1 to 5 μm) and capable of entering the lower respiratory tract; and (b) that bronchial challenges with *Penicillium* species spores cause immediate and delayed-type asthma in sensitized subjects (Licorish et al., 1985).

In a detailed study of the nature and variation of fungi inside and outside homes in the greater New Haven, CT area, Ren et al. (1999) found that fungi in living room, bedroom, and outdoor air varied across seasons but did not differ seasonally in basement air. They reported that *Claudosporium spp.* dominated both indoor and outdoor air during summer months, whereas *Penicillium* and *Aspergillus* were dominant in indoor air in winter, but neither were dominant in outdoor air during any season. Ren et al. further noted: (a) the fungi isolated in their study are broadly the same as those found in European studies (Beaumont et al., 1984, 1985; Verhoeff et al., 1988; Hunter and Lea, 1994); (b) the seasonal trend found by them for fungal propagules indoors and outdoors were generally comparable with those reported by Hunter and Lea (1994) for British homes, i.e., lowest in winter, increasing in spring, reaching the maximum in summer, and decreasing in fall; (c) their results support current concepts that outdoor air may affect cultural fungal propagules indoors, but the presence of cultural molds in indoor air may not always reflect the presence of such molds in outdoor air, especially in problem indoor

environments; and (d) no associations were found between fungal types and their concentrations in dust and in air, suggesting that types of fungi and concentrations measured in housedust do not necessarily reflect those in indoor air, with air samples likely providing a more direct and better measure of inhalation exposure to fungi. Lastly, Ren et al. (1999) noted that: 50% of the 342 air samples taken during the 1996-1997 study period had < 575 CFU/m^3 total cultural fungal propagules; 97% < 100 CFU/m^3 of *Alternaria*; < 28% > 50 CFU/m^3 of *Aspergillus*; and ~90% < 250 CFU/m^3 of *Penicillium*; and none had *Cladosporium spp.* over the 3000 CFU/m^3 level set as an allergic threshold by Gravesen (1979).

Koch et al. (2000) obtained data on fungi concentrations in a study that evaluated if differences in types of seasonal variations in concentrations of fungi in indoor and/or outdoor air occur and could perhaps account for lower prevalence of allergies and asthma in western than in eastern Germany. During 1995 to 1997, 405 homes in Hamburg (West) and Erfurt (East) Germany were visited twice and samples of settled dust taken by vacuuming from carpets in the living room. No significant differences were found between the two cities for total genera or single fungi species (*Alternaria*, *Aspergillus*, *Cladosporium*, and *Penicillium*) with regard to concentrations of viable fungi detected in settled housedust. Similar seasonal variations were observed for outdoor air and indoor dust, i.e., with a late summer peak detected in outdoor air (~2400 CFU/m^3 viable fungi in August) and a parallel peak in such concentrations in housedust. Koch et al. also noted: (a) that recent studies indicate that outdoor air spora influence the presence of fungi in indoor environments, but indoor air levels of fungi in indoor environments do not simply reflect the presence of fungi or spora in outdoor air; and (b) that the genera commonly isolated in housedust (e.g., *Cladosporium*, *Penicillium*, *Alternaria*, *Aspergillus*) reflect their relative occurrence in outdoor spore counts.

Takahashi (1997) evaluated fungal types and concentrations in indoor and outdoor air in Yokahama, Japan and found the number of outdoor total fungal colony-forming units to vary from < 13 to 2750 CFU/m^3. *Cladosporium spp.* again was found to predominate in outdoor air, followed by *Alternaria spp.* and *Penicillium spp.*, with fungal concentrations peaking in September. Outdoor fungal concentrations were significantly correlated with maximum, minimum, and average temperature of the day, as well as average wind velocity of the day, relative humidity, and precipitation for the month. The ranges of concentrations of fungi in outdoor air were reported by Takahashi to be the same as reported for many European,

North American countries, and Israel — with most showing peak levels during the summer and early fall (July to October) and lowest means during winter months (January to February).

In another East Asia study, Su et al. (2001) compared concentrations of airborne fungi, endotoxin, and housedust mite allergens in the homes of asthmatic and nonasthmatic children in southern Taiwan, where temperature and relative humidity are high throughout the year. With regard to fungi, their results paralleled those of other studies noted above in many respects, except for some differences in seasonal variations — not too surprisingly given the more constant warm temperature/high humidity conditions in this study area. The most predominant indoor genera were *Cladosporium*, *Aspergillus*, *Penicillium*, *Alternaria*, and yeast. *Cladosporium* ranked highest, it being in ~85% of the colonies from indoor samples and its highest CFU/m^3 concentration in winter and other seasonal variation patterns also applying for the other types of fungi. Outdoor air *Cladosporium* levels were significantly correlated with indoor air values during all seasons; and the indoor/outdoor concentrations for the other fungi were also positively correlated during the spring. This suggests that outdoor levels of fungi and/or their spores are important determinants of indoor air levels of fungi in southern Taiwan.

7B.2.4 Endotoxins

Endotoxins and lipopolysaccharides (LPS; chemically purified version of endotoxin) are present in the outer cell membrane of all Gram-negative (Gram-) bacteria. Endotoxins are toxic to most mammals. When released into the blood stream, it is thought that endotoxins/LPS interact with receptors on monocytes and macrophages and other types of receptors on endothelial cells, triggering the production of cytokines, which in turn stimulate production of prostaglandins and leukotrienes, arachidonic acid metabolites (e.g., prostacyclin and thromboxane A_2, and nitric oxide). These mediators can induce physiological changes, e.g., inflammation, smooth muscle constriction, and vasodilatation (Young et al., 1998).

Some of the more recent inhalation studies on endotoxin exposure are summarized in Table 7B-3. In vitro studies on particle-associated endotoxin are discussed in Section 7.5.2.2. Heederik et al. (2000) noted that animal feces and plant materials contaminated with bacteria contribute most to organic dust-related endotoxin exposure. Although there is strong evidence that inhaled endotoxin plays a major role in the toxic effects of bioaerosols encountered in the work place (Castellan et al., 1984, 1987; Rose et al., 1998; Vogelzang et al., 1998; Zock et al.,

1998), it is not clear as to what extent typical ambient concentrations of endotoxin are sufficient to produce toxic pulmonary or systemic effects in healthy or compromised individuals.

Several new occupational exposure studies have yielded potentially useful information for estimating exposure-response relationships for health effects associated with exposure to airborne endotoxin. For example, Vogelzang et al. (1998) evaluated exposure-response relationships for lung function decline in relation to endotoxin exposure of pig farmers in the Netherlands. Long-term average exposure to endotoxin and dust was evaluated via personal monitoring during summer and winter for a cohort of 171 pig farmers over a three-year period. Mean age at start was 39.6 years and mean number of years worked in pig farming was 16.7 years. Linear regression analyses were used to analyze relationships between declines in FEV_1 or FVC (based on measures taken in the first or third years of the studies) and dust concentrations or endotoxin levels in the inhalable dust. Statistically significant ($p < .05$) associations (correcting for age, baseline values, and smoking) were found by regression analysis between estimated long-term average exposure (typically $\geq$ 5 h/day) to endotoxin (105 ng/m^3) and annual decline in $FEV_{1.0}$ (73 mL/year) and FVC (55 mL/year). The FVC, but not the $FEV_{1.0}$, declines were also significantly correlated with inhalable dust concentrations (long-term average = 2.6 mg/m^3). The $FEV_{1.0}$ annual average decline is large in relation to the expected age-related decline of 29 mL/year but equal to that of 73 mL/year reported by Iversen et al. (1994) based on a 5-year study of farmers. The least exposed pig farmers in the Vogelzang et al. study showed an average $FEV_{1.0}$ decline similar to the expected age-related decline, whereas the predicted decline for the most exposed pig farmers ranged up to 100 mL/year. The authors noted that their results support the selection of the lower of two proposed (Clark, 1986; Palchak et al., 1988) occupational exposure threshold levels of 30 or 100 ng/m^3 for airborne endotoxin.

Some health effects have been reported for occupational exposure to complex aerosols containing endotoxin at concentrations likely more relevant to ambient levels. Zock et al. (1998) reported a decline in FEV_1 (~3%) across a shift in a potato processing plant with up to 56 endotoxin units (EU)/m^3 in the air. Rose et al. (1998) reported a high incidence (65%) of BAL lymphocytes in lifeguards working at a swimming pool where endotoxin levels in the air were on the order of 28 EU/m^3. Although these latter two studies may point towards possible pulmonary changes at low concentrations (25 to 50 EU/m^3) of airborne endotoxin, it is not

possible to rule out the contribution to observed effects by other agents present in the complex airborne organic aerosols in the occupational settings studied.

In another European study, Heinrich et al. (2003) recently carried out temporal-spatial analyses of endotoxin in fine ($PM_{2.5}$) and coarse ($PM_{10-2.5}$) particle mass of ambient aerosols from two East German towns about 80 km apart. The authors noted that one town, Hettstedt, showed consistently higher prevalence of hay fever and strong allergic sensitization for children than the prevalence rates seen in the other town, Zerbst, even into the late 1990's when levels of ambient air pollutants (TSP, SO_2) had converged in areas earlier differing in such air pollution levels (Heinrich et al., 2002a,b). From January to June 2002, weekly $PM_{2.5}$ and $PM_{10-2.5}$ samples were taken by dichotomous samplers in each of the two towns and analyzed for endotoxin in the collected ambient PM. The arithmetic mean for the $PM_{2.5}$ sample mass average 10.2 and 12.4 $\mu g/m^3$ for Hettstedt and Zerbst, respectively; and $PM_{10-2.5}$ sample mass 6.1 and 6.8 $\mu g/m^3$, respectively. Comparable ranges for Hettstedt and Zerbst were 0.3 to 25.8 and 4.2 to 26.3 $\mu g/m^3$ for $PM_{2.5}$ and 1.2 to 10.6 and 3.0 to 10.7 $\mu g/m^3$ for $PM_{10-2.5}$. Mass levels for both particle size fractions showed notable week-to-week fluctuations (mostly closely parallel for both towns), with weekly means in each town being highest in late March/early April. Airborne endotoxin levels for both towns showed strong seasonality in parallel patterns for both the fine and the coarse particle fractions, with endotoxin mass concentrations generally being low during late winter/early spring in comparison to their generally increasing from late April to highest points seen in early June (except for a brief episode of elevated endotoxin in Hettsted fine PM seen in late January/early February). Fine PM endotoxin mass concentrations for Hettstedt (1.2 EU/mg^3 arith. mean) were not significantly different from such concentrations for Zerbst (1.1 EU/mg^3 arith. mean), but endotoxin levels expressed per mg dust were significantly higher in Zerbst, suggesting that there may be a higher biogenic content or more bioactive particles in the Zerbst fine PM fraction. The endotoxin levels in the coarse fraction were about 10 times those in the fine fraction, whether expressed in EU/mg dust or EU/m^3 air and did not significantly differ between the two towns. The range of endotoxin levels for Hettsted were 0.2 to 3.6 EU/mg dust and 0.002 to 0.21 EU/m^3 air for $PM_{2.5}$ versus 4.0 to 25.2 EU/mg dust and 0.01 to 0.24 EU/m^3 air for $PM_{10-2.5}$. The comparable concentrations for Zerbst were 0.2 to 4.3 EU/mg dust and 0.004 to 0.031 EU/m^3 for $PM_{2.5}$ versus 3.1 to 24.2 EU/mg dust and 0.02-0.17 EU/m^3 air for $PM_{10-2.5}$. The authors concluded that, given the generally similar levels and patterns in seasonal variations of

endotoxin concentrations in Hettstedt and Zerbst, it was unlikely that differential exposures to endotoxin could explain differences in hay fever or allergic reaction prevalence between the two towns.

The levels of endotoxin concentrations found in Hettsted and Zerbst are similar to those reported for other ambient or rural aerosols and dusts, with those in coarse PM fractions typically exceeding those in fine fractions, as noted by Heinrich et al. (2003). They also noted that measurements in livestock buildings (poultry, pig, cattle) often show endotoxin levels up to several thousand EU/mg dust, with levels in the inhalable PM_{10} fraction being higher by ~10-fold than in the fine PM. The finding of notably higher concentrations and absolute mass amounts of endotoxin in coarse-mode particle samples versus fine particle samples thus appears to hold, in general, across a number of geographic areas and for both occupational and environmental situations. The authors also noted the seasonal variation observed in their study with increased airborne levels of endotoxin in May and June apparently following increased growth of fungi, other plants, and presumably of microbes due to increasing outdoor spring temperatures under moderate climatic conditions in Germany. They also noted that increased levels of plant-related materials and leaf surfaces (Rylander, 2002), as well as pollen surfaces (Spiewak et al., 1996a), may provide additional sources of growth of Gram- bacteria (from which endotoxin is derived). The seasonal variation in endotoxin concentrations observed by Heinrich et al. appear to parallel those seen in other studies for ambient airborne endotoxin levels (i.e., lower in winter and high during warmer weather in late spring/summer).

Park et al. (2000) evaluated endotoxin levels in indoor dust of 20 homes, indoor air of 15 homes, and outdoor air at two locations in the Boston, MA, area. Endotoxin levels in indoor dust (from the bed and bedroom/kitchen floors) were not significantly associated with indoor airborne endotoxin concentrations. The airborne endotoxin levels were, however, significantly associated with absolute humidity; and a significant seasonal effect for kitchen dust (spring > fall) and indoor airborne endotoxin (spring > winter) was seen, as was a significant seasonal pattern for outdoor airborne endotoxin (summer > winter). The authors indicated that, overall, the indoor airborne endotoxin levels (geometric mean = 0.64 EU/m^3) were higher than outdoor concentrations (geometric mean = 0.46 EU/m^3); but seasonal variations were evident, in that indoor airborne endotoxin levels were generally higher than outdoor airborne endotoxin levels during September-April and lower than outdoor levels during late spring/summer

(May-August). Outdoor airborne endotoxin levels showed significant seasonality, varying by more than 4-fold across seasons, with decreases in outdoor levels beginning at the end of summer/early fall and remaining at lowest levels during winter before starting to increase again with onset of the growing season in late spring. The authors noted that this pattern is consistent with data suggesting that outdoor Gram- bacteria (and thus airborne) endotoxins are shed from leaves of growing plants (Edmonds, 1979; Andrews, 1992). Further, the overall mean outdoor airborne endotoxin levels at an urban sampling location (geometric mean = 0.51 EU/m^3) were somewhat (but not significantly) higher than at a suburban location (geometric mean = 0.39 EU/m^3).

Thorn and Rylander (1998a) examined the effect of endotoxin inhalation on inflammatory responses in 21 healthy subjects from 20 to 30 years old. All subjects were known smokers, currently did not have a respiratory infection, no self-reported allergies or chronic bronchitis, and no physician diagnosed asthma. Subjects were examined before exposure to up to 40 µg LPS. The LPS was suspended in saline, aerosolized, and then delivered to the subject by a nebulizer adjusted to give 4 µl per nebulizer dose. The subjects inhaled 20 puffs of LPS at a concentration of 500 µg/mL, for a total of 40 µg of inhaled LPS. Cell counts, eosinophilic cationic protein (ECP), and myeloperoxidase (MPO) were monitored in the blood and sputum before and 24 h following exposure. Following LPS inhalation, MPO was significantly increased in both the blood and sputum and ECP was increased, but only significantly so in sputum. The ratio of MPO and neutrophils was significantly decreased in blood and sputum. Spirometric testing demonstrated a significant decrease in FEV_1 and FVC values following LPS inhalation. Some subjects experienced symptoms (throat irritation, dry cough, breathlessness, unusual tiredness, headache, and heaviness in the head) that developed 4 to 6 h after exposure and persisted for 6 to 8 h.

Michel et al. (1997) examined the dose-response relationships for effects of inhaled LPS (the purified derivative of endotoxin) in normal healthy volunteers exposed to 0, 0.5, 5, and 50 µg of LPS solubilized in sterile saline administered via a jet nebulizer. The nebulizer produces a calibrated aerosol consisting of heterodispersed droplets in the range of 1 to 4 µm (MMAD). Inhalation of 5 µg of LPS resulted in significantly increased blood c-reactive protein (CRP) and PMNs, as well as PMNs and monocytes in sputum. Inhalation of 50 µg LPS significantly increased body temperature, blood PMNs, blood and urine CRP and sputum PMNs,

monocytes, and lymphocytes. At the higher concentration, a slight (3%) but nonsignificant decrease in FEV_1 was also seen.

Other controlled exposure studies of laboratory animals (rat) by Elder et al. (2000a,b) indicate that priming of the respiratory tract by inhaled endotoxin increases the effect of inhaled ultrafine surrogate particles and ozone (as discussed in more detail in Section 7.6).

In vitro studies of potential endotoxin contributions to toxic effect of ambient PM are discussed in Section 7.4.2.

7B.2.5 (1 → 3)-β-D-Glucan

Studies from different countries have reported relationships between damp/humid indoor environments and various symptoms in both adults and children (Meklin et al., 2002b). Such symptoms consist of eye, nose, and throat irritation, dry cough, headache, tiredness, and sometime skin problems. Fungi and their byproducts (discussed above) and bacteria commonly present in damp/humid indoor environments contain several substances that have known inflammatory properties. Of the substances associated with these symptoms, (1→3)-β-D-glucan, a polyglucose compound in the cell walls of fungi, certain Gram+ bacteria, and plants, has begun to be accorded increasing attention.

The (1 → 3)-β-D-glucan can induce several biological responses in vertebrates, including stimulation of the reticulo-endothelial system, activation of neutrophils, macrophages, and complement, and possibly activation of eosinophils. T-lymphocyte activation and proliferation have been reported in experimental animals (Heederik et al., 2000). Rylander (1996) suggested that an acute exposure to (1 → 3)-β-D-glucan can produce symptoms of airway inflammation in normal subjects without a history of airway reactivity after exposing subjects to 210 ± 147 ng/m^3 (1 → 3)-β-D-glucan for 3 separate 4 h sessions 5 to 8 days apart. Exposure to (1 → 3)-β-D-glucan alone did not significantly impact FEV_1 values; but there was a slight decrease in FEV_1 values following administration of the two highest doses of methacholine (MCh). Methacholine was administered in increasing doses in 3 min intervals for a total of 1.25 mg. Forced vital capacity (FVC) and FEV_1/FVC were also unchanged following (1 → 3)-β-D-glucan exposure and MCh challenge. There was a significant, negative correlation between MCh-induced decrease in FEV_1 values and the intensity of throat irritation after 1 h exposure. The intensity of nasal irritation and stuffy nose and throat irritation was increased at 1 and 4 h. Dry cough, cough with phlegm,

chest tightness and wheezy chest was not affected. No effects on airway responsiveness or inflammatory symptoms were noted in subjects exposed to endotoxins (9.9 ng/m^3) under the same exposure conditions.

Thorn and Rylander (1998b) examined the relationship between exposure to airborne (1 → 3)-β-D-glucan and airways inflammation. The study was conducted on a group of 75 houses in Gothenburg, Sweden where there had been numerous complaints about dampness and respiratory symptoms, fatigue, and mold odors. Measurements of (1 → 3)-β-D-glucan and endotoxins in airborne dust were made with Limulus lysates. Study participants included 67 females and 62 males 18 to 83 years old and included 34 smokers and 9 physician-diagnosed asthmatics. The average number of years the subjects lived in their house was 18 years (range 2 to 36 years). Study participants provided questionnaire information for assessment of organic dust-induced effects. The questionnaire inquired about existing diseases states; occupation; length of time the subject had lived in the house; the presence of pets; and the occurrence of cough (dry or with phlegm); shortness of breath; nose, throat, and eye irritation; nasal and chest congestion; and joint and muscle pains, headache, fatigue, and dermal disorders. Other questions addressed subjective airway reactivity, chronic bronchitis, asthma, and episodes of fever and influenza-like symptoms gone the next day. Chronic bronchitis was defined as a cough with sputum for at least 3 months a year for a period of at least 2 years. Asthma was defined as physician-diagnosed asthma. Spirometry was performed on test subjects to exclude subjects with less than 70% of predicted values in FEV_1 and/or FEV_1/FVC. Airway responsiveness was assessed using MCh for a total of 1.2 mg MCh, administered in increasing doses at 3-min intervals. Serum eosinophilic cationic protein (ECP), myeloperoxidase (MPO), and C-reactive protein (CRP) were measured. Atopy was determined using the Phadiatop test to measure the concentration of specific IgE antibodies against airborne allergens.

No detectable levels of endotoxin were found in the homes, but (1 → 3)-β-D-glucan levels ranged from 0 to 19 ng/m^3. Of 75 homes studied, 20 had (1 → 3)-β-D-glucan concentrations below 1 ng/m^3 and 13 homes had levels above 6 ng/m^3. Twenty-four subjects had positive Phadioatop test; but there was no significant correlation between exposure and atopy. However, when evaluated by age, there was a significantly larger number of atopic subjects in the > 65-year-old group exposed to > 3 ng/m^3 (1 → 3)-β-D-glucan. There was a significant inverse correlation between baseline FEV_1 and number of years the subjects lived in the house when

controlled for age, gender, cigarette smoking status, asthma, atopy, and pets among male subjects < 65 years old that was not seen in the female subjects < 65 years old and in > 65 years old subjects. The relationship was present only for those male subjects exposed to > 1 ng/m^3 (1 → 3)-β-D-glucan. Atopic subjects exposed to > 1 ng/m^3 (1 → 3)-β-D-glucan had significantly higher serum MPO. Serum ECP and CRP were also higher in these subjects but not significantly so.

Douwes et al. (2000) examined the relationship between exposure to (1 → 3)-β-D-glucan and endotoxins and peak expiratory flow (PEF) in children (ages 7 to 11 years) with and without chronic respiratory symptoms. The children were monitored twice a day for PEF variability. House dust samples from living room and bedroom floors and the children's mattresses were taken during the PEF monitoring period. As indicated by linear regression analysis (adjusting for dust mite allergen levels, the presence of pets, and the type of flooring in the home), peak expiratory flow variability in the children with chronic respiratory symptoms was strongly associated with (1→3)-β-D-glucan levels in dust from living room floors when expressed in micrograms per square meter. The association was strongest for atopic children with asthma.

7B.3 SUMMARY

Bioaerosols, from sources such as plants, fungi, and microorganisms, range in size from 0.01 to μm to > 20 μm. They comprise a small fraction of ambient PM, but have been shown to contribute to health effects associated with PM exposure.

Pollen from flowering plants, trees and grasses, deposits in upper airways to induce allergic rhinitis. Allergen-containing cytoplasmic fragments from ruptured pollen grains can enter the deep lung, where they can exacerbate asthma. Synergistic interactions between pollen debris and other ambient PM (e.g., the polycyclic hydrocarbon component of DE) are thought to be a mechanism that may explain the increased incidence of asthma morbidity and mortality.

Fungal spores and other fungal materials are the largest and most consistently present outdoor bioaerosol. Some airborne fungal materials cause allergic rhinitis and asthma, which are highly dependent on seasonal variations in airborne fungi concentrations (being highest in spring/summer and lowest in winter). Exposures have been linked to asthma hospitalization and death. Exposures to airborne dust containing elevated concentrations of a soil-dwelling fungus

common to dry areas of central California and certain desert areas of the southwestern United States have been linked to outbreaks of "Valley Fever", a respiratory infection that can be potentially deadly (especially for those > 65 years old and immune suppressed persons).

Human handling and burning of plant material contributes to increased airborne bioaerosols, some of which have been shown to contribute to human health effects.

Animals and insects produce bioaerosols capable of producing hypersensitivity diseases. Most notably, exposure to dust mite and cockroach material has been linked to sensitization in children.

Also, bacteria and viruses are significant bioaerosols. Much of the toxicity of bacteria is due to the endotoxins present in the outer cell membrane, which trigger production of cytokines and a cascade of inflammation. Concentrations of endotoxins are seasonal (highest in warm months — lowest in cold months), and are typically associated more with coarse-mode than with fine-mode particles. Another component, (1→3)-β-D-glucan, of cell walls of fungi, certain bacteria, and plants, has also been shown to cause respiratory inflammation.

REFERENCES

Alberts, W. M.; Brooks, S. M. (1992) Advances in occupational asthma. Clin. Chest Med. 13: 281-302.

Anderson, R. L.; Owens, J. W.; Timms, C. W. (1992) The toxicity of purified cellulose in studies with laboratory animals. Cancer Lett. 63: 83-92.

Andrews, J. H.; Hirano, S. S., eds. (1992) Microbial ecology of leaves. New York, NY: Springer-Verlag.

Arlian, L. G. (1989) Biology and ecology of house dust mites, *Dermatophagoides* spp. and *Euroglyphus* spp. Immunol. Allergy Clin. North Am. 9: 339-356.

Bauer, H.; Kasper-Giebl, A.; Löflund, M.; Giebl, H.; Hitzenberger, R.; Zibuschka, F.; Puxbaum, H. (2002) The contribution of bacteria and fungal spores to the organic carbon content of cloud water, precipitation and aerosols. Atmos. Res. 64: 109-119.

Baxter, C. S.; Wey, H. E.; Burg, W. R. (1981) A prospective analysis of the potential risk associated with inhalation of aflatoxin-contaminated grain dusts. Food Cosmet. Toxicol. 19: 765-769.

Bayram, H.; Devalia, J. L.; Khair, O. A.; Abdelaziz, M. M.; Sapsford, R. J.; Sagai, M.; Davies, R. J. (1998) Comparison of ciliary activity and inflammatory mediator release from bronchial epithelial cells of nonatopic nonasthmatic subjects and atopic asthmatic patients and the effect of diesel exhaust particles *in vitro*. J. Allergy Clin. Immunol. 102: 771-782.

Beaumont, F.; Kauffman, H. F.; Sluiter, H. J.; De Vries, K. (1984) A volumetric-aerobiologic study of seasonal fungus prevalence inside and outside dwellings of asthmatic patients living in northeast Netherlands. Ann. Allergy 53: 486-492.

Beaumont, F.; Kauffman, H. F.; Sluiter, H. J.; De Vries, K. (1985) Sequential sampling of fungal air spores inside and outside the homes of mould-sensitive, asthmatic patients: a search for a relationship to obstructive reactions. Ann. Allergy 55: 740-746.

Behrendt, H.; Becker, W. M.; Friedrichs, K. H.; Darsow, U.; Tomingas, R. (1992) Interaction between aeroallergens and airborne particulate matter. Int. Arch. Allergy Immunol. 99: 425-428.

Behrendt, H.; Friedrichs, K.-H.; Krämer, U.; Hitzfeld, B.; Becker, W.-M.; Ring, J. (1995) The role of indoor and outdoor air pollution in allergic diseases. In: Johansson, S. G. O., ed. Prog. Allergy Clin. Immunol., Proceedings of the 15th international congress, Allergol. Clin. Immunol.; 1994. Seattle, WA: Hogrefe & Huber; pp. 83-89.

Behrendt, H.; Becker, W. M.; Fritzsche, C.; Sliwa-Tomczok, W.; Tomczok, J.; Friedrichs, K. H.; Ring, J. (1997) Air pollution and allergy: experimental studies on modulation of allergen release from pollen by air pollutants. Int. Arch. Allergy Immunol. 113: 69-74.

Behrendt, H.; Krämer, U.; Schäfer, T.; Kasche, A.; Eberlein-König, B.; Darsow, U.; Ring, J. (2001) Allergotoxicology–a research concept to study the role of environmental pollutants in allergy. Allergy Clin. Immunol. Int. 13: 122-128.

Bellomo, R.; Gigliotti, P.; Treloar, A.; Holmes, P.; Suphioglu, C.; Singh, M. B.; Knox, Bruce. (1992) Two consecutive thunderstorm associated epidemics of asthma in the city of Melbourne: the possible role of rye grass pollen. Med. J. Aust. 156: 834-837.

Brunekreef, B.; Hoek, G.; Fischer, P.; Spieksma, F. T. M. (2000) Relation between airborne pollen concentrations and daily cardiovascular and respiratory-disease mortality. Lancet 355: 1517-1518.

Burge, H. A. (1995) Bioaerosols in the residential environment. In: Cox, C. S.; Wathes, C. M., eds. Bioaerosols handbook. Boca Raton, FL: CRC Press, Inc.; pp. 579-597.

Burge, H. A.; Rogers, C. A. (2000) Outdoor allergens. Environ. Health Perspect. 108(suppl. 4): 653-659.

Castellan, R. M.; Olenchock, S. A.; Hankinson, J. L.; Millner, P. D.; Cocke, J. B.; Bragg, C. K.; Perkins, H. H., Jr.; Jacobs, R. R. (1984) Acute bronchoconstriction induced by cotton dust: dose-related responses to endotoxin and other dust factors. Ann. Intern. Med. 102: 157-163.

Castellan, R. M.; Olenchock, S. A.; Kinsley, K. B.; Hankinson, J. L. (1987) Inhaled endotoxin and decreased spirometric values: an exposure-response relation for cotton dust. N. Engl. J. Med. 317: 605-610.

Celenza, A.; Fothergill, J.; Kupek, E.; Shaw R. J. (1996) Thunderstorm associated asthma: a detailed analysis of environmental factors. Br. Med. J. 312: 604-607.

Centers for Disease Control and Prevention. (1996) Coccidioidomycosis–Arizona, 1990-1995. Morb. Mortal. Wkly. Rep. 45: 1069-1073.

Clark, S. (1986) Report on prevention and control. Am. J. Ind. Med. 10: 267-273.

Cooley, J. D.; Wong, W. C.; Jumper, C. A.; Straus, D. C. (1998) Correlation between the prevalence of certain fungi and sick building syndrome. Occup. Environ. Med. 55: 579-584.

Cox, C. (1987) Threshold dose-response models in toxicology. Biometrics 43: 511-523.

Cox, C. S.; Wathes, C. M., eds. (1995) Bioaerosols handbook. Boca Raton, FL: CRC Press, Inc.
Croft, W. A.; Jarvis, B. B.; Yatawara, C. S. (1986) Airborne outbreak of trichothecene toxicosis. Atmos. Environ. 20: 549-552.
Cullen, R. T.; Searl, A.; Miller, B. G.; Davis, J. M.; Jones, A. D. (2000) Pulmonary and intraperitoneal inflammation induced by cellulose fibres. J. Appl. Toxicol. 20: 49-60.
Delfino, R. J.; Coate, B. D.; Zeiger, R. S.; Seltzer, J. M.; Street, D. H.; Koutrakis, P. (1996) Daily asthma severity in relation to personal ozone exposure and outdoor fungal spores. Am. J. Respir. Crit. Care Med. 154: 633-641.
Delfino, R. J.; Murphy-Moulton, A. M.; Burnett, R. T.; Brook, J. R.; Becklake, M. R. (1997) Effects of air pollution on emergency room visits for respiratory illnesses in Montreal, Quebec. Am. J. Respir. Crit. Care Med. 155: 568-576.
Diaz-Sanchez, D.; Tsien, A.; Fleming, J.; Saxon, A. (1997) Combined diesel exhaust particulate and ragweed allergen challenge markedly enhances human in vivo nasal ragweed-specific IgE and skews cytokine production to a T helper cell 2-type pattern. J. Immunol. 158: 2406-2413.
Diaz-Sanchez, D.; Jyrala, M.; Ng, D.; Nel, A.; Saxon, A. (2000) *In vivo* nasal challenge with diesel exhaust particles enhances expression of the CC chemokines rantes, MIP-1α, and MCP-3 in humans. Clin. Immunol. 97: 140-145.
Douwes, J.; Zuidhof, A.; Doekes, G.; Van der Zee, S.; Wouters, I.; Boezen, H. M.; Brunekreef, B. (2000) (1 → 3)-β-D-glucan and endotoxin in house dust and peak flow variability in children. Am. J. Respir. Crit. Care Med. 162: 1348-1354.
Edmonds, R. L., ed. (1979) Aerobiology: the ecological systems approach. Stroudsburg, PA: Dowden, Hutchinson & Ross, Inc. (US/IBP synthesis series 10).
Elder, A. C. P.; Gelein, R.; Finkelstein J. N.; Cox, C.; Oberdörster, G. (2000a) Endotoxin priming affects the lung response to ultrafine particles and ozone in young and old rats. In: Phalen, R. F., ed. Inhalation toxicology: proceedings of the third colloquium on particulate air pollution and human health (first special issue); June, 1999; Durham, NC. Inhalation Toxicol. 12(suppl. 1): 85-98.
Elder, A. C. P.; Gelein, R.; Finkelstein, J. N.; Cox, C.; Oberdörster, G. (2000b) Pulmonary inflammatory response to inhaled ultrafine particles is modified by age, ozone exposure, and bacterial toxin. In: Grant, L. D., ed. PM2000: particulate matter and health. Inhalation Toxicol. 12(suppl. 4): 227-246.
Facchini, M. C.; Fuzzi, S.; Zappoli, S.; Andracchio, A.; Gelencsér, A.; Kiss, G.; Krivácsy, Z.; Mészáros, E.; Hansson, H.-C.; Alsberg, T.; Zebühr, Y. (1999) Partitioning of the organic aerosol component between fog droplets and interstitial air. J. Geophys. Res. [Atmos.] 104: 26,821-26,832.
Fraser, M. P.; Lakshmanan, K. (2000) Using levoglucosan as a molecular marker for the long-range transport of biomass combustion aerosols. Environ. Sci. Technol. 34: 4560-4564.
Fujieda, S.; Diaz-Sanchez, D.; Saxon, A. (1998) Combined nasal challenge with diesel exhaust particles and allergen induces *in vivo* IgE isotype switching. Am. J. Respir. Cell Mol. Biol. 19: 507-512.
Fujimaki, H.; Nohara, O.; Ichinose, T.; Watanabe, N.; Saito, S. (1994) IL-4 production in mediastinal lymph node cells in mice intratracheally instilled with diesel exhaust particulates and antigen. Toxicology 92: 261-268.
Galgiani, J. N.; Ampel, N. M. (1990) Coccidioidomycosis in human immunodeficiency virus-infected patients. J. Infect. Dis. 162: 1165-1169.
Gelencsér, A.; Hoffer, A.; Kiss, G.; Tombácz, E.; Kurdi, R.; Bencze, L. (2003) *In-situ* formation of light-absorbing organic matter in cloud water. J. Atmos. Chem. 45: 25-33.
Girgis, S. T.; Marks, G. B.; Downs, S. H.; Kolbe, A.; Car, G. N.; Paton, R. (2000) Thunderstorm-associated asthma in an inland town in south-eastern Australia. Who is at risk? Eur. Respir. J. 16: 3-8.
Gravesen, S. (1979) Fungi as a cause of allergic disease. Allergy 34:135-154.
Grote, M.; Vrtala, S.; Niederberger, V.; Valenta, R.; Reichelt, R. (2000) Expulsion of allergen-containing materials from hydrated rye grass (Lolium perenne) pollen revealed by using immunogold field emission scanning and transmission electron microscopy. J. Allergy Clin. Immunol. 105: 1140-1145.
Hastie, A. T.; Peters, S. P. (2001) Interactions of allergens and irritants in susceptible populations in producing lung dysfunction: implications for future research. Environ. Health Perspect. 109(suppl. 4): 605-607.
Havers, N.; Burba, P.; Lambert, J.; Klockow, D. (1998) Spectroscopic characterisation of humic-like substances in airborne particulate matter. J. Atmos. Chem. 29: 45-54.
Heederik, D.; Douwes, J.; Wouters, I.; Doekes, G. (2000) Organic dusts: beyond endotoxin. Inhalation Toxicol. 12(suppl. 3): 27-33.
Heinrich, J.; Hoelscher, B.; Frye, C.; Meyer, I.; Pitz, M.; Cyrys, J.; Wjst, M.; Neas, L.; Wichmann, H.-E. (2002a) Improved air quality in reunified Germany and decreases in respiratory symptoms. Epidemiology 13: 394-401.

Heinrich, J.; Hoelscher, B.; Frye, C.; Meyer, I.; Wjst, M.; Wichmann, H. E. (2002b) Trends in prevalence of atopic diseases and allergic sensitization in children in eastern Germany. Eur. Respir. J. 19: 1040-1046.
Heinrich, J.; Pitz, M.; Bischof, W.; Krug, N.; Borm, P. J. A. (2003) Endotoxin in fine ($PM_{2.5}$) and coarse ($PM_{2.5-10}$) particle mass of ambient aerosols. A tempero-spatial analysis. Atmos. Environ. 37: 3659-3667.
Hodgson, M. J.; Morey, P.; Leung, W.-Y.; Morrow, L.; Miller, D.; Jarvis, B. B.; Robbins, H.; Halsey, J. F.; Storey, E. (1998) Building-associated pulmonary disease from exposure to *Stachybotrys chartarum* and *Aspergillus versicolor*. J. Occup. Environ. Med. 40: 241-249.
Hunter, C. A.; Lea, R. G. (1994) The airborne fungal population of representative British homes. In: Samson, R. A.; Flannigan, B.; Flannigan, M. E.; Verhoeff, A. P.; Adan, O. C. G.; Hoekstra, E. S., eds. Health implications of fungi in indoor environments. New York, NY: Elsevier, pp. 141-153. (Air Quality Monographs, v. 2).
Iversen, M.; Brink, O.; Dahl, R. (1994) Lung function in a five year follow-up study of farmers. Ann. Agric. Environ. Med. 1: 39-43.
Kendrick, B. (1992) The fifth kingdom. 2nd ed. Newburyport, MA: Focus Information Group.
Knox, R. B.; Suphioglu, C.; Taylor, P.; Desai, R.; Watson, H. C.; Peng, J. L.; Bursill, L. A. (1997) Major grass pollen allergen Lol p 1 binds to diesel exhaust particles: implications for asthma and air pollution. Clin. Exp. Allergy 27: 246-251.
Koch, A.; Heilemann, K.-J.; Bischof, W.; Heinrich, J.; Wichmann, H. E. (2000) Indoor viable mold spores - a comparison between two cities, Erfurt (eastern Germany) and Hamburg (western Germany) Allergy 55: 176-180.
Kuhn, D. M.; Ghannoum, M. A. (2003) Indoor mold, toxigenic fungi, and *Stachybotrys chartarum*: infectious disease perspective. Clin. Microbiol. Rev. 16: 144-172.
Larsen, F. O.; Christensen, L. H. R.; Clementsen, P.; Gravesen, S.; Stahl Skov, P.; Norn, S. (1996) Microfungi in indoor air are able to trigger histamine release by non-IgE-mediated mechanisms. Inflammation Res. 45(suppl. 1): S23-S24.
Lewis, W. H.; Vinay, P.; Zenger, V. E. (1983) Airborne and allergenic pollen of North America. Baltimore, MD: The Johns Hopkins University Press.
Licorish, K.; Novey, H. S.; Kozak, P.; Fairshter, R. D.; Wilson, A. F. (1985) Role of *Alternaria* and *Penicillium* spores in the pathogenesis of asthma. J. Allergy Clin. Immunol. 76: 819-825.
Lighthart, B.; Mohr, A. J. (1994) Atmospheric microbial aerosols: theory and applications. New York, NY: Chapman & Hall.
Mathews, K. P. (1989) Inhalant insect-derived allergens. Immunol. Allergy Clin. North Am. 9: 321-338.
Matthias-Maser, S.; Jaenicke, R. (1995) The size distribution of primary biological aerosol particles with radii > 0.2 μm in an urban/rural influenced region. Atmos. Res. 39: 279-286.
Meklin, T.; Reponen, T.; Toivola, M.; Koponen, V.; Husman, T.; Hyvärinen, A.; Nevalainen, A. (2002a) Size distributions of airborne microbes in moisture-damaged and reference school buildings of two construction types. Atmos. Environ. 36: 39-40.
Meklin, T.; Husman, T.; Vepsäläinen, A.; Vahteristo, M.; Koivisto, J.; Halla-Aho, J.; Hyvärinen, A.; Moschandreas, D.; Nevalainen, A. (2002b) Indoor air microbes and respiratory symptoms of children in moisture damaged and reference schools. Indoor Air 12: 175-183.
Michel, O.; Nagy, A.-M.; Schroeven, M.; Duchateau, J.; Nève, J.; Fondu, P.; Sergysels, R. (1997) Dose-response relationship to inhaled endotoxin in normal subjects. Am. J. Respir. Crit. Care Med. 156: 1157-1164.
Nel, A. E.; Diaz-Sanchez, D.; Ng, D.; Hiura, T.; Saxon, A. (1998) Enhancement of allergic inflammation by the interaction between diesel exhaust particles and the immune system. J. Allergy Clin. Immunol. 102: 539-554.
Newson, R.; Strachan, D.; Archibald, E.; Emberlin, J.; Hardaker, P.; Collier, C. (1997) Effect of thunderstorms and airborne grass pollen on the incidence of acute asthma in England, 1990-94. Thorax 52: 680-685.
Oikonen, M.; Laaksonen, M.; Laippala, P.; Oksaranta, O.; Lilius, E.-M.; Lindgren, S.; Rantio-Lehtimäki, A.; Anttinen, A.; Koski, K.; Erälinna, J.-P. (2003) Ambient air quality and occurrence of multiple sclerosis relapse. Neuroepidemiology 22: 95-99.
Ong, E. K. (1994) Grass pollen allergens: molecular characterization and environmental monitoring [dissertation]. Melbourne, Australia: The University of Melbourne.
Ormstad, H. (2000) Suspended particulate matter in indoor air: adjuvants and allergen carriers. Toxicology 152: 53-68.
Ormstad, H.; Johansen, B. V.; Gaarder, P. I. (1998) Airborne house dust particles and diesel exhaust particles as allergen carriers. Clin. Exp. Allergy 28: 702-708.
Palchak, R. B.; Cohen, R.; Ainslie, M.; Hoerner, C. L. (1988) Airborne endotoxin associated with industrial-scale production of protein products in gram-negative bacteria. Am. Ind. Hyg. Assoc. J. 49: 420-421.

Park, J.-H.; Spiegelman, D. L.; Burge, H. A.; Gold, D. R.; Chew, G. L.; Milton, D. K. (2000) Longitudinal study of dust and airborne endotoxin in the home. Environ. Health Perspect. 108: 1023-1028.
Piecková, E.; Kunová, Z. (2002) Indoor fungi and their ciliostatic metabolites. Ann. Agric. Environ. Med. 9: 59-63.
Platts-Mills, T. A. E.; Chapman, M. D. (1987) Dust mites: immunology, allergic disease, and environmental control. J. Allergy Clin. Immunol. 80: 755-775.
Poore, M. W. (2002) Levoglucosan in PM2.5 at the Fresno supersite. J. Air Waste Manage. Assoc. 52: 3-4.
Pope, A. M.; Patterson, R.; Burge, H. (1993) Indoor allergens: assessing and controlling adverse health effects. Washington, DC: National Academy Press.
Puxbaum, H.; Tenze-Kunit, M. (2003) Size distribution and seasonal variation of atmospheric cellulose. Atmos. Environ. 37: 3693-3699.
Ren, P.; Jankun, T. M.; Leaderer, B. P. (1999) Comparisons of seasonal fungal prevalence in indoor and outdoor air and in house dusts of dwellings in one northeast American county. J. Exposure Anal. Environ. Epidemiol. 9: 560-568.
Rippon, J. W. (1988) Medical mycology: the pathogenic fungi and the pathogenic actinomycetes. 3rd ed. Philadelphia, PA: W. B. Saunders Company.
Rogge, W. F.; Mazurek, M. A.; Hildemann, L. M.; Cass, G. R.; Simoneit, B. R. T. (1993) Quantification of urban organic aerosols at a molecular level: identification, abundance and seasonal variation. Atmos. Environ. Part A 27: 1309-1330.
Rosas, I.; McCartney, H. A.; Payne, R. W.; Calderón, C.; Lacey, J.; Chapela, R.; Ruiz-Velazco, S. (1998) Analysis of the relationships between environmental factors (aeroallergens, air pollution, and weather) and asthma emergency admissions to a hospital in Mexico City. Allergy 53: 394-401.
Rose, C. S.; Martyny, J. W.; Newman, L. S.; Milton, D. K.; King, T. E., Jr.; Beebe, J. L.; McCammon, J. B.; Hoffman, R. E.; Kreiss, K. (1998) "Lifeguard lung": endemic granulomatous pneumonitis in an indoor swimming pool. Am. J. Public Health 88: 1795-1800.
Rylander, R. (1996) Airway responsiveness and chest symptoms after inhalation of endotoxin or (1 → 3)-β-D-glucan. Indoor Built Environ. 5: 106-111.
Rylander, R. (2002) Endotoxin in the environment - exposure and effects. J. Endotoxin Res. 8: 241-252.
Schäppi, G. F.; Taylor, P. E.; Staff, I. A.; Suphioglu, C.; Knox, R. B. (1997) Source of Bet v 1 loaded inhalable particles from birch revealed Sex. Plant Reprod. 10: 315-323.
Schäppi, G. F.; Taylor, P. E.; Pain, M. C. F.; Cameron, P. A.; Dent, A. W.; Staff, I. A.; Suphioglu, C. (1999) Concentrations of major grass group 5 allergens in pollen grains and atmospheric particles: implications for hay fever and allergic asthma sufferers sensitized to grass pollen allergens. Clin. Exp. Allergy 29: 633-641.
Schauer, J. J.; Rogge, W. F.; Hildemann, L. M.; Mazurek, M. A.; Cass, G. R. (1996) Source apportionment of airborne particulate matter using organic compounds as tracers. Atmos. Environ. 30: 3837-3855.
Schneider, E.; Hajjeh, R. A.; Spiegel, R. A.; Jibson, R. W.; Harp, E. L.; Marshall, G. A.; Gunn, R. A.; McNeil, M. M.; Pinner, R. W.; Baron, R. C.; Burger, R. C.; Hutwagner, L. C.; Crump, C.; Kaufman, L.; Reef, S. E.; Feldman, G. M.; Pappagianis, D.; Werner, S. B. (1997) A coccidioidomycosis outbreak following the Northridge, California earthquake. JAMA J. Am. Med. Assoc. 277: 904-908.
Śpiewak, R.; Krysińska-Traczyk, E.; Sitkowska, J.; Dutkiewicz, J. (1996a) Microflora of allergenic pollens - a preliminary study. Ann. Agric. Environ. Med. 3: 127-130.
Śpiewak, R.; Skórska, C.; Prażmo, Z.; Dutkiewicz, J. (1996b) Bacterial endotoxin associated with pollen as a potential factor aggravating pollinosis. Ann. Agric. Environ. Med. 3: 57-59.
Stanley, R. G.; Linskens, H. F. (1985) Pollen: biologie biochemie gewinnung und verwendung (Pollen: biology, biochemistry, production and uses). Greifenberg, German Federal Republic: Urs Freund Verlag.
Su, H.-J.; Wu, P.-C.; Chen, H.-L.; Lee, F.-C.; Lin, L.-L. (2001) Exposure assessment of indoor allergens, endotoxin, and airborne fungi for homes in Southern Taiwan. Environ. Res. 85: 135-144.
Suphioglu, C.; Singh, M. B.; Taylor, P.; Bellomo, R.; Holmes, P.; Puy, R.; Knox, R. B. (1992) Mechanism of grass-pollen-induced asthma. Lancet 339: 569-572.
Takahashi,T. (1997) Airborne fungal colony-forming units in outdoor and indoor environments in Yokohama, Japan. Mycopathologia 139: 23-33.
Targonski, P. V.; Persky, V. W.; Ramekrishnan, V. (1995) Effect of environmental molds on risk of death from asthma during the pollen season. J. Allergy Clin. Immunol. 95: 955-961.
Taylor, P. E.; Staff, I. A.; Singh, M. B.; Knox, R. B. (1994) Localization of the two major allergens in rye-grass pollen using specific monoclonal antibodies and quantitative analysis of immunogold labelling. Histochem. J. 26: 392-401.
Taylor, P. E.; Flagan, R. C.; Valenta, R.; Glovsky, M. M. (2002) Release of allergens as respirable aerosols: a link between grass pollen and asthma. J. Allergy Clin. Immunol. 109: 51-56.

Taylor, P. E.; Flagan, R.; Miguel, A. G.; Valenta, R.; Glovsky, M. M. (2003) Identification of birch pollen respirable particles [abstract]. Chest 123(suppl. 3): 433S.

Thorn, J.; Rylander, R. (1998a) Inflammatory response after inhalation of bacterial endotoxin assessed by the induced sputum technique. Thorax 53: 1047-1052.

Thorn, J.; Rylander, R. (1998b) Airways inflammation and glucan in a rowhouse area. Am. J. Respir. Crit. Care Med. 157: 1798-1803.

Tuomi, T.; Engström, B.; Niemelä, R.; Svinhufvud, J.; Reijula, K. (2000) Emission of ozone and organic volatiles from a selection of laser printers and photocopiers. Appl. Occup. Environ. Hyg. 15: 629-634.

U.S. Environmental Protection Agency. (1996) Air quality criteria for particulate matter. Research Triangle Park, NC: National Center for Environmental Assessment-RTP Office; report nos. EPA/600/P-95/001aF-cF. 3v.

U.S. Environmental Protection Agency. (2002) Health assessment document for diesel engine exhaust. Washington, DC: Office of Research and Development, National Center for Environmental Assessment; report no. EPA/600/8-90/057F. Available: http://cfpub.epa.gov/ncea/ [22 May, 2003].

Venables, K. M.; Allitt, U.; Collier, C. G.; Emberlin, J.; Greig, J. B.; Hardaker, P. J.; Highham, J. H.; Laing-Morton, T.; Maynard, R. L.; Murray, V.; Strachan, D.; Tee, R. D. (1997) Thunderstorm-related asthma–the epidemic of 24/25 June 1994. Clin. Exp. Allergy 27: 725-736.

Verhoeff, A. P.; Van Wijnen, H. J.; Attwood, P.; Versloot, P.; Boleij, J. S. M.; Van Reenen-Hoekstra, E. S.; Samson, R. A. (1988) Quantification and qualification of airborne fungi in houses. A comparison of measurement techniques. Amsterdam, The Netherlands: Municipal Health Service.

Vogelzang, P. F. J.; Van Der Gulden, J. W. J.; Folgering, H.; Kolk, J. J.; Heederik, D.; Preller, L.; Tielen, M. J. M.; Van Schayck, C. P. (1998) Endotoxin exposure as a major determinant of lung function decline in pig farmers. Am. J. Respir. Crit. Care Med. 157: 15-18.

Yang, C. S.; Johanning, E. (2002) Airborne fungi and mycotoxins. In: Hurst, C. J., Crawford, R. L.; Knudsen, G. R.; McInerney, M. J.; Stetzenbach, L. D. eds. Manual of environmental microbiology. 2nd ed. Washington, DC: American Society for Microbiology; pp. 839-852.

Yozwiak, M. L.; Lundergan, L. L.; Kerrick, S. S.; Galgiani, J. N. (1988) Symptoms and routine laboratory abnormalities associated with coccidioidomycosis. West. J. Med. 149: 419-421.

Young, R. S.; Jones, A. M.; Nicholls, P. J. (1998) Something in the air: endotoxins and glucans as environmental troublemakers. J. Pharm. Pharmacol. 50: 11-17.

Zappoli, S.; Andracchio, A.; Fuzzi, S.; Facchini, M. C.; Gelencsér, A.; Kiss, G.; Krivácsy, Z.; Molnár, A.; Mészáros, E.; Hansson, H.-C.; Rosman, K.; Zebühr, Y. (1999) Inorganic, organic and macromolecular components of fine aerosol in different areas of Europe in relation to their water solubility. Atmos. Environ. 33: 2733-2743.

Zock, J.-P.; Hollander, A.; Heederik, D.; Douwes, J. (1998) Acute lung function changes and low endotoxin exposures in the potato processing industry. Am. J. Ind. Med. 33: 384-391.

8. EPIDEMIOLOGY OF HUMAN HEALTH EFFECTS ASSOCIATED WITH AMBIENT PARTICULATE MATTER

8.1 INTRODUCTION

Epidemiologic studies linking community ambient PM concentrations to health effects played an important role in the 1996 PM Air Quality Criteria Document (PM AQCD; U.S. Environmental Protection Agency, 1996a). Many of those studies reported that measurable excesses in pulmonary function decrements, respiratory symptoms, hospital and emergency department admissions, and mortality in human populations are associated with ambient levels of various indicators of PM exposure, including most notably PM_{10} as well as other indicators of fine-fraction particles (e.g., $PM_{2.5}$). Numerous more recent epidemiologic studies discussed in this chapter have also evaluated ambient PM relationships to morbidity and mortality, using various PM indicators, with greater emphasis on $PM_{2.5}$ and other indicators of fine-fraction particles and, to much lesser extent, $PM_{10-2.5}$ as an indicator of coarse thoracic particles.

The epidemiology studies assessed here are best considered in combination with information on ambient PM concentrations presented in Chapter 3, studies of human PM exposure (Chapter 5), and PM dosimetry and toxicology (Chapters 6 and 7). Such epidemiologic studies contribute important information on associations between health effects and exposures of human populations to "real-world" ambient PM; and they also help to identify susceptible subgroups and associated risk factors. Chapter 9 provides an interpretive synthesis of information drawn from this and other chapters.

This chapter opens with brief discussion of approaches used for identifying, presenting, and assessing studies; general features of the different types of epidemiologic studies assessed and key methodological issues that arise in analyzing and interpreting study results; and salient aspects of epidemiologic evidence that are considered in their critical assessment. Sections 8.2 and 8.3 assess epidemiologic studies of PM effects on mortality and morbidity, respectively. Section 8.4 then provides an interpretive assessment of the overall PM epidemiologic data base

reviewed in Sections 8.2 and 8.3 in relation to various key issues and aspects of the evidence. The overall key findings and conclusions for this chapter are summarized in Section 8.5.

8.1.1 Approaches for Identifying, Presenting, and Assessing Studies

Numerous PM epidemiologic papers have been published since completion of the 1996 PM AQCD, and U.S. EPA (NCEA-RTP) has used a systematic approach to identifying pertinent epidemiologic studies for consideration in this chapter. In general, an ongoing continuous MEDLINE search has been employed in conjunction with other strategies to identify PM literature pertinent to developing criteria for PM NAAQS. The literature search method is similar to those used by others (e.g., Basu and Samet, 1999). A publication base was first established by using MEDLINE and other data bases and a set of key words (particles, air pollution, mortality, morbidity, cause of death, PM, etc.) in a search strategy which was later reexamined and modified to enhance identification of pertinent published papers. Since literature searches encounter not a static but a changing, growing stream of information, searches were not run just for the most recent calendar quarter but were also backdated in an attempt to capture references added to that time period since the previous search was conducted. Papers were also added to the publication base by EPA staff (a) through review of advance tables of contents of thirty journals in which relevant papers are published and (b) by requesting scientists known to be active in the field to identify papers recently accepted for publication.

While the above search regime builds a certain degree of redundancy into the system, which ensures good coverage of the relevant literature and lessens the possibility of important papers being missed, additional approaches have augmented traditional search methods. First, at the beginning of the process, a Federal Register Notice was issued, requesting information and published papers from the public at large. Next, experts in this field serving as non-EPA chapter authors were not only provided with the outcomes of EPA literature searches, but also were charged with identifying pertinent literature on their own. Finally, a keystone in the literature identification process was that, at several review stages in the process, both the public and CASAC offered comments which identified additional potentially relevant publications. The combination of these approaches produced a rather comprehensive collection of pertinent studies

appropriate for review and assessment here. This collection of studies includes pertinent new studies published or accepted for publication through April, 2002, as well as some published since then that provide important new information bearing on key scientific issues.

Those epidemiologic studies that relate measures of ambient air PM to human health outcomes are assessed in this chapter, whereas studies of (typically much higher) occupational exposures are generally not considered here. Criteria used for selecting literature for the present assessment include mainly whether a given study includes information on: (1) ambient PM indices (e.g., PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, etc.) of short- and long-term exposures as a key element; (2) analyses of health effects of specific PM chemical or physical constituents (e.g., metals, sulfates, nitrates or ultrafine particles, etc.) or indicators related to PM sources (e.g., motor vehicle emissions, combustion-related particles, earth crustal particles); (3) evaluation of health endpoints and populations not previously extensively researched; (4) multiple pollutant analyses and other approaches to addressing issues related to potential confounding of effects and effects modification; and/or (5)studies addressing important methodological issues (e.g., lag structure, model specification, thresholds, mortality displacement) related to PM exposure effects.

In assessing the evidence, key points derived from the 1996 PM AQCD assessment of the available information are first concisely highlighted. Then, key new information is presented in succinct text summary tables for important new studies that have become available since the 1996 PM AQCD. More detailed information on various methods and results for these and other newly available studies are summarized in tabular form in Appendices 8A and 8B. These appendix tables are generally organized to include: information about (1) study location and ambient PM levels; (2) description of study methods employed; (3) results and comments; and (4) quantitative outcomes for PM measures. In the main body of the chapter, greater emphasis is placed on integrating and interpreting findings from the array of evidence provided by the more important newer studies than on detailed evaluation of each of the numerous newly available studies. In presenting quantitative effects estimates in tables in the chapter and appendices, study results were normalized to standard PM increments, as was done in the 1996 PM AQCD. In selecting PM increments for use in this review, more recent air quality data were considered, resulting in no changes to the increments previously used for short-term exposure studies, but smaller increments than those used in the 1996 PM AQCD for long-term exposure studies. More

specifically, the pollutant concentration increments used here to report relative risks (RR's) or odds ratios for various health effects are as follow for short term (≤ 24 h) exposure studies: 50 μg/m^3 for PM_{10}; 25 μg/m^3 for $PM_{2.5}$ and $PM_{10-2.5}$; 155 nmoles/m^3 (15 μg/m^3 for SO_4^{2-}; and 75 nmoles/m3 (3.6 μg/m^3, if as H_2SO_4) for H^+. For long-term exposure studies, the increments used here are 20 μg/m^3 for PM_{10} and 10 μg/m^3 for $PM_{2.5}$ and $PM_{10-2.5}$.

Particular emphasis is focused in the text on those studies and analyses thought to provide information most directly applicable for United States standard setting purposes. Specifically, North American studies conducted in the U.S. or Canada are generally accorded more text discussion than those from other geographic regions; and analyses using gravimetric (mass) measurements are generally accorded more text attention than those using nongravimetric ambient PM measures, e.g., black smoke (BS) or coefficient of haze (CoH). In addition, emphasis is placed on text discussion of (a) new multicity studies that employ standardized methodological analyses for evaluating PM effects across several or numerous cities and often provide overall effects estimates based on combined analyses of information pooled across multiple cities; (b) other studies providing quantitative PM effect-size estimates for populations of interest; and (c) studies that consider PM as a component of a complex mixture of air pollutants, including in particular the gaseous criteria pollutants (O_3, CO, NO_2, SO_2).

In assessing the relative scientific quality of epidemiologic studies reviewed here and to assist in interpreting their findings, the following considerations were taken into account, as was done in the 1996 PM AQCD:

- To what extent are the aerometric data/exposure metrics used of adequate quality and sufficiently representative to serve as credible exposure indicators, well reflecting geographic or temporal differences in study population pollutant exposures in the range(s) of pollutant concentrations evaluated?
- Were the study populations well defined and adequately selected so as to allow for meaningful comparisons between study groups or meaningful temporal analyses of health effects results?
- Were the health endpoint measurements meaningful and reliable, including clear definition of diagnostic criteria utilized and consistency in obtaining dependent variable measurement
- Were the statistical analyses used appropriate and properly performed and interpreted, including accurate data handling and transfer during analyses?

- Were likely important covariates (e.g., potential confounders or effect modifiers) adequately controlled for or taken into account in the study design and statistical analyses?
- Were the reported findings internally consistent, biologically plausible, and coherent in terms of consistency with other known facts?

These guidelines provide benchmarks for judging the relative quality of various studies and for focusing on the highest quality studies in assessing the body of epidemiologic evidence. Detailed critical analysis of all epidemiologic studies on PM health effects, especially in relation to all of the above questions, is beyond the scope of this document. Of most importance for present purposes are those studies which provide useful qualitative or quantitative information on exposure-effect or exposure-response relationships for health effects associated with ambient air levels of PM currently likely to be encountered in the United States.

8.1.2 Types of Epidemiologic Studies Reviewed

Definitions of various types of epidemiologic studies assessed here were provided in the 1996 PM AQCD (U.S. Environmental Protection Agency, 1996a) and are briefly summarized here. Briefly, the epidemiologic studies are divided into *mortality* studies and *morbidity* studies. Mortality studies evaluating PM effects on total (nonaccidental) mortality and cause-specific mortality provide the most unambiguous evidence related to a clearly adverse endpoint. The morbidity studies further evaluate PM effects on a wide range of health endpoints, such as: cardiovascular and respiratory-related hospital admissions, medical visits, reports of respiratory symptoms, self-medication in asthmatics, changes in pulmonary function; changes in cardiovascular physiology/functions, and blood coagulation; low birthweight infants, etc.

The epidemiologic strategies most commonly used in PM health studies are of four types: (1) *ecologic studies;* (2) *time-series semi-ecologic studies;* (3) *prospective cohort studies;* and (4) *case-control and crossover studies*. In addition, time-series analyses or other analytic approaches have been used in so-called intervention studies or "natural experiments." All of these are observational studies rather than experimental studies. In general, the exposure of the participant is not directly observed; and the concentration of airborne particles and other air

pollutants at one or more stationary air monitors is used as a proxy for individual exposure to ambient air pollution.

In *ecologic studies*, the responses are at a community level (for example, annual mortality rates), as are the exposure indices (for example, annual average PM concentrations) and covariates (for example, the percentage of the population greater than 65 years of age). No individual data are used in the analysis; therefore, the relationship between health effect and exposure calculated across different communities may not reflect individual-level associations between health outcome and exposure. The use of proxy measures for individual exposure and covariates or effect modifiers may also bias the results, and within-city or within-unit confounding may be overlooked.

Time-series studies are more informative because they allow the study of associations between *changes* in a health outcome and *changes* in exposure indicators preceding or simultaneous with the outcome. The temporal relationship supports a conclusion of a causal relation, even when both the outcome (for example, the number of nonaccidental deaths in a city during a day) and the exposure (for example, daily air pollution concentration) are community indices.

Prospective cohort studies use data from individuals, including health status (where available), individual exposure (not usually available), and individual covariates or risk factors, observed over time. The participants in a prospective cohort study are ideally recruited (using a simple or stratified random sample) so as to represent a target population for which individual or community exposure of the participants is known before and during the interval up to the time the health endpoint occurs. The use of individual-level data is believed to give prospective cohort studies greater inferential strength than other epidemiologic strategies. The use of community-level or estimated exposure data, if necessary, may weaken this advantage, as it does in time-series studies.

Case-control studies are retrospective studies in that exposure is determined after the health endpoint occurs (as is common in occupational health studies). As Rothman and Greenland (1998) describe it, "Case-control studies are best understood by defining a source population, which represents a hypothetical study population in which a cohort study might have

been conducted . . . In a case-control study, the cases are identified and their exposure status is determined just as in a cohort study . . . [and] a control group of study subjects is sampled from the entire source population that gives rise to the cases . . . the cardinal requirement of control selection is that the controls must be sampled independently of their exposure status."

The *case-crossover design* is suited to the study of a transient effect of an intermittent exposure on the subsequent risk of an acute-onset health effect thought to occur shortly after exposure. In the original development of the method, effect estimates were based on within-subject comparisons of exposures associated with incident disease events with exposures at times before the occurrence of disease, using matched case-control methods or methods for stratified follow-up studies with spare data within each stratum. The principle of the analysis is that the exposures of cases just before the event are compared with the distribution of exposure estimated from some separate time period, the former being assumed to be representative of the distribution of exposures for those individuals while they were at risk for the outcome of interest.

When measurements of exposure or potential effect modifiers are available on an individual level, it is possible to incorporate this information into a case-crossover study (unlike a time-series analysis). A disadvantage of the case-crossover design, however, is the potential for bias due to time trends in the exposure time-series. Because case-crossover comparisons are made between different points in time, the case-crossover analysis implicitly depends on an assumption that the exposure distribution is stable over time (stationary). If the exposure time-series is nonstationary and case exposures are compared with referent exposures systematically selected from a different period in time, a bias may be introduced into estimates of the measure of association for the exposure and disease. These biases are particularly important when examining the small relative risks that appear to exist for PM health outcomes.

Intervention studies (often involving features of time-series or other types of analyses noted above) provide another useful approach for evaluating possible causal relationships between ambient air pollution variables (e.g., PM) and health effects in human populations. In such studies, the effects of active interventions that result in reductions of one or another or several air pollutants (constituting essentially a "found experiment") are evaluated in relation to changes in mortality or morbidity outcomes among population groups affected by the reduction

in air pollution exposure. To date, only a few epidemiologic studies have evaluated the consequences of interventions that allow for comparison of PM-health outcome associations before and after certain relatively discrete events resulting in notable changes in concentrations of ambient PM and/or one or more other co-pollutants. Given that the etiology of health outcomes related to PM or other air pollutants are typically also affected by other risk factors, it is important for intervention studies not only to measure air pollution exposure and health status before and after air pollution reductions but also to identify and evaluate potential effects of other risk factors before and after the air pollution reductions. The proposition that intervention studies can provide strong support for causal inferences was emphasized by Hill (1965), as discussed further in Section 8.1.4. In his classic monograph (The Environment and Disease: Association or Causation?), Hill (1965) addressed the topic of preventive action and its consequences under Aspect 8, stating:

> "Experiment: Occasionally it is possible to appeal to experimental, or semi-experimental, evidence. For example, because of an observed association some preventive action is taken. Does it in fact prevent? The dust in the workshop is reduced, lubricating oils are changed, persons stop smoking cigarettes. Is the frequency of the associated events affected? Here the strongest support for the causation hypothesis may be revealed."

8.1.3 Overview of Key Methodological Issues

There are a number of methodological issues that arise in analyzing and interpreting epidemiologic studies that are more fully discussed in Section 8.4 below. The following brief overview of two such key issues is intended to orient the reader to these issues so as to provide context for the presentation and assessment of the epidemiologic studies on mortality and morbidity effects in Sections 8.2 and 8.3.

8.1.3.1 Issues Related to Use of Generalized Additive Models (GAM) in PM Epidemiology

In the spring of 2002, the original investigators of an important newly available multicity study (the National Mortality and Morbidity Air Pollution Study; NMMAPS) cosponsored by the Health Effects Institute (HEI) reported that use of the default convergence criteria setting used in the GAM routine of certain widely-used statistical software (Splus) could result in biased

estimates of air pollution effects when at least two nonparametric smoothers are included in the model (Health Effects Institute letter, May 2002). The NMMAPS investigators also reported (Dominici et al., 2002), as determined through simulation, that such bias was larger when the size of risk estimate was smaller and when the correlation between the PM and the covariates (i.e., smooth terms for temporal trend and weather) was higher. While the NMMAPS investigators reported that reanalysis of the 90 cities air pollution-mortality data (using stringent convergence criteria) did not qualitatively change their original findings (i.e., the positive association between PM_{10} and mortality; lack of confounding by gaseous pollutants; regional heterogeneity of PM, etc.), the reduction in the PM_{10} risk estimate was apparently not negligible (dropping, upon reanalysis, from 2.1% to 1.4% excess deaths per 50 $\mu g/m^3$ increase in PM_{10}) with GAM using strict convergence criteria and a further reduction to 1.1% using a generalized linear model (GLM).

Issues surrounding potential bias in PM risk estimates from time-series studies using GAM analyses and default convergence criteria were raised by EPA and discussed in July 2002 at the CASAC review of the Third External Review Draft of this PM AQCD. In keeping with a follow up consultation with CASAC in August 2002, EPA encouraged investigators for a number of important published studies to reanalyze their data by using GAM with more stringent convergence criteria, as well as by using GLM analyses with parametric smoothers that approximated the original GAM model. EPA, working closely with HEI, also arranged for (a) the resulting reanalyses first to be discussed at an EPA-sponsored Workshop on GAM-Related Statistical Issues in PM Epidemiology held in November 2002; (b) then for any revamping of the preliminary analyses in light of the workshop discussions; before (c) submittal by the investigators of short communications describing the reanalyses approaches and results to EPA and HEI for peer-review by a special panel assembled by HEI; and (d) the publication of the short communications on the reanalyses, along with commentary by the HEI peer-review panel, in an HEI Special Report (2003a). Some of the short communications included in the HEI Special Report (2003a) included discussion of reanalyses of data from more than one original publication because the same data were used to examine different issues of PM-mortality

associations (e.g., concentration/response function, harvesting, etc.). In total, reanalyses were reported for more than 35 originally published studies.

8.1.3.2 Confounding and Effect Modification

A pervasive problem in the analysis of epidemiologic data, no matter what design or strategy, is the unique attribution of a given health outcome to a nominal causal agent (e.g., to airborne particles in this document). The health outcomes attributed to particles are not specific; and, as such, they may also be attributable to high or low temperatures, influenza and other diseases, and/or exposure to other air pollutants. Some of these co-variables may be *confounders* and others *effect modifiers*. The distinctions are important.

Confounding is " . . . a confusion of effects. Specifically, the apparent effect of the exposure of interest is distorted because the effect of an extraneous factor is mistaken for or mixed with the actual exposure effect (which may be null)" (Rothman and Greenland, 1998, p. 120).

Causal events occur prior to some initial bodily response. A causal association may usually be defined as an association in which alteration in the frequency or quality of one category (e.g., level of PM in ambient air) is followed by a change in the other (e.g, increased mortality). The concept of the chain mechanism is that many variables may be related to a single effect through a direct-indirect mechanism. In fact, events are not dependent on single causes. A given chain of causation may represent only a fraction of a web (MacMahon and Pugh, 1970). A causal pathway refers to the network of relationships among factors in one or more causal chains in which the members of the population are exposed to causal agents that produce the observed health effect. The primary cause may be mediated by secondary causes (possibly proximal to exposure) and may have either a direct effect on exposure or an indirect effect through the secondary causes, or both, as illustrated below. A noncausal pathway may involve factors not actually associated or correlated with population exposure to the pollutant of interest, but are coincidentally (spuriously) also associated with health outcome.

The determination of whether a potential confounder is an actual confounder may be elucidated from biological or physical knowledge about its exposure and health effects. Patterns

of association in epidemiology may be helpful in suggesting where to look for this knowledge, but do not replace it. In evaluating effects of ambient PM exposures, gaseous criteria pollutants (CO, NO_2, SO_2, O_3) are candidates for confounders because all of these are known to cause at least some types of adverse health effects that are also associated with particles (CO more often being associated with cardiovascular effects and the other gases with respiratory effects, including symptoms and hospital admissions). In addition, the gaseous criteria pollutants may be associated with particles for several reasons, including common sources and correlated changes in response to wind and weather. Lastly, SO_2 and NO_2 may be precursors to sulfate and nitrate components of ambient particle mixes, while NO_2 contributes also to the formation of organic aerosols during photochemical transformations.

The problem of disentangling the effects of other pollutants is especially difficult when high correlation exists between ambient PM measurements and one or more of them. For example, both CO and particles are emitted from motor vehicles. These and other fossil fuel combustion sources also often emit SO_2 and/or NO, which converts to NO_2 upon emission. SO_2 and NO_2, in turn, are precursors to sulfates and nitrates as two widely common contributors to secondary ambient PM aerosol components. Ozone (O_3) also contributes to ambient PM via (a) hydroxyl radicals which oxidize SO_2 to H_2SO_4 and NO_2 to HNO_3 and (b) participation in chemical reactions underlying the formation of ultrafine particles from naturally occurring terpenes, isoprene, and other hydrocarbons. A common source, such as combustion of gasoline in motor vehicles emitting CO, NO_2, and primary particles (and often resulting in high correlations), may play an important role in confounding among these pollutants, as do weather and seasonal effects. Even though O_3 is a secondary pollutant also associated with emission of NO_2, it is often more variably correlated with ambient PM concentrations, depending on location, season, etc. Levels of SO_2 in the western U.S. are often quite low, so that secondary formation of particle sulfates plays a much smaller role there, resulting in usually relatively little confounding of SO_2 with PM mass concentration in the West. On the other hand, in the industrial Midwest and northeastern states, SO_2 and sulfate levels during many of the epidemiology studies were relatively high and highly correlated with fine particle mass concentrations. If the correlation between PM and SO_2 is not too high, it may be possible to

estimate some part of their independent effects, which depend on the assumption of independence under the particular model analyzed. If there is a causal pathway, then it may be difficult to determine whether the observed relationship of exposure to health effect is a direct effect of the exposure (to sulfate or fine PM as an example), an indirect effect mediated by the potential confounder (e.g., exposure to SO_2), or a mixture of these. Consideration of additional (e.g., exposure, dosimetric, toxicologic) information beyond narrow reliance on observed correlations among the PM measure(s), other pollutants, and health outcome indicators is often useful in helping to elucidate the plausibility of PM or other pollutants being causally related to statistically-associated health effects.

Some variables fall into the category of *effect modifiers*. "Effect-measure modification differs from confounding in several ways. The main difference is that, whereas confounding is a bias that the investigator hopes to prevent or remove from the effect estimate, effect-measure modification is a property of the effect under study . . . In epidemiologic analysis one tries to eliminate confounding but one tries to detect and estimate effect-measure modification" (Rothman and Greenland, 1998, p. 254). Examples of effect modifiers in some of the studies evaluated in this chapter include environmental variables (such as temperature or humidity), individual risk factors (such as education, cigarette smoking status, age in a prospective cohort study), and community factors (such as percent of population > 65 years old). It is often possible to stratify the relationship between health outcome and exposure by one or more of these risk factor variables. Effect modifiers may be encountered (a) within single-city time-series studies or (b) across cities in a two-stage hierarchical model or meta-analysis.

Potential confounding is usually much more difficult to identify; and several statistical methods are available, none of them being completely satisfactory. The usual methods include the following:

Within a city:

(A) Fit both a single-pollutant model and then several multipollutant models, and determine if including the co-pollutants greatly changes the estimated effect;

(B) If the PM index and its co-pollutants are nearly multi-colinear, carry out a factor analysis, and determine which gaseous pollutants are most closely associated with PM in one or more common factors;

Using data from several cities:

(C) Proceed as in Method A and pool the effect size estimates across cities for single- and multipollutant models;

(D) Carry out a hierarchical regression of the PM effects versus the mean co-pollutant concentration and determine if there is a relationship; and

(E) First carry out a regression of PM versus the co-pollutant concentration within each city and the regression coefficient of PM versus health effect for each city. Then fit a second-stage model regressing the PM-health effect coefficient versus the PM-co-pollutant coefficient, concluding that the co-pollutant is a confounder if there is an association at the second stage.

Each of the above methods (A through E) are subject to one or more disadvantages. The multipollutant regression coefficients in method A, for example, may be unstable and have greatly inflated standard errors, weakening their interpretation. In method B, the factors may be sensitive to the choice of co-pollutants and the analysis method, and may be difficult to relate to real-world entities. In method C, as with any meta-analysis, it is necessary to consider the heterogeneity of the within-city effects before pooling them. Some large multicity studies have revealed unexpected heterogeneity, not fully explained at present. While method D is sometimes interpreted as showing confounding if the regression coefficient is nonzero, this is an argument for effect modification, not confounding. Method E is sensitive to the assumptions being made; for instance, if PM is the primary cause and the co-pollutant the secondary cause, then the two-stage approach may be valid. However, if the model is mis-specified and there are two or more secondary causes, some of which may not be identified, then the method may give misleading results.

Given the wide array of considerations and possibilities discussed above, it is extremely important to recognize that there is no single "correct" approach to modeling ambient PM-health effects associations that will thereby provide the "right" answer with regard to precise quantification of PM effect sizes for different health outcomes. Rather, it is clear that emphasis needs to be placed here on (a) looking for convergence of evidence derived from various acceptable analyses of PM effects on a particular type of health endpoint (e.g., total mortality, respiratory hospital admissions, etc.); (b) according more weight to those well-conducted analyses having greater power to detect effects and yielding narrower confidence intervals; and

(c) evaluating the coherence of findings across pertinent health endpoints and effect sizes for different health outcomes.

The issue of what PM effect sizes should be the main focus of presentation and discussion in ensuing text – i.e., those derived from single-pollutant models including only PM or effect sizes derived from multipollutant models that include one or more other co-pollutants along with the PM indicator(s) – is an important one. Again, there is not necessarily any single "correct" answer on this point. Implicit in arguments asserting that multipollutant model results must be reported and accorded equal or more weight than single-pollutant model PM results is a functional construct that has been widely used in epidemiologic modeling of health effects of air pollution, a functional construct that considers the various air pollutants to be acting mainly independently of one another in terms of their health effects, which may not necessarily be the case. This may be causing either over- or under-estimation of PM health effects, depending on the modeling choices made by the investigator and the study situation. For example, O_3 and $PM_{2.5}$ can share some similar oxidative formation and effect pathways in exerting adverse health effects on the lung, yet are often modeled as independent pollutants or are placed in models simultaneously, even though they may sometimes have high correlations over space and time and in their human health effects. Another complication is that other pollutants can be derived from like sources and may serve less as a measure of direct effects than as a marker of pollution from a specific source. As an example noted earlier, SO_2 and $PM_{2.5}$ are often predominantly derived from the same sources in a locale (e.g., coal-fired power plants in the midwestern United States), so that putting these two pollutants in a model simultaneously may cause a diminution of the $PM_{2.5}$ coefficient that can be misleading.

One approach that has been taken is to look at pollutant interactions (either multiplicative or additive, depending on the model assumed), but until we understand (and appropriately model) underlying biological mechanisms, such models are assumptions on the part of the researcher. Present modeling practices represent the best methods now available and provide useful assessments of PM health effects. However, ultimately, more biological-plausibility based models are needed that more accurately model pollutant interactions and allow more biologically-based interpretations of modeling results.

Until more is known about multiple pollutant interactions, it is important to avoid over-interpreting model results regarding the relative sizes and significance of specific pollutant effects, but instead to use biological plausibility in interpreting model results. For example, as discussed later, Krewski et al (2000) found significant associations for both PM and SO_2 in their reanalysis for the Health Effects Institute of the ACS data set published by Pope et al. (1995). Regarding these pollutant associations, they concluded that: "The absence of a plausible toxicological mechanism by which sulfur dioxide could lead to increased mortality further suggests that it might be acting as a marker for other mortality-associated pollutants." (Note: Annual mean SO_2 averaged < 10 ppb across ~125 cities in the ACS data set.) Rather than letting statistical significance be the sole determinant of the "most important" pollutant, the authors utilized biological plausibility to dray conclusions about which association was most likely driving the pollution-health effects association in question. Such biological plausibility/mechanistic considerations need to be taken into account more broadly in the future in modeling and assessing possible pollutant interactions in contributing to health effects attributed to PM. In the meantime, the results from single-pollutant models of PM effects are emphasized here, as being those most likely reflecting overall effects exerted by ambient PM either acting alone and/or in combination with other ambient air pollutants.

8.1.4 Approach to Assessing Epidemiologic Evidence

The critical assessment of epidemiologic evidence presented in this chapter is conceptually based upon consideration of salient aspects of the evidence of associations so as to reach fundamental judgments as to the likely causal significance of the observed associations. In so doing, it is appropriate to draw from those aspects initially presented in Hill's classic monograph (Hill, 1965) and widely used by the scientific community in conducting such evidence-based reviews. A number of these aspects are judged to be particularly salient in evaluating the body of evidence available in this review, including the aspects described by Hill as strength, experiment, consistency, plausibility, and coherence. Other aspects identified by Hill, including temporality and biological gradient, are also relevant and considered here (e.g., in characterizing lag structures and concentration-response relationships), but are more directly addressed in the

design and analyses of the individual epidemiologic studies included in this assessment. (As noted below, Hill's remaining aspects of specificity and analogy are not considered to be particularly salient in this assessment.) As discussed below, these salient aspects are interrelated and considered throughout the evaluation of the epidemiologic evidence presented in this chapter, and are more generally reflected in the integrative synthesis presented in Chapter 9.

In the following sections, the general evaluation of the strength of the epidemiological evidence reflects consideration not only of the magnitude of reported PM effects estimates and their statistical significance, but also of the precision of the effects estimates and the robustness of the effects associations. Consideration of the robustness of the associations takes into account a number of factors, including in particular the impact of alternative models and model specifications and potential confounding by co-pollutants, as well issues related to the consequences of measurement error. Another aspect that is related to the strength of the evidence in this assessment is the availability of evidence from "found experiments", or so-called intervention studies, which have the potential to provide particularly strong support for making causal inferences.

Consideration of the consistency of the effects associations, as discussed in the following sections, involves looking across the results of multi- and single-city studies conducted by different investigators in different places and times. In this assessment of ambient PM-health effects associations, it is important to consider the aspect of consistency in the context of understanding that ambient PM in different locations and at different times originates from different sources, such that its composition and physical characteristics can vary greatly across studies using the same indicator for size-differentiated PM mass. Other relevant factors are also known to exhibit much variation across studies. These include, for example, the presence and levels of co-pollutants, the relationships between central measures of PM and exposure-related factors, relevant demographic factors related to sensitive subpopulations, as well as climatic and meteorological conditions. Thus, in this case, consideration of consistency, and the related heterogeneity of effects issue, is appropriately understood as an evaluation of the similarity or general concordance of results, rather than an expectation of finding quantitative results within a very narrow range. Particular weight is given in this assessment, consistent with Hill's views,

to the presence of "similar results reached in quite different ways, e.g., prospectively and retrospectively" (Hill, 1965). On the other hand, in light of complexities in the chemical and physical properties of the mix of ambient PM and its spatial and temporal variations, Hill's specificity of effects and analogy aspects are not viewed as being particularly salient here.

Looking beyond the epidemiological evidence, evaluation of the biological plausibility of the PM-health effect associations observed in epidemiologic studies reflects consideration of both exposure-related factors and dosimetric/toxicologic evidence relevant to identification of potential biological mechanisms. Similarly, consideration of the coherence of health effects associations reported in the epidemiologic literature reflects broad consideration of information pertaining to the nature of the various respiratory- and cardiac-related mortality and morbidity effects and biological markers evaluated in toxicologic and epidemiologic studies. These broader aspects of the assessment are only touched upon in this chapter but are more fully integrated in the discussion presented in Chapter 9.

In identifying these aspects as being particularly salient in this assessment, it is also important to recognize that no one aspect is either necessary or sufficient for drawing inferences of causality. As Hill (1965) emphasized:

> "None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a sine qua non. What they can do, with greater or less strength, is to help us to make up our minds on the fundamental question — is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?"

Thus, while these aspects frame considerations weighed in assessing the epidemiologic evidence, they do not lend themselves to being considered in terms of simple formulas or hard-and-fast rules of evidence leading to answers about causality (Hill, 1965). One, for example, cannot simply count up the numbers of studies reporting statistically significant results for the various PM indicator and health endpoints evaluated in this assessment and reach credible conclusions about the relative strength of the evidence and the likelihood of causality. Rather, these important considerations are taken into account throughout this assessment with a goal of

producing an objective appraisal of the evidence (informed by peer and public comment and advice), which includes the weighing of alternative views on controversial issues.

8.2 MORTALITY EFFECTS ASSOCIATED WITH AIRBORNE PARTICULATE MATTER EXPOSURE

8.2.1 Introduction

The relationship of PM and other air pollutants to excess mortality has been studied extensively and represents an important issue addressed in previous PM criteria assessments (U.S. Environmental Protection Agency, 1986, 1996a). Recent findings are evaluated here mainly for the two most important epidemiology designs by which mortality is studied: time-series mortality studies (Section 8.2.2) and prospective cohort studies (Section 8.2.3). The time-series studies mostly assess acute responses to short-term PM exposure, although some recent work suggests that time-series data sets can also be useful in evaluating responses to exposures over a longer time scale. Time-series studies use community-level air pollution measurements to index exposure and community-level response (i.e., the total number of deaths each day by age and/or by cause of death). Prospective cohort studies usefully complement time-series studies; they typically evaluate human health effects of long-term PM exposures indexed by community-level measurements, using individual health records with survival lifetimes or hazard rates adjusted for individual risk factors.

8.2.2 Mortality Effects of Short-Term Particulate Matter Exposure

8.2.2.1 Summary of 1996 Particulate Matter Criteria Document Findings and Key Issues

The time-series mortality studies reviewed in the 1996 and other past PM AQCD's provided much evidence that ambient PM air pollution is associated with increases in daily mortality. The 1996 PM AQCD assessed about 35 PM-mortality time-series studies published between 1988 and 1996. Of these studies, only five studies used GAM with default convergence criteria. Recent reanalyses (Schwartz, 2003a; Klemm and Mason, 2003) using GAM with stringent convergence criteria and other non-GAM approaches for one of these five studies, i.e.,

the Harvard Six Cities time-series analysis (the only multicity study among the five studies), essentially confirmed the original findings. Thus, information provided in the 1996 PM AQCD can be summarized without major concern with regard to the GAM convergence issue. The evidence derived from those studies was generally consistent with the hypothesis that PM is a causal agent in contributing to short-term air pollution exposure effects on mortality.

The PM_{10} relative risk estimates derived from short-term PM_{10} exposure studies reviewed in the 1996 PM AQCD suggested that an increase of 50 $\mu g/m^3$ in the 24-h average of PM_{10} is most clearly associated with an increased risk of premature total nonaccidental mortality (total deaths minus those from accident/injury), on the order of relative risk (RR) = 1.025 to 1.05 in the general population or, in other words, 2.5 to 5.0% excess deaths per 50 $\mu g/m^3$ PM_{10} increase. Higher relative risks were observed for the elderly and for those with preexisting cardiopulmonary conditions. Also, based on the Schwartz et al. (1996a) analysis of Harvard Six City data (as later confirmed in the reanalysis by Schwartz [2003a] and Klemm and Mason [2003]), the 1996 PM AQCD found the RR (combined across the six cities) for excess total mortality in relation to 24-h fine particle concentrations to be about 3% excess risk per 25 $\mu g/m^3$ $PM_{2.5}$ increment.

While numerous studies reported PM-mortality associations, important issues needed to be addressed in interpreting their findings. The 1996 PM AQCD evaluated in considerable detail several critical issues, including: (1) seasonal confounding and effect modification; (2) confounding by weather; (3) confounding by co-pollutants; (4) measurement error; (5) functional form and threshold; (6) harvesting and life shortening; and (7) the role of PM components. As important issues related to model specification became further clarified, more studies began to address the most critical issues, some of which were at least partially resolved, whereas others required still further investigation. The next several paragraphs summarize the status of these issues at the time of the 1996 PM AQCD publication.

One of the most important components in time-series model specification is adjustment for seasonal cycles and other longer-term temporal trends; not adequately adjusting for them could result in biased RRs. Modern smoothing methods allow efficient fits of temporal trends and reduce such statistical problems (but may also introduce some additional issues as discussed in

later sections). Most recent studies controlled for seasonal and other temporal trends, and it was considered unlikely that inadequate control for such trends seriously biased estimated PM coefficients. Effect modification by season was examined in several studies. Season-specific analyses are often not feasible in small-sized studies (due to marginally significant PM effect size), but some studies (e.g., Samet et al., 1996; Moolgavkar and Luebeck, 1996) suggested that estimated PM coefficients varied from season to season. It was not fully resolved, however, as to whether these results represent real seasonal effect modifications or are due to varying extent of correlation between PM and co-pollutants or weather variables by season.

While most available studies included control for weather variables, some reported sensitivity of PM coefficients to weather model specification, leading some investigators to speculate that inadequate weather model specifications may still have erroneously ascribed residual weather effects to PM. Two PM studies (Samet et al., 1996; Pope and Kalkstein, 1996) involved collaboration with a meteorologist and utilized more elaborate weather modeling, e.g., use of synoptic weather categories. These studies found that estimated PM effects were essentially unaffected by the synoptic weather variables and also indicated that the synoptic weather model did not provide better model fits in predicting mortality when compared to other weather model specifications used in previous PM-mortality studies. Thus, these results suggested at the time that the reported PM effects were not explained by more sophisticated synoptic weather models. However, some analyses in both of these studies used GAM, presumably with default convergence criteria, and therefore need to be interpreted with caution, especially in light of their not having been reanalyzed with more stringent GAM convergence criteria and/or by GLM or other types of modeling specifications. Also, reanalyses of other studies originally using GAM with default convergence criteria have contributed to reopening of renewed debate on weather model specification issues, as discussed later (in Section 8.4).

Many earlier PM studies considered at least one co-pollutant in the mortality regression, and some also examined several co-pollutants. In most cases, when PM indices were significant in single pollutant models, addition of a co-pollutant diminished the PM effect size somewhat, but did not eliminate the PM associations. When multiple pollutant models were performed by season, the PM coefficients became less stable, again, possibly due to PM's varying correlation

with co-pollutants among season and/or smaller sample sizes. However, in many studies, PM indices showed the highest significance (versus gaseous co-pollutants) in single and multiple pollutant models. Thus, it was concluded that PM-mortality associations were not seriously distorted by co-pollutants, but interpretation of the relative significance of each pollutant in mortality regression as relative causal strength was difficult because of limited quantitative information on relative exposure measurement/characterization errors among air pollutants.

Measurement error can influence the size and significance of air pollution coefficients in time-series regression analyses and is also important in assessing confounding among multiple pollutants, as varying the extent of such error among the pollutants could also influence the corresponding relative statistical significance. The 1996 PM AQCD discussed several types of such exposure measurement errors, including site-to-site variability and site-to-person variability — errors thought to bias the estimated PM coefficients downward in most cases. However, there was not sufficient quantitative information available to estimate such bias.

The 1996 PM AQCD also reviewed evidence for threshold and various other functional forms of short-term PM mortality associations. Several studies appeared to suggest that associations were seen monotonically below the existing PM standards. It was considered difficult, however, to statistically test for a threshold from available data because of low data density at lower ambient PM concentrations, potential influence of measurement error, and adjustments for other covariates. Thus, the use of relative risk (rate ratio) derived from the log-linear Poisson models was considered adequate and appropriate, although threshold-related issues remained to be more fully resolved.

The extent of prematurity of death (i.e., mortality displacement or "harvesting") in observed PM-mortality associations has important public-health-policy implications. At the time of the 1996 PM AQCD review, only a few studies had investigated this issue. While one of the studies suggested that the extent of such prematurity might be only a few days, this may not be generalizable because this estimate was obtained for identifiable PM episodes. There was not sufficient evidence to suggest the extent of prematurity for non-episodic periods from which most of the recent PM relative risks were derived. The 1996 PM AQCD concluded:

> "In summary, most available epidemiologic evidence suggests that increased mortality results from both short-term and long-term ambient PM exposure. Limitations of available evidence prevent quantification of years of life lost to such mortality in the population. Life shortening, lag time, and latent period of PM-mediated mortality are almost certainly distributed over long time periods, although these temporal distributions have not been characterized." (p. 13-45)

Only a limited number of PM-mortality studies analyzed fine particles and chemically specific components of PM. The Harvard Six Cities Study (Schwartz et al., 1996a) analyzed size-fractionated PM ($PM_{2.5}$, $PM_{10/15}$, and $PM_{10/15\text{-}2.5}$) and PM chemical components (sulfates and H^+). The results suggested that, among the components of ambient PM, $PM_{2.5}$ was most significantly associated with mortality. Because the original study was conducted using GAM with default convergence criteria, the data were recently reanalyzed (a) by Schwartz (2003a), who provided reanalyzed $PM_{2.5}$ results for each of the six cities and a combined risk estimate across the six, but only excess risk estimates for individual cities for $PM_{10/15\text{-}2\text{-}5}$, and (b) by Klemm and Mason (2003), who analyzed $PM_{2.5}$, $PM_{10\text{-}15}$, $PM_{10/15\text{-}2.5}$, and sulfate. Although the excess risk estimates were somewhat lower than those in the original study, both the Schwartz (2003a) and Klemm and the Mason (2003) reanalyses confirmed the original findings with regard to the relative importance of fine versus coarse particles. While H^+ was not significantly associated with mortality in the original and an earlier analysis (Dockery et al., 1992), the smaller sample size for H^+ than for other PM components made a direct comparison difficult. The 1996 PM AQCD also noted that mortality associations with BS or CoH reported in earlier studies in Europe and the United States during the 1950s to 1970s most likely reflected contributions from fine particles, as those PM indices had low 50% cut-points ($\leq$ 4.5 μm). Furthermore, certain respiratory morbidity studies showed associations between hospital admissions/visits with components of PM in the fine particle range. Thus, the U.S. EPA 1996 PM AQCD concluded that there was adequate evidence to suggest that fine particles play especially important roles in observed PM mortality effects.

Overall, then, the status of key issues as addressed in the 1996 PM AQCD can be summarized as follows: (1) it was thought that the observed PM effects were unlikely to be seriously biased by inadequate statistical modeling (e.g., control for seasonality); (2) it also appeared unlikely that the observed PM effects were seriously confounded by weather (at least

by synoptic weather models); (3) the observed PM effects appeared to some extent to be confounded or modified by co-pollutants, and such extent may vary from season to season; (4) determining the extent of confounding and effect modification by co-pollutants would likely require knowledge of relative exposure measurement characterization error among pollutants (there was not sufficient information on this); (5) no compelling evidence substantiating a threshold for PM-mortality associations was available (statistically identifying a threshold from existing data was also considered difficult, if not impossible); (6) some limited evidence for harvesting, a few days of life-shortening, was reported for episodic periods (no study was yet conducted to evaluate possible harvesting in non-episodic U.S. data); (7) only a relatively limited number of studies suggested a causal role of fine particles in PM-mortality associations, but in the light of historical data, biological plausibility, and the results from morbidity studies, a greater role for fine particles than coarse particles was suggested in the 1996 PM AQCD as being likely. The 1996 PM AQCD concluded:

> The evidence for PM-related effects from epidemiologic studies is fairly strong, with most studies showing increases in mortality, hospital admissions, respiratory symptoms, and pulmonary function decrements associated with several PM indices. These epidemiologic findings cannot be wholly attributed to inappropriate or incorrect statistical methods, mis-specification of concentration-effect models, biases in study design or implementation, measurement of errors in health endpoint, pollution exposure, weather, or other variables, nor confounding of PM effects with effects of other factors. While the results of the epidemiologic studies should be interpreted cautiously, they nonetheless provide ample reason to be concerned that there are detectable human health effects attributable to PM at levels below the current NAAQS. (p. 13-92)

8.2.2.2 Newly Available Information on Short-Term Mortality Effects

Since the 1996 PM AQCD, numerous new studies have examined short-term associations between PM indices and mortality. Of these studies (more than 80), nearly 70% used GAM (presumably with default convergence criteria). In the summer of 2002, U.S. EPA asked the original investigators of some of these studies to reanalyze the data using GAM with more stringent convergence criteria and GLM with parametric smoothers such as natural splines. Because the extent of possible bias caused by the default criteria setting in the GAM models is difficult to estimate for individual studies, the discussion here will focus only on those studies that did not use GAM Poisson models and those studies that have reanalyzed data using more

stringent convergence criteria and/or alternative approaches. Newly available U.S. and Canadian studies on relationships between short-term PM exposure and daily mortality that meet these criteria are summarized in Table 8-1. More detailed summaries of all the short-term exposure PM-mortality studies, including other geographic areas (e.g., Europe, Asia, etc) are described in Appendix Table 8A-1. These include the studies that apparently used GAM with default convergence criteria, and those studies are noted as such. Information on study location and period, levels of PM, health outcomes, methods, results, and reported risk estimates and lags is provided in Table 8A-1. In addition to these summary tables, discussion in the text below highlights findings from several multicity studies (Section 8.2.2.3) and single-city studies (Section 8.2.2.4). Discussion of implications of new study results for types of issues identified in foregoing text is mainly deferred to Section 8.4.

The summary of studies in Table 8-1 and 8A-1 (and in other tables) is not meant to imply that all listed studies should be accorded equal weight in the overall interpretive assessment of evidence regarding PM-associated health effects. In general, for those studies not clearly flawed and having adequate control for confounding, increasing scientific weight should be accorded to in proportion to the precision of their estimate of a health effect. Small studies and studies with an inadequate exposure gradient generally produce less precise estimates than large studies with an adequate exposure gradient. Therefore, the range of exposures (e.g., as indicated by the IQR), the size of the study as indexed by the total number of observations (e.g., days) and total number of events (i.e., total deaths), and the inverse variance for the principal effect estimate are all important indices useful in determining the likely precision of health effects estimates and in according relative scientific weight to the findings of a given study.

As can be seen in Tables 8-1 and 8A-1, many of the newly reported analyses continue to show statistically significant associations between short-term (24 h) PM exposures indexed by a variety of ambient PM measurements and increases in daily mortality in numerous U.S. and Canadian cities, as well as elsewhere around the world. Several newly available PM epidemiologic studies that conducted time-series analyses in multiple cities, as discussed first below, are of particular interest.

TABLE 8-1. RECENT U.S. AND CANADIAN TIME-SERIES STUDIES OF PM-RELATED DAILY MORTALITY*

Reference	Type**	Location(s)/Period	Pollutants	Comments
Multicity Mortality Studies in the U.S. and Canada				
PM_{10} studies using NMMAPS data				
Samet et al. (2000a, b, c); Dominici et al. (2000a, b); Dominici et al. (2003a)	A	88 cities in the 48 contiguous U.S. states plus AK and HI, 1987-1994; mainly 20 largest.	PM_{10}, O_3, CO, NO_2, SO_2	Numerous models; range of PM_{10} values depending on city, region, co-pollutants. Pooled estimates for 88 cities, individual estimates for 20 largest with co-pollutant models.
Daniels et al. (2000); Dominici et al. (2003a)	A	20 cities in the 48 contiguous U.S. states, 1987-1994	PM_{10} only	Smooth nonparametric spline model for concentration- response functions. Average response curve nearly linear.
Dominici et al. (2002) Dominici et al. (2003a)	A	88 cities in the 48 contiguous U.S. states, 1987-1994.	PM_{10} only	Smooth nonparametric spline models for PM_{10} concentration-response functions. Average response curves are nearly linear in the industrial Midwest, Northeast regions, and overall, but nonlinear (usually concave) in the other regions. Possible thresholds in Southeast.
Studies using every day PM_{10} data				
Schwartz (2000a); Schwartz (2003b)	A	Ten U.S. cities: New Haven, CT; Pittsburgh, PA; Detroit, MI; Birmingham, AL; Canton, OH; Chicago, IL; Minneapolis-St. Paul, MN; Colorado Springs, CO; Spokane, WA; and Seattle, WA. 1986-1993.	PM_{10} , O_3, CO, NO_2, SO_2	Pooled PM_{10} (0 and 1 day lag average) mortality estimates for the ten cities were presented. Confounding and/or effect modification was examined for season, co-pollutants, in- versus out-of-hospital deaths.
Schwartz (2000b); Schwartz (2003b).	A	Same ten U.S. cities as in (Schwartz, 2000a)	PM_{10} only.	Several pooled estimates across 10 cities for single day, moving average, and distributed lags.
Braga et al. (2001a); Schwartz (2003b)	A	Same ten U.S. cities as in (Schwartz, 2000a)	PM_{10} only.	Pooled estimates across cities evaluated for deaths due to pneumonia, COPD, CVD, and MI using distributed lags models.

TABLE 8-1 (cont'd). RECENT U.S. AND CANADIAN TIME-SERIES STUDIES OF PM-RELATED DAILY MORTALITY*

Reference	Type**	Location(s)/Period	Pollutants	Comments
Multicity Mortality Studies in the U.S. and Canada (cont'd)				
Other multicity studies				
Schwartz (1996a) Schwartz (2003a)		Six cities in Harvard Six City Study, with Harvard air monitors and community daily mortality time-series: Boston (Watertown), MA, Harriman-Kingston, TN; Portage-Madison, WI; St. Louis, MO; Steubenville, OH; Topeka, KS.	PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, sulfates	City-specific associations and combined effect estimates recalculated for mortality due to all causes (total), ischemic heart disease, COPD, and pneumonia. Associations with $PM_{2.5}$ recalculated by several techniques, including natural splines, penalized splines, etc. Associations with $PM_{10-2.5}$ only recalculated by use of penalized splines for individual cities.
Klemm et al., (2000); Klemm and Mason (2003)	A	Same six cities as Harvard Six City Study (Schwartz et al., 1996a), 1979-1988.	PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, sulfates	Replicated Schwartz et al. (1996a) and did additional sensitivity analyses.
Laden et al.. (2000); Schwartz (2003a)	A	Same six cities as Harvard Six City Study (Schwartz et al., 1996a), 1979-1988.	Chemically speciated $PM_{2.5}$ and factors aligned with putative sources for each city identified by specific chemical elements as tracers.	Different coefficients in different cities, depending on source type, chemical indicators, and principal factor method. The motor vehicle combustion component was significant, other factors occasionally, but not the crustal element component.
Tsai et al. (1999, 2000)	B	Camden, Elizabeth, and Newark, NJ, 1981-1983.	$PM_{2.5}$, PM_{15}, sulfates, trace elements.	Significant effects of $PM_{2.5}$, PM_{10}, and sulfates in Newark, Camden at most lags, but not Elizabeth. Source-specific factors (oil burning, automobiles) were also associated with mortality.
Burnett et al. (2000); Burnett and Goldberg (2003)	A	Eight Canadian cities: Montreal, Ottawa, Toronto, Windsor, Calgary, Edmonton, Winnipeg, Vancouver, 1986-1996.	PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, sulfates, O_3, CO, NO_2, SO_2.	The results of reanalysis indicate no clear difference between $PM_{2.5}$ and $PM_{10-2.5}$ in associations with mortality.

TABLE 8-1 (cont'd). RECENT U.S. AND CANADIAN TIME-SERIES STUDIES OF PM-RELATED DAILY MORTALITY*

Reference	Type**	Location(s)/Period	Pollutants	Comments
Single-City Mortality Studies in the U.S. and Canada				
Moolgavkar (2000a); Moolgavkar (2003).	A	Three large U.S. counties (cities): Cook Co., IL; Los Angeles Co., CA; Maricopa Co., (Phoenix), AZ, 1987-1995 in the original analysis. In the reanalysis, Maricopa Co. was not analyzed.	PM_{10} in all three; $PM_{2.5}$ in Los Angeles. O_3, CO, NO_2, and SO_2 in some models. In the GAM reanalysis, O_3 was not analyzed.	Gaseous pollutants were at least as significantly associated as PM indices. In particular, CO was the best single index of air pollution association with mortality in Los Angeles.
Ostro et al. (1999a, 2000); Ostro et al. (2003)	A	Coachella Valley (Palm Springs), CA, 1989-1998.	PM_{10} in earlier study, $PM_{2.5}$ and $PM_{10-2.5}$ in later study; O_3, CO, NO_2. Reanalysis reported PM risk estimates only.	PM_{10} (~65% of which was coarse particles) and $PM_{10-2.5}$ (missing values predicted from PM_{10}) were associated with cardiovascular mortality. $PM_{2.5}$ was available for shorter period.
Fairley (1999); Fairley (2003)	A	Santa Clara County (San Jose), CA, 1989-1996.	PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, sulfates, nitrates, O_3, CO, NO_2.	All significant in one-pollutant models, nitrates significant in all multipollutant models, $PM_{2.5}$ significant except with particle nitrates.
Schwartz et al. (1999)	B	Spokane, WA, 1989-1995.	PM_{10}	No association between mortality and high PM_{10} concentrations on dust storm days with high concentrations of crustal particles.
Clyde (1999)	B	Chicago/Cook County 1985-1990	PM_{10}	Various lags and fourth degree orthogonal polynomials of PM10 evaluated using Bayesian model averaging (BMA). Detected PM_{10} association with mortality in the elderly (> 65 years old).
Lippmann et al. (2000); Ito (2003)	A	Detroit, MI, 1985-1990; 1992-1994 (separate analysis for two periods).	PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, sulfates, acidity, TSP, O_3, CO, NO_2, SO_2	PM mass indices were more strongly associated with mortality than sulfate or acidity. The extent of association with health outcomes was similar for $PM_{2.5}$ and PM_{10-25}.

TABLE 8-1 (cont'd). RECENT U.S. AND CANADIAN TIME-SERIES STUDIES OF PM-RELATED DAILY MORTALITY*

Reference	Type**	Location(s)/Period	Pollutants	Comments
Single-City Mortality Studies in the U.S. and Canada (cont'd)				
Chock et al. (2000)	B	Pittsburgh, PA, 1989-1991.	PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, O_3, CO, NO_2, SO_2	Fine and coarse particle data on about ½ of days with PM_{10}. Data split into ages < 75 and 75+, and seasons. Significant effects for PM_{10} but not for other size fractions.
Klemm and Mason (2000)	B	Atlanta, GA, 1998-1999 (one year).	PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, oxygenated hydrocarbons (HC), elemental carbon (EC), organic carbon (OC), sulfates, acidity	No significant effects likely due to short time-series (ca. one year).
Clyde (2000a)	B	Birmingham, AL August 1985 through December 1988	PM_{10}	PM_{10} lags up to 3 days and area-wide average of PM_{10} for these lags evaluated using Bayesian model averaging (BMA). Probability intervals for PM_{10} effect included both one (suggesting no effect) and higher estimates reported earlier by other investigations.
Schwartz (2000c); Schwartz (2003a)	A	Boston, MA, 1979-1986.	$PM_{2.5}$	Larger effects with longer-term $PM_{2.5}$ and mortality moving averages (span 15 to 60 days) for total and cause-specific mortality.
Lipfert et al. (2000a)	B	Philadelphia, PA- Camden, NJ seven- county area, 1995-1997.	PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, sulfates, acidity, metals, O_3, CO, NO_2, SO_2	Exploration of mortality in different areas relative to air monitor location. Peak O_3 very significant, greatly reduced PM coefficients.
Mar et al. (2000); Mar et a. (2003)	A	Phoenix, AZ, near the EPA platform monitor, 1995-1997.	PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, $PM_{2.5}$ metals, EC, OC, O_3, CO, NO_2, SO_2, and source-apportioned factor scores.	Only cardiovascular mortality was reanalyzed; it was significantly associated with PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, EC, OC, factors associated with motor vehicle, vegetative-burning, and regional sulfate.
Clyde et al. (2000b)	B	Phoenix, AZ, 1995-1997.	$PM_{2.5}$ and $PM_{10-2.5}$	Effect on elderly mortality consistently higher for $PM_{10-2.5}$ among 25 "best" models. Estimates combined using Bayesian model averaging.

TABLE 8-1 (cont'd). RECENT U.S. AND CANADIAN TIME-SERIES STUDIES OF PM-RELATED DAILY MORTALITY*

Reference	Type**	Location(s)/Period	Pollutants	Comments
Single-City Mortality Studies in the U.S. and Canada (cont'd)				
Smith et al. (2000)	B	Phoenix, AZ (within city and within county), 1995-1997.	$PM_{2.5}$ and $PM_{10-2.5}$	Significant linear relationship with $PM_{10-2.5}$, not $PM_{2.5}$ Piecewise linear models with possible $PM_{2.5}$ threshold for elderly mortality at 20-25 $\mu g/m^3$.
Ostro (1995)	B	San Bernardino and Riverside Counties, CA, 1980- 1986.	$PM_{2.5}$ estimated from visual range, O_3	Positive, significant $PM_{2.5}$ association only in summer.
Murray and Nelson (2000)	B	Philadelphia, PA, 1973- 1990	TSP only	Kalman filtering used to estimate hazard function in a state space model. Both TSP and the product of TSP and average temperature are significant, but not together. Includes estimate of risk population.
Goldberg et al. (2000, 2001a,b,c,d; 2003); Goldberg and Burnett (2003)	A	Montreal, PQ, Canada, 1984-1995	CoH and extinction were available daily. $PM_{2.5}$ and PM_{10} every sixth day until 1992, daily through 1993.	Reanalysis indicated attenuation of PM risk estimates, especially sensitive to weather model specification. Congestive heart failure, as classified based on medical records from insurance plan, was associated with CoH, SO_2, and NO_2.

*Brief summary of new time-series studies on daily mortality since the 1996 Air Quality Criteria Document for Particulate Matter (U.S. Environmental Protection Agency, 1996a). More complete descriptive summaries are provided in Appendix Table 8A-1. The endpoint is total daily non-trauma mortality, unless noted otherwise. Due to the large number of models reported for sensitivity analyses for some of these papers, some evaluating various lags and co-pollutant models, some for individual cities, and others for estimates pooled across cities, quantitative risk estimates are not presented in this table.

**Type: Type of studies: (A) Original study used GAM model including nonparametric smoothing terms with default or other lax convergence criteria, but was reanalyzed using stringent convergence criteria and/or using parametric smoothers; (B) Original study used GLM with parametric smoothers or other approaches, or used GAM but with only one nonparametric smoother.

8.2.2.3 New Multicity Studies

The new multicity studies are of interest here due to their evaluation of a wide range of PM exposures and large numbers of observations, thus holding promise of possibly providing more precise effects estimates than most smaller scale independent studies of single cities. Another potential advantage of the multicity studies, over meta-analyses for multiple "independent" studies, is consistency in data handling and model specifications that eliminates variation due to study design. Also, unlike regular meta-analysis, they clearly do not suffer from potential omission of negative analyses due to "publication bias." Furthermore, geographic patterns of air pollution effects can be systematically evaluated in multiple-city analyses. Thus, results from multicity studies have the potential to provide especially valuable evidence regarding relative homogeneity and/or heterogeneity of PM-health effects relationships across geographic locations. Also, many of the cities included in these multicity studies were ones for which no time-series analyses had been previously reported. Most of these new multicity studies used GAM Poisson models, but the data sets have recently been reanalyzed using GAM models with more stringent convergence criteria, as well as by using GLM with parametric smoothers.

8.2.2.3.1 U.S. Multicity Studies

U.S. PM_{10} 90-Cities NMMAPS Analyses

The National Morbidity, Mortality, and Air Pollution Study (NMMAPS) focused on time-series analyses of PM_{10} effects on mortality during 1987-1994 in the 90 largest U.S. cities (Samet et al., 2000a,b,c), in the 20 largest U.S. cities in more detail (Dominici et al., 2000a,b), and PM_{10} effects on emergency hospital admissions in 14 U.S. cities (Samet et al., 2000a,b). These NMMAPS analyses employed sophisticated statistical approaches addressing issues of measurement error biases, co-pollutant evaluations, regional spatial correlation, and synthesis of results from multiple cities by hierarchical Bayesian meta-regressions and metaanalyses. These analyses provide extensive new information of much relevance to the setting of U.S. PM standards, because no other study has examined so many U.S. cities in such a consistent manner. That is, NMMAPS used only one consistent PM index (PM_{10}) across all cities (based on PM_{10} samples collected only every 6 days in most of the 90 cities); death records were collected in a

uniform manner; and demographic variables were uniformly addressed. The 90-cities analyses studies employ multistage models (see Table 8-1) in which heterogeneity in individual city's coefficients in the first stage Poisson models were evaluated in the second stage models with city- or region-specific explanatory variables.

As noted earlier, the original investigators of the NMMAPS study reported in 2002 a potential problem with using the GAM Poisson models with default convergence criteria available in widely-used statistical software in estimating air pollution risks (Dominici et al., 2002). The default convergence criteria were too lax to attain convergence in the setting of air pollution, weather, and mortality/morbidity parameters where "small" PM regression coefficients were estimated and at least two covariates were modeled with nonparametric smoothers. The NMMAS investigators simulation analysis also suggested that the extent of bias could be more serious when the magnitude of risk coefficient was smaller and when PM correlations with covariates were stronger. The investigators have since reanalyzed the 90 cities data, using more stringent convergence criteria as well as using fully parametric smoothers, and reported revised results. The following description of the NMMAPS mortality study therefore focuses on the results of the reanalysis of the 90 cities study.

In both the original and reanalyzed NMMAPS 90 cities studies, the combined estimates of PM_{10} coefficients were positively associated with mortality at all the lags examined (0, 1, and 2 day lags), although the 1-day lag PM_{10} gave the largest overall combined estimate. Figure 8-1 shows the reanalyzed results for the estimated percent excess total deaths per 10 $\mu g/m^3$ PM_{10} at lag 1 day in the 88 (90 minus Honolulu and Anchorage) largest cities, as well as (weighted average) combined estimates for U.S. geographic regions depicted in Figure 8-2. The majority of the coefficients were positive for the various cities listed along the left axis of Figure 8-1. The estimates for the individual cities were first made separately. The cities were then grouped into the 7 regions seen in Figure 8-2 (based on characteristics of the ambient PM mix typical of each region, as delineated in the 1996 PM AQCD). The bolded segments represent the posterior means and 95% posterior intervals of the pooled regional effects without borrowing information from other regions. The triangle and bolded segment at the bottom of Figure 8-1 display the combined estimate of overall nationwide effects of PM_{10} for all the cities.

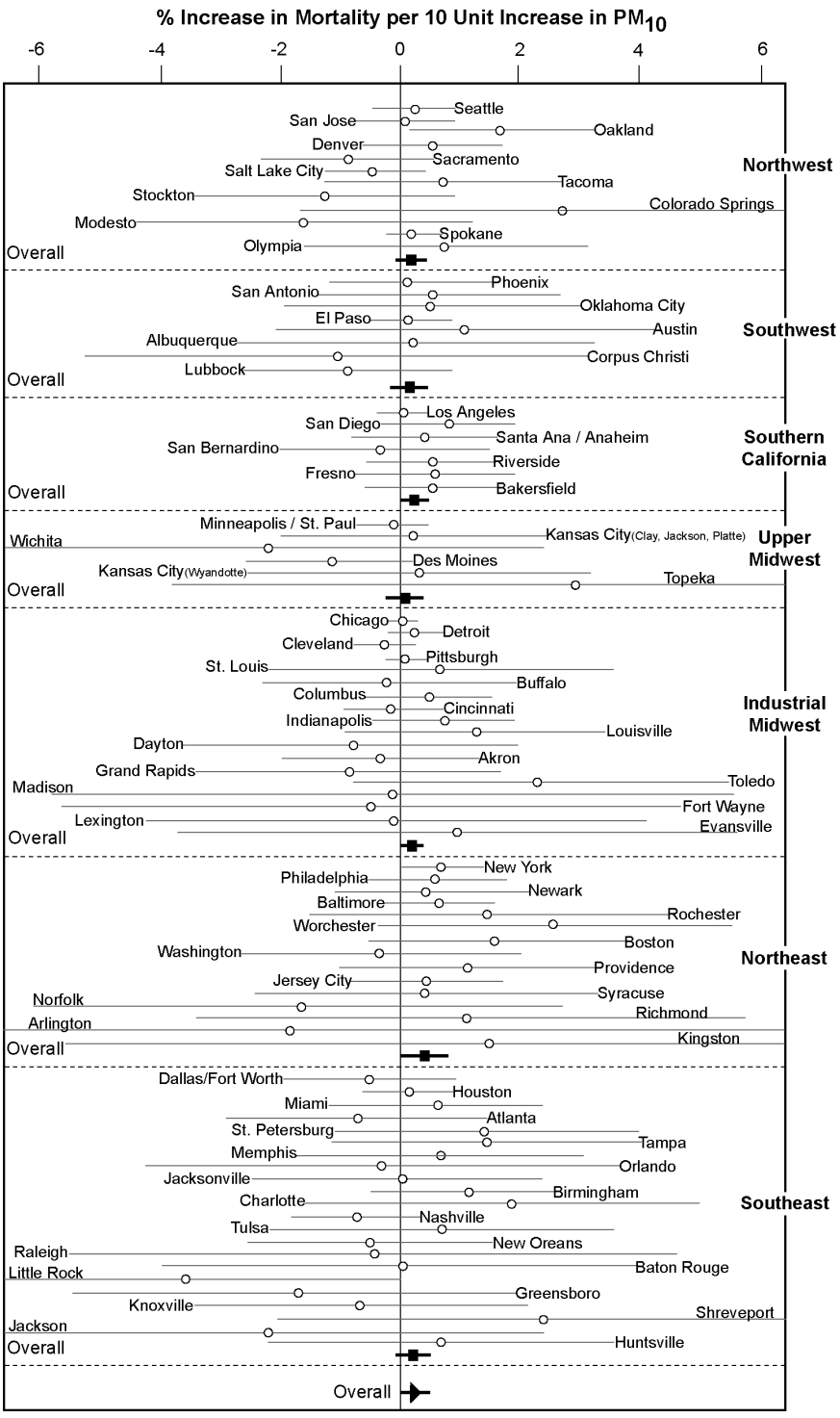

Figure 8-1. Estimated excess risks for PM mortality (1-day lag) for the 88 largest U.S. cities as shown in the revised NMMAPS analysis.

Source: Dominici et al. (2002, 2003b).

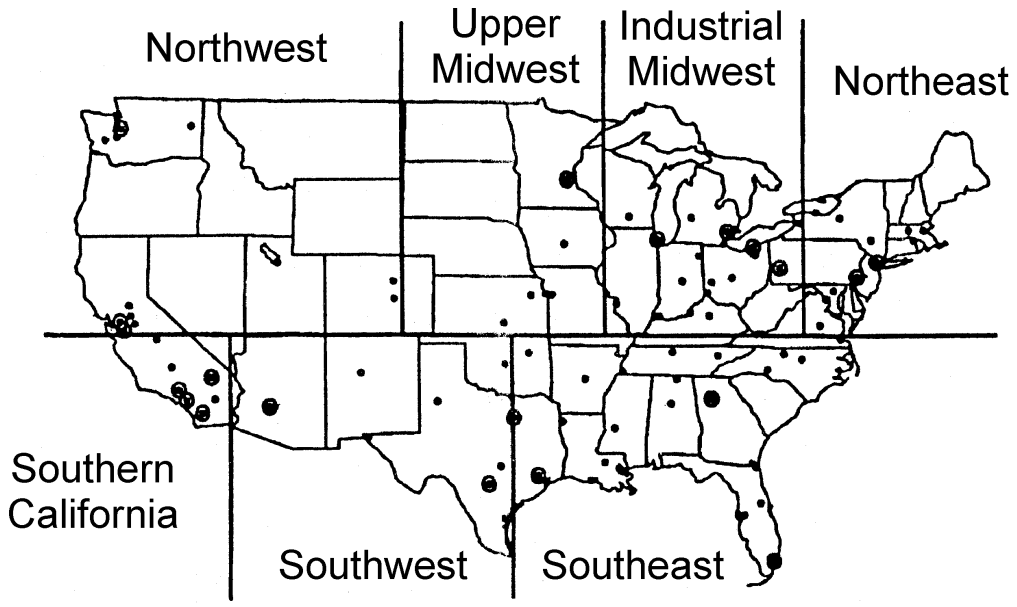

Figure 8-2. Map of the United States showing the 88 cities (the 20 cities are circled) and the seven U.S. regions considered in the NMMAPS geographic analyses.

Note that there appears to be some regional-specific variation in the overall combined estimates for all the cities in a given region. This can be discerned most readily in Figure 8-3, which depicts overall region-specific excess risk estimates for 0-, 1-, and 2-day lags. For example, the coefficients for the Northeast for any given lag are generally higher than for other regions. The NMMAPS investigators noted that the extent of the regional heterogeneity seen with the reanalysis was reduced slightly compared to the original finding (between-city standard deviation changed from 0.112 to 0.088 in the unit of percent excess deaths per 10 $\mu g/m^3$ PM_{10}), but the pattern of heterogeneity remained the same. The overall national combined estimate (i.e., at lag 1 day, 1.4% excess total deaths per 50 $\mu g/m^3$ increase in PM_{10} using GAM with stringent convergence criteria) for the 90 cities is somewhat lower than the range of available estimates reported in the 1996 PM AQCD (i.e., 2.5 to 5.0%) for the general U.S. population.

In the original 90 cities study, the weighted second-stage regression included five types of county-specific variables: (1) mean weather and pollution variables; (2) mortality rate (crude mortality rate); (3) sociodemographic variables (% not graduating from high school and median

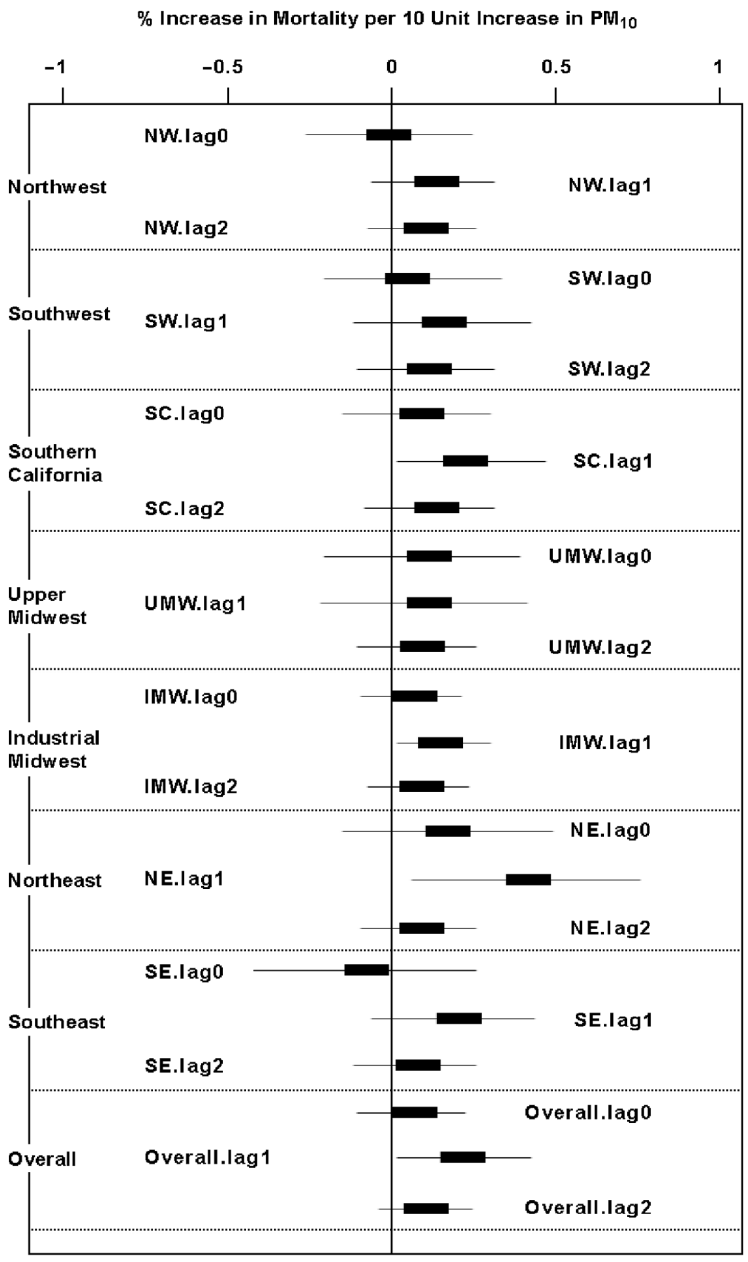

Figure 8-3. Percent excess mortality risk (lagged 0, 1, or 2 days) estimated in the NMMAPS 90-City Study to be associated with 10-μg/m^3 increases in PM_{10} concentrations in cities aggregated within U.S. regions shown in Figure 8-2.

Source: Dominici et al. (2002, 2003b).

household income); (4) urbanization (public transportation); and (5) variables related to measurement error (median of all pair-wise correlations between monitors). Some of these variables were apparently correlated (e.g., mean PM_{10} and NO_2, household income and education) so that the sign of coefficients in the regression changed when correlated variables were included in the model. Thus, while some of the county-specific variables were statistically significant (e.g., mean NO_2 levels), interpreting the role of these county-specific variables may require caution. Regarding the heterogeneity of PM_{10} coefficients, the investigators concluded that they "did not identify any factor or factors that might explain these differences."

Another important finding from Samet and coworkers' analyses was the weak influence of gaseous co-pollutants on the PM_{10} effect size estimates (see Figure 8-4). In the reanalysis of 90 cities data, PM_{10} coefficients slightly increased when O_3 was added to regression models. Additions of a third pollutant (i.e., PM_{10} + O_3 + another gaseous pollutant) hardly changed the posterior means of PM_{10} effect size estimates, but widened the distribution. However, the posterior probabilities that the overall PM_{10} effects are greater than zero remained at or above 0.96. The gaseous pollutants themselves in single-, two-, and three-pollutant models were less consistently associated with mortality than PM_{10}. Ozone was not associated with mortality using year-round data; but, in season-specific analyses, it was associated with mortality negatively in winter and positively in summer. SO_2, NO_2, and CO were weakly associated with mortality, but additions of PM_{10} and other gaseous pollutants did not always reduce their coefficients, possibly indicative of their independent effects. As noted in Section 8.1, CO and NO_2 from motor vehicles are likely confounders of $PM_{2.5}$ and, thus, of PM_{10} when it is not dominated by the coarse particle fraction. The investigators stated that the PM_{10} effect on mortality "was essentially unchanged with the inclusion of either O_3 alone or O_3 with additional pollutants."

The reanalyses of the 90 cities data by the original NMMAPS investigators also included a sensitivity analysis of lag 1day PM_{10} GLM results to the alternative degrees of freedom for adjustment of the confounding factors: season, temperature, and dewpoint. The degrees of freedom for each of these three smoothing terms were either doubled or halved, resulting in nine scenarios in addition to the degrees of freedom in the original GLM model. The PM_{10} effect posterior means were generally higher when the degrees of freedom were halved for season, and

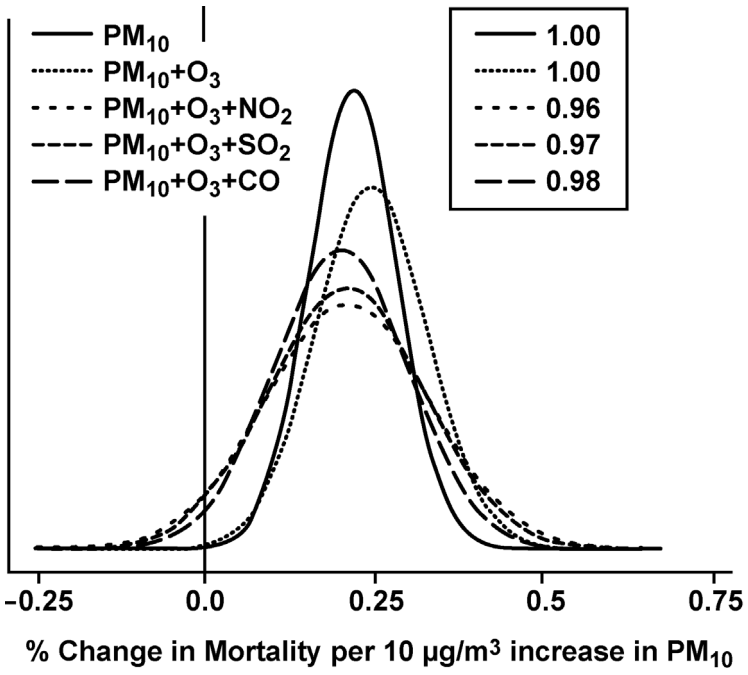

Figure 8-4. Marginal posterior distributions for effect of PM_{10} on total mortality at lag 1, with and without control for other pollutants, for the NMMAPS 90 cities. The numbers in the upper right legend are the posterior probabilities that the overall effects are greater than 0.

Source: Dominici et al. (2003b).

lower when they were doubled, ranging between 1.6% to 0.9% (the main GLM result was 1.1%) excess total mortality per 50 $\mu g/m^3$ PM_{10} increase. These results underscore the fact that the magnitude of sensitivity of the results due to model specification (in this case, degrees of freedom alone) can be as great as the potential bias caused by the GAM convergence problem.

HEI (2003a) states that the revised NMMAPS 90 individual-city mortality results show that, in general, the estimates of PM effect are shifted downward and the confidence intervals are widened. In the revised analyses, a second stage meta-analysis was used to combine results on effects of PM and other pollutants on health outcomes across cities. Tightening the convergence criteria in GAM obtained a substantially lower estimate of effect of PM_{10} combined over all cities, and use of GLM with natural splines decreased the estimate further. The revised analyses yielded a small, but statistically significant, effect of PM_{10} at lag 1 on total mortality, now

estimated to be 0.21% per 10 μg/m^3, with a posterior standard error of 0.06%. HEI (2003a) agrees with the investigators' conclusions that the qualitative conclusions of NMMAPS II have not changed, although the evidence for an effect of PM_{10} at lag 0 and lag 2 is less convincing under the new models. The NMMAPS II report found that the PM_{10} effect remained when co-pollutants were introduced into the model (Samet et al., 2000a); and this conclusion has not changed.

The extent of reduction in PM_{10} excess risk estimate due to the change in the convergence criteria (2.3% per 50 μg/m^3 PM_{10} using default versus 1.4% using stringent) using GAM models in the 90 cities study appears to be greater than those reported for most of the other reanalysis studies. This may be partly due to the smaller risk estimate (2.3%) in the original study compared to other studies (> 3%), as the smaller coefficient is likely more strongly affected as a relative reduction. This may also be in part due to the more "aggressive" adjustment for possible weather effects (discussed later) used in this study, which may have increased the concurvity between PM and the covariates (which included four smoothing terms for weather adjustment). Dominici et al. (2002) reported that the higher the concurvity, the larger the potential bias that a GAM model with default convergence criteria could produce.

In summary, the 90-cities NMMAPS study provides useful information regarding: (1) the magnitude of the combined PM_{10} risk estimate; (2) lack of sensitivity of PM_{10} risk estimates to gaseous co-pollutants; (3) indications of regional heterogeneity in PM_{10} risk estimates across the United States; (4) the shape of concentration-response relationship (discussed later in Section 8.4); and (5) the range of sensitivity of PM_{10} risk estimates to the extent of smoothing of covariates in the original weather model specification. A major uncertainty not extensively examined in this study is the sensitivity of the PM_{10} risk estimates to different weather model specifications.

U.S. 10-Cities Studies

In another set of multicity analyses, Schwartz (2000a,b), Schwartz and Zanobetti (2000), Zanobetti and Schwartz (2000), Braga et al. (2000), and Braga et al. (2001a) analyzed 1987-1995 air pollution and mortality data from ten U.S. cities (New Haven, CT; Birmingham, AL;

Pittsburgh, PA; Detroit, MI; Canton, OH; Chicago, IL; Minneapolis-St. Paul, MN; Colorado Springs, CO; Spokane, WA; and Seattle, WA.) or subsets (4 or 5 cities) thereof. The selection of these cities was based on the availability of daily (or near daily) PM_{10} data. All of these original studies utilized GAM Poisson models with default convergence criteria. Of these studies, Schwartz (2003b) reanalyzed the data from Schwartz (2000a), Schwartz (2000b), and Braga et al. (2001a) using GAM with stringent convergence criteria as well as alternative models such as GLM with natural cubic splines or penalized splines, both of which are expected to give correct standard errors. The main original results of the study were presented in the Schwartz (2000a) paper; and the other studies noted above focused on each of several specific issues, including potential confounding, effect modification, distributed lag, and threshold. In this section, the results for the three reanalysis studies noted above are discussed.

In the reanalysis (Schwartz, 2003b) of the main results (Schwartz, 2000a), daily total (nonaccidental) mortality in each of the 10 cities was fitted using a GAM Poisson model (with stringent convergence criteria) or a GLM Poisson model with natural splines, adjusting for temperature, dewpoint, barometric pressure, day-of-week, season, and time. The data were also analyzed by season (November through April as heating season). The inverse-variance weighted averages of the ten cities' estimates were used to combine results. PM_{10} (average of lag 0 and 1 days) was significantly associated with total deaths, and the effect size estimates were comparable in summer and winter. Adjusting for other pollutants did not substantially change the PM_{10} effect size estimates. The combined percent-excess-death estimate for total mortality was 3.4% (CI: 2.6, 4.1)[1] per 50 $\mu g/m^3$ increase in the average of lag 0 and 1 days PM_{10} (essentially unchanged from the original study) using GAM with stringent convergence criteria. The PM_{10} risk estimate using GLM with natural splines was 2.8% (CI: 2.0, 3.6).

In the reanalysis (Schwartz, 2003b) of the study of multiday effects of air pollution (Schwartz, 2000b), constrained (quadratic model over 0 through 5 day lags) and unconstrained (0 through 5 day lags) distributed lag models were fitted in each city. The overall estimate was computed using the inverse-variance weighted average of individual city estimates. Among the

[1] 95% Confidence Intervals for a given percent risk estimate are standardly provided in parenthesis following the risk estimate in this chapter. For example, 95% CI = 2.6 to 4.1% is expressed as (CI: 2.6,4.1).

results obtained using GAM with stringent convergence criteria, the PM_{10} effect size estimate was 6.3% (CI: 4.9, 7.8) per 50 μg/m^3 increase for the quadratic distributed lag model, and 5.8% (CI: 4.4, 7.3) for the unconstrained distributed lag model. Corresponding values using the penalized splines were somewhat smaller (~5.3%). These values are about twice the effect-size estimate for single-day PM_{10} in the original report or the two-day mean PM_{10} reported in the reanalysis above (this reanalysis did not report results for single-day or 2-day mean PM_{10}).

Schwartz (2003b) also reanalyzed the data from Braga et al.'s (2001a) study to examine the lag structure of PM_{10} association with specific cause of mortality in the 10 cities. Unconstrained distributed lags for 0 through 5 days as well as two-day mean were fitted in each city for COPD, pneumonia, all cardiovascular, and myocardial infarction deaths using GAM with stringent convergence criteria and penalized spline models. Combined estimates by lag were obtained across the 10 cities. The distributed lag estimates were generally larger than the two-day mean estimates for COPD and pneumonia mortality, but they were comparable for all cardiovascular and myocardial infarction mortality. For example, in the results using GAM with stringent convergence criteria, the PM_{10} effect size estimate for COPD mortality was 11.0% (CI: 7.2, 14.8) per 50 μg/m^3 increase for two-day mean model and 16.8% (CI: 8.3, 25.9) for the unconstrained distributed lag model. Note that these values are substantially larger than those reported for total nonaccidental deaths.

The PM_{10} risk estimates from these 10 cities analyses are larger than those from the NMMAPS 90 cities study and these results suggest a possibility that PM effects may be underestimated when only single-day PM indices are used. That is, if ambient PM effects on mortality occur only very immediately, e.g., the same day, then the full risk would be reflected by single day lag analyses. However, if PM-associated deaths occurred over a more extended time, e.g., the next several days, then the fuller PM-related mortality risk would presumably be more closely reflected by distributed lag models and, overall, would logically be higher than for any single lag day. Differences in the number of cities analyzed, in weather model specification, and/or in the extent of smoothing for temporal trends may also have contributed to the differences in the size of PM_{10} risk estimates found by the NMMAPS 90 cities versus the Schwartz 10 cities studies. These issues are further discussed in Section 8.2.2.3.5.

Reanalyses of Harvard Six Cities Study

Both the original Harvard Six Cities Study time-series analysis (Schwartz et al., 1996a) and the replication analysis by Klemm et al. (2000), which essentially replicated Schwartz et al.'s original findings, used GAM Poisson models with default convergence criteria. Schwartz (2003a) and Klemm and Mason (2003) conducted reanalyses of the Harvard Six Cities data to address the GAM statistical issues.

Schwartz (2003a) not only reported risk estimates for $PM_{2.5}$ and $PM_{10\text{-}2.5}$, but also provided results using several other spline smoothing methods (natural splines, B-splines, penalized splines, and thin plate splines) in addition to GAM with stringent convergence criteria. The risk estimate combined across the six cities per 25 $\mu g/m^3$ in $PM_{2.5}$ (average of lag 0 and 1 day) using GAM with stringent convergence criteria was 3.5% (CI: 2.5, 4.5), as compared to the original value of 3.7% (CI: 2.7, 4.7). The corresponding value from a GLM model with natural splines was 3.3% (CI: 2.2, 4.3); and the values using B-splines, penalized splines, and thin plate splines were somewhat lower (3.0%, 2.9%, and 2.6%, respectively). However, when the Harvard Six Cities were examined individually in the reanalysis of Schwartz using GLM and penalized splines, Boston and St. Louis gave significant associations with $PM_{2.5}$ and Steubenville gave a significant association with "thoracic" coarse PM (i.e. $PM_{10\text{-}2.5}$).

The Klemm and Mason (2003) reanalysis calculated risk estimates for $PM_{2.5}$, $PM_{10\text{-}2.5}$, PM_{10} (PM_{15} or PM_{10}), and SO_4^{2-}. They also conducted sensitivity analyses using GLM with natural splines that approximated the degrees of freedom used in the LOESS smoothers in the GAM models, as well as 12 knots per year and 4 knots per year for smoothing of temporal trends. The $PM_{2.5}$ and $PM_{10\text{-}2.5}$ total nonaccidental mortality risk estimates combined across the six cities per 25 $\mu g/m^3$ (average of lag 0 and 1 day) using GAM with stringent convergence criteria were 3.0% (CI: 2.1, 4.0) and 0.8% (CI: −0.5, 2.0), respectively. The corresponding PM_{10} mortality excess risk estimate per 50 $\mu g/m^3$ (average of lag 0 and 1 day) was 3.6% (CI: 2.1, 5.0). In their sensitivity analysis, increasing the degrees of freedom for temporal trends for natural splines in GLM models from 4 knots/year to 12 knots/year markedly reduced PM risk estimates. For example, the $PM_{2.5}$ risk estimate per 25 $\mu g/m^3$ was reduced from 2% in the 4 knots/year model to 1% in the 12 knots/year model. The results showing the smaller PM risk estimates for larger

degrees of freedom for smoothing of temporal trends are consistent with similar findings reported for the reanalysis of the NMMAPS 90 cities study. It also should be noted that Klemm and Mason (2003) reported positive (but not significant at $p < .05$) associations between total mortality and $PM_{10-2.5}$ in Steubenville, which parallels the Schwartz (2003a) finding of a positive (and statistically significant at $p < .05$) total mortality association with $PM_{10-2.5}$ for Steubenville.

Although PM effect estimates from the Klemm and Mason (2003) reanalysis are somewhat smaller than those from Schwartz (2003a); e.g., 3.5% by Schwartz versus 3.0% by Klemm and Mason for $PM_{2.5}$ using strict convergence criteria, the results are very similar. Both studies also showed that the comparable GLM models produced smaller risk estimates than GAM models.

8.2.2.3.2 Canadian Multicity Studies

Burnett et al. (2000) analyzed various PM indices (PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, sulfate, CoH, and 47 elemental component concentrations for fine and coarse fractions) and gaseous air pollutants (NO_2, O_3, SO_2, and CO) for association with total mortality in the 8 largest Canadian cities: Montreal, Ottawa-Hull, Toronto, Windsor, Winnipeg, Calgary, Edmonton, and Vancouver. This study differs from Burnett et al. (1998a) in that it included fewer cities but more recent years of data (1986 to 1996 versus 1980 to 1991) and detailed analyses of particle mass components by size and elemental composition. Each city's mortality, pollution, and weather variables were separately filtered for seasonal trends and day-of-week patterns. The residual series from all cities were then combined and analyzed in a GAM Poisson model.

In Burnett and Goldberg's reanalysis (2003) of the eight Canadian cities data, they only evaluated the PM indices ($PM_{2.5}$, $PM_{10-2.5}$, and PM_{10}) using GAM models with more stringent convergence criteria. The reanalysis used co-adjustment regression (i.e., simultaneous regression), rather than the regression with prefiltered data that was the main approach of the original analysis. The reanalysis also considered several sensitivity analyses, including models with and without day-of-week adjustment and several alternative approaches (fitting criteria and extent of smoothing) to adjust for temporal trends using natural splines. Adjusting for temporal trends, smoothing of same-day temperature, pressure, and day-of-week effects, the pooled PM effect estimates across the eight Canadian cities were: 2.2% (CI: 0.1, 4.2) per 25 $\mu g/m^3$ increase

in $PM_{2.5}$; 1.8% (CI: −0.6, 4.4) per 25 μg/m^3 increase $PM_{10-2.5}$; and 2.7% (CI: −0.1, 5.5) per 50 μg/m^3 increase PM_{10}. These effect size estimates are fairly close to the estimates reported in the original study, despite the differences in the regression approach (prefiltering and GAM with default convergence criteria in the original study versus use of co-adjustment and GAM with stringent convergence criteria in the reanalyses).

The temporal adjustment of the above model used LOESS smoothing with a span of ~0.022 (= 90 days/4,012 study days). Sensitivity analysis included several choices of degrees of freedom for natural splines of temporal trend, with two fitting criteria (i.e., Bartlett's test for white noise and Akaike Information Criterion [AIC]) and either using the same degrees of freedom for all eight cities or varying degrees of freedom for each city. The PM risk estimates based on natural splines were generally smaller than those based on LOESS smoothers. The PM risk estimates also varied inversely with the number of knots for temporal trend. That is, the more details of the temporal trend were described by natural splines, the smaller the PM risk estimates became. The reported $PM_{2.5}$ risk estimates per 25 μg/m^3 increase were 3.0% (t = 3.12), 2.8% (t = 2.28), 2.2% (t = 2.14), 2.1% (t = 2.07), and 1.9% (t = 1.72) for knot/year, knot/6 months, knot/3 months, knot/2 months, and knot/1 month, respectively. The corresponding values for 25 μg/m^3 increase in $PM_{10-2.5}$ were 3.9% (t = 3.42), 2.9% (t = 2.52), 2.1% (t = 1.69), 1.8% (t = 1.46), and 1.2% (t = 0.91), suggesting greater sensitivity of $PM_{10-2.5}$ risk estimates to the extent of temporal smoothing. The authors suggested that this was likely due to the stronger correlation between (and temporal trends in) mortality and mass concentrations for $PM_{10-2.5}$ (average correlation among cities of –0.45) than for $PM_{2.5}$ (−0.36). Because the relative size and significance of $PM_{2.5}$ and $PM_{10-2.5}$ risk estimates varied depending on the model and extent of smoothing for temporal trend, it is difficult to compare the relative importance of the two size-fractionated PM indices in this study; but, overall, they do not appear to be markedly different.

8.2.2.3.3 European Multicity APHEA Study Analyses

The Air Pollution and Health: A European Approach (APHEA) project is a multicenter study of short-term effects of air pollution on mortality and hospital admissions within and across a number of European cities having a wide range of geographic, climatic, air quality, and

sociodemographic patterns. The obvious strength of this approach is its ability to evaluate potential confounders or effect modifiers in a consistent manner. However, it should be noted that PM indices measured in those cities varied. In APHEA1, the PM indices measured were mostly black smoke (BS), except for: Paris and Lyon (PM_{13}); Bratislava, Cologne, and Milan (TSP); and Barcelnoa (BS and TSP). In APHEA2, 10 out of the 29 cities used direct PM_{10} measurements; and, in 11 additional cities, PM_{10} levels were estimated based on regression models relating collocated PM_{10} measurements to BS or TSP. In the remaining 8 cities, only BS measurements were available (14 cities had BS measurements). As discussed below, there have been several papers published that present either a meta-analysis or pooled summary estimates of these multicity mortality results: (1) Katsouyanni et al. (1997) — SO_2 and PM results from 12 cities; (2) Touloumi et al. (1997) — ambient oxidants (O_3 and NO_2) results from six cities; (3) Zmirou et al. (1998) — cause-specific mortality results from 10 cities (see Section 8.2.2.5); (4) Samoli et al. (2001) — a reanalysis of APHEA1 using a different model specification (GAM) to control for long-term trends and seasonality; and (5) Katsouyanni et al. (2001) — APHEA2, with emphasis on the examination of confounding and effect modification. The original APHEA protocol used sinusoidal terms for seasonal adjustment and polynomial terms for weather variables in Poisson regression models. Therefore, publications 1 through 3 above are not subject to the GAM default convergence issue. Publications 4 and 5 did use GAM Poisson model with default convergence criteria, but the investigators have reanalyzed the data using GAM with more stringent convergence criteria, as well as GLM with natural splines (Katsouyani et al., 2003; Samoli et al., 2003). The discussions presented below on publications 4 and 5 are focused on the results from the reanalyses.

APHEA1 Sulfur Dioxide and Particulate Matter Results for 12 Cities

The Katsouyanni et al. (1997) analyses evaluated data from the following cities: Athens, Barcelona, Bratislava, Cracow, Cologne, Lodz, London, Lyon, Milan, Paris, Poznan, and Wroclaw. In the western European cities, an increase of 50 $\mu g/m^3$ in BS or SO_2 was associated with a 3% (CI: 2.0, 4.0) increase in daily mortality; and 2% (CI: 1.0, 3.0) per 50 $\mu g/m^3$ increase in estimated PM_{10} (based on PM_{10} = TSP*0.55 conversion). In the 31 central/eastern European

cities, the increase in mortality was 0.6% (CI: 0.1, 1.1) per 50 μg/m^3 change in BS and 0.8% (CI: 0.1, 2.4) per 50 μg/m^3 change for SO_2. Estimates of cumulative effects of prolonged (two to four days) exposure to air pollutants were comparable to those for one day effects. The effects of both pollutants (BS, SO_2) were stronger during the summer and were mutually independent. Regarding the contrast between the western and central/eastern Europe results, the authors speculated that this could be due to differences in exposure representativeness; differences in pollution toxicity or mix; differences in proportion of sensitive subpopulation; and differences in model fit for seasonal control. Bobak and Roberts (1997) commented that the heterogeneity between central/eastern and western Europe could be due to the difference in mean temperature. However, Katsouyanni and Touloumi (1998) noted that, having examined the source of heterogeneity, other factors could apparently explain the difference in estimates as well as or better than temperature.

APHEA1 Ambient Oxidants (Ozone and Nitrogen Dioxide) Results for Six Cities

Touloumi et al. (1997) reported on additional APHEA data analyses, which evaluated (a) short-term effects of ambient oxidants on daily deaths from all causes (excluding accidents), and (b) impacts on effect estimates for NO_2 and O_3 of including a PM measure (BS) in multipollutant models. Six cities in central and western Europe provided data on daily deaths and NO_2 and/or O_3 levels. Poisson autoregressive models allowing for overdispersion were fitted. Significant positive associations were found between daily deaths and both NO_2 and O_3. Increases of 50 μg/m^3 in NO_2 (1-h maximum) or O_3 (1-h maximum) were associated with a 1.3% (CI: 0.9, 1.8) and 2.9% (CI: 1.0, 4.9) increase in the daily mortality, respectively. There was a tendency for larger effects of NO_2 in cities with higher levels of BS; that is, when BS was included in the model, the coefficient for NO_2 was reduced by half (but remained significant) whereas the pooled estimate for the O_3 effect was only slightly reduced. The authors speculated that the short-term effects of NO_2 on mortality might be confounded by other vehicle-derived pollutants (e.g., airborne ambient PM indexed by BS measurements). Thus, while this study reports only relative risk levels for NO_2 and O_3 (but not for BS), it illustrates the potential

importance of confounding between NO_2 and PM effects and relative limited confounding between O_3 and PM effects.

APHEA1: A Sensitivity Analysis for Controlling Long-Term Trends and Seasonality

The original study (Samoli et al., 2001) examined the sensitivity of APHEA1 results to how the temporal trends were modeled (i.e., sine/cosine in the APHEA1 versus LOESS smoother using GAM with default convergence criteria). Samoli et al. (2003) reanalyzed the data using GAM with more stringent convergence criteria, as well as GLM with natural splines. The reanalysis allowed a comparison of results across a fixed functional model (sine/cosine), a nonparametric smoother (GAM with LOESS), and a parametric smoother (GLM with natural splines). The combined estimate across cities for percent excess in total nonaccidental mortality per 50 $\mu g/m^3$ increase in BS using GAM with stringent convergence criteria (2.3%; CI: 1.9, 2.7) was bigger than that using sine/cosine (1.3%; CI: 0.9, 1.7). The GAM with stringent convergence criteria reduced the combined estimate by less than 10% versus that from GAM with default convergence criteria. The corresponding estimate using GLM with natural splines (1.2%; CI: 0.7, 1.7) was comparable to that from the sine/cosine model but smaller than that using GAM. The contrast between western and eastern Europe in the original APHEA1 study (2.9% for west versus 0.6% for east) was less clear in results using GAM with stringent convergence criteria (2.7% versus 2.1%) or GLM with natural splines (1.6% versus 1.0%). This suggests that the apparent regional heterogeneity found in the original APHEA1 study could be sensitive to model specification. Because the number of cities used in the APHEA1 study was relatively small (eight western and five central-eastern cities), apparent regional heterogeneity found in the earlier publications could be due to chance. These reanalysis findings also suggest that the results are somewhat sensitive to model specification for temporal trends.

APHEA2: Confounding and Effect Modification Using Extended Data

The APHEA2 original study (Katsouyanni et al. 2001) included more cities (29 cities) and a more recent study period (variable years in 1990-1997, compared to 1975-1992 in APHEA1). Also, the APHEA2 original study used a GAM (with default convergence criteria) Poisson

model with LOESS smoothers to control for season and trends. Katsouyanni et al. (2003) reanalyzed the data using GAM with more stringent convergence criteria and two parametric approaches: natural splines and penalized splines. Because the reanalysis GAM results changed the PM_{10} risk estimates only slightly from the original estimates and the investigators mention that the patterns of effect modification were preserved in their reanalyses regardless of model specification, the qualitative description below of the effect modification relies on the original study, but PM_{10} estimates for various models are from the reanalysis.

The analyses put emphasis on effect modification by city-specific factors. Thus, the city-specific coefficients from the first stage of Poisson regressions were modeled in the second stage regression using city-specific characteristics as explanatory variables. Inverse-variance weighted pooled estimates (fixed-effects model) were obtained as part of this model. When substantial heterogeneity was observed, the pooled estimates were obtained using random-effects models. These city-specific variables included (1) air pollution level and mix, such as average air pollution levels and PM/NO_2 ratio (as an indicator of traffic-generated PM); (2) climatic variables, such as mean temperature and relative humidity; (3) health status of the population, such as the age-adjusted mortality rates, the percentage of persons over 65 years of age, and smoking prevalence; and (4) geographic area (three regions: central-eastern, southern, and north-western Europe). The study also addressed the issue of confounding by simultaneous inclusion of gaseous co-pollutants in city-specific regressions and obtained pooled PM estimates for each co-pollutant included. Unlike APHEA1, in which the region (larger PM estimates in western Europe than in central-eastern Europe) was highlighted as the important factor, APHEA2 found several effect modifiers. NO_2 (i.e., index of high pollution from traffic) was an important one. Cities with higher NO_2 levels showed larger PM effects, as did cities with a warmer climate. The investigators noted that this might be due to better indexing of population exposures by outdoor community monitors (because of more open windows). Also, cities with low standardized mortality rate showed larger PM effects. The investigators speculated that this may be because a smaller proportion of susceptible people (to air pollution) are available in a population with a large age-standardized mortality rate. Interestingly, in the pooled PM risk estimates from models with gaseous pollutants, it was also NO_2 that affected (reduced) PM risk

estimates most. For example, in the fixed-effects models, ~50% reductions in both PM_{10} and BS coefficients were observed when NO_2 was included in the model. SO_2 only minimally reduced PM coefficients; whereas O_3 actually increased PM coefficients. Thus, in this analysis, NO_2 was implicated as a confounder, an effect modifier, and/or as an indicator of PM source. The overall random-effects model combined estimates for total mortality for 50 $\mu g/m^3$ increase in PM_{10} were 3.0% (CI: 2.0, 4.1), 2.1% (CI: 1.2, 3.0), and 2.8% (CI: 1.8, 3.8), for GAM (stringent convergence criteria), natural splines, and penalized splines models, respectively. The original excess mortality risk estimate (3.1%) using GAM with default convergence criteria was thusly reduced by 3 to 33% in the different reanalyses models. While the effect estimates varied somewhat depending on the choice of GAM with LOESS, natural splines, or penalized splines, the patterns of effect modification (by NO_2, etc.) were preserved.

8.2.2.3.4 Comparison of Effect Size Estimates from Multicity Studies

Based on different pooled analyses of data combined across multiple cities, the percent excess total (nonaccidental) deaths estimated per 50 $\mu g/m^3$ increase in PM_{10} in the above multicity studies were (a) 1.4% using GAM (1.1% using GLM) at lag 1-day in the 90 largest U.S. cities (the Northeast region results being about twice as high); (b) 3.4% using GAM (2.8% using GLM) for average of 0 and 1 day lags in 10 U.S. cities; (c) 3.6% using GAM (2.7% using GLM) for 1 day lag PM_{10} in the 8 largest Canadian cities; and (d) 3.0% using GAM (2.1% using GLM) in APHEA2 for average of 0 and 1 day lags for 29 European cities during 1990-1997.

The estimate for NMMAPS 90 cities study is somewhat smaller than those for the other multicity studies and the range reported in the previous PM AQCD (2.5 to 5%). There are several possible explanations for this, including differences in (a) model specifications for weather, (b) extent of smoothing to adjust for temporal trends, (c) use of different specific smoothing approaches, and (d) consequent effects of each of these differences on ranges of degrees of freedom assigned for different aspects of the analyses.

Model specification for weather appears to be one of the more crucial factors. The NMMAPS 90 cities study used much more "aggressive" adjustment for possible weather effects than did most other studies. The 90 cities analysis included four separate weather terms:

(1) smoothing splines (natural splines when GLM was used) of same-day temperature with 6 degrees of freedom; (2) smoothing splines of the average of lag 1 through 3 day temperature with 6 degrees of freedom; (3) smoothing splines of same-day dewpoint with 3 degrees of freedom; and (4) smoothing splines of the average of lag 1 through 3 day dewpoint with 3 degrees of freedom. In contrast, most of the other studies used only one or two terms for weather variables. For example, the Harvard Six Cites Study used a LOESS smoother (or natural splines or other smoothers in reanalysis) of same-day temperature with a span of 0.5 and a LOESS smoother of same-day dewpoint with a span of 0.5. Note, too, that the NMMAPS 90 cities study not only used more terms for weather effects, but it also used more degrees of freedom for temperature than the Schwartz (2003b) analysis (according to the Klemm and Mason [2003] reanalysis, the span of 0.5 in LOESS corresponds to ~3.5 degrees of freedom). It should be noted that the purpose for inclusion of dewpoint in these models is often explained as to adjust for possible effects of humidity; but there are differing perspectives related to the need for inclusion of dewpoint along with temperature, given that dewpoint and temperature tend to be highly correlated ($r > 0.9$) in most cities. Thus, although the inclusion of these terms may statistically (i.e., by AIC, etc.) provide a better fit, the epidemiologic implications of the use of these terms are not yet fully clear. On the one hand, extreme temperatures, hot or cold, are known to cause excess mortality and the combined effects of high temperature and high humidity occurring together can cause especially high excess mortality. Thus, it is clear that these models need somehow to control for high "heat index" effects when notable increases in weather-related mortality occur (hence the need for heat index forecasts) and/or for cold-induced deaths when sufficiently low temperatures occur in a given locale. On the other hand, it is also not clear at this time as to whether these models may be overcorrecting for weather effects in the more moderate range that is typical of much of the data. These issues are further discussed later in Section 8.4.3.

Another factor that may contribute to the difference in PM risk estimates is the extent of smoothing to adjust for temporal trends. Several of the reanalysis studies (Dominici et al., 2002; Burnett and Goldberg, 2003; Ito, 2003; Klemm and Mason, 2003) consistently reported, though to varying extents, that using more degrees of freedom for temporal trends tended to reduce PM

coefficients. That is, when more details in the short-term fluctuations of mortality were ascribed to temporal trends, PM risk estimates were reduced. For example, in Dominici et al.'s (2002) sensitivity analysis, the PM_{10} risk estimate was larger (1.6% per 50 $\mu g/m^3$ increase in PM_{10}) for the GLM model with 3 degrees of freedom per year that the estimate using 7 degrees of freedom (1.1%). Note that, in general, the presumed objective of including temporal trends in the mortality regression is to adjust for potential confounding (measured or unmeasured) by time-varying factors that change seasonally or in shorter time spans (e.g., influenza epidemics). However, ascribing "too short" temporal fluctuations to these "confounding temporal trends" may inadvertently take away PM effects. Because the "right" extent of smoothing is not known, these sensitivity analyses are useful. In the reanalyses mentioned above, the PM risk estimates changed, at times, by a factor of two when a range of degrees of freedom was applied even for a model specification in which all the other terms were kept unchanged.

Based on the results from the reanalysis studies, it has become apparent that different smoothing approaches can also affect PM risk estimates. For example, the models with natural splines (parametric smoothing) appear, in general but not always, to result in smaller PM risk estimates than GAM models with LOESS or smoothing splines. GAM models may possibly suffer from biased standard error of risk estimates, but they also seem to fit the data better (i.e., based on AIC) than GLM models with natural splines. In any case, the choice of these smoothers does not seem to affect PM risk estimates (~10 to 30%) as much as the range of weather model specifications or the range of the degrees of freedom for temporal trends adjustment do (as large as a factor of two).

A less explored issue is the effect of multiday effects of PM. The PM_{10} risk estimates summarized above are either for a single-day lag (U.S. NMMAPS 90 cities study, Canadian 8 cities study, and APHEA1), or an average of two days (U.S. 10 cities study and APHEA2). However, the reanalysis of U.S. 10 cities study data suggests that the multiday PM effect, accounting for 0 through 5 day lag, could be twice as large as the effect sizes estimated from single or two-day average models and even bigger (~3 to 4 fold) when more specific cause of death categories are examined. This issue warrants further investigation.

In summary, considering the wide variability in possible reasonable model specification choices that can affect the PM risk estimates, the reported combined PM_{10} total nonaccidental mortality risk estimates from multicity studies are in reasonably good agreement. That is, they fall mainly in the range of ~1.0 to 3.5% per 50 $\mu g/m^3$ increase in single or two-day average PM_{10}. Combinations of choices in model specifications (the number of weather terms and degrees of freedom for smoothing of mortality temporal trends) alone may explain the extent of the difference in PM_{10} risk estimates across studies. The range for these newly available combined estimates from multicities studies overlap with the range of PM_{10} estimates (2.5 to 5%, obtained from single cities studies) previously reported in the 1996 PM AQCD, but extends to somewhat lower values.

8.2.2.4 U.S. Single-City Studies

In addition to the new multicity studies assessed above, many studies newly available since the 1996 PM AQCD evaluated relationships between mortality and short-term exposure to PM using data from individual cities. The results of such studies are summarized in tabular form in Appendix 8A-1. The ensuing discussion focuses on the results of recent U.S. single-city studies, especially those including PM_{10}, $PM_{2.5}$ and $PM_{10-2.5}$ data. Results of analyses using $PM_{2.5}$ and $PM_{10-2.5}$ measurements are also discussed further in Section 8.2.2.5.

Lippmann et al. (2000; reanalyzed Ito, 2003) used aerometric data from Detroit which included measurements of PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, sulfate, $H+$, O_3, SO_2, NO_2, and CO for a 1992-1994 study period. Associations with total (nonaccidental), cardiovascular, respiratory, and other deaths were analyzed using GAM Poisson models, adjusting for season, temperature, and relative humidity. Analyses were also done for an earlier 1985-1990 study period that included measurements of PM_{10} and TSP along with the gaseous co-pollutants. Reanalyses were done using stringent convergence criteria as well as natural splines, as well as additional sensitivity analyses to examine the influence of alternative weather models and selection of degrees of freedom on model results. In the reanalyses, PM coefficients were often reduced (but sometimes unchanged or increased somewhat) when GAM with stringent convergence criteria or GLM/natural splines were used. The reductions in coefficients were not different across PM

components; the original conclusion regarding the relative importance of PM components remained the same. PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ were more significantly associated with mortality outcomes than sulfate or H+. PM coefficients were generally not sensitive to inclusion of gaseous pollutants. PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ effect size estimates were comparable in terms of the same distributional increment (5th to 95th percentile). Both PM_{10} (lag 1 and 2 day) and TSP (lag 1 day), but not TSP-PM_{10} or TSP- SO_4^{2-}, were significantly associated with respiratory mortality for the 1985-1990 period. The simultaneous inclusions of gaseous pollutants with PM_{10} or TSP reduced the PM effect size by 0 to 34%. Effect size estimates for total, circulatory, and "other" categories were smaller than for respiratory mortality.

Chock et al. (2000) evaluated associations between daily mortality in two age groups (< 75 years, > 75 years) and several air pollution variables (PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, CO, O_3, NO_2, SO_2) in Pittsburgh, PA, during 1989 to 1991 (data on $PM_{2.5}$ and $PM_{10-2.5}$ were only available for half of the 3-year study period). Poisson GLM regression was used, including filtering of data based on cubic B-spline functions to adjust for seasonal trends; models included indicators for day of week, and temperature was modeled as a V-shape function. Single- and multipollutant models were run for 0, 1, 2, and 3 day lags. Single- and multipollutant nonseasonal models showed significant positive associations between PM_{10} and daily mortality, but seasonal models showed much multicolinearity, masking association of any pollutant with mortality. $PM_{2.5}$ and $PM_{10-2.5}$ were both positively associated with mortality, but the coefficients were unstable in this data set when stratified by age group and season and no conclusions were drawn on the relative roles of $PM_{2.5}$ and $PM_{10-2.5}$. In their conclusions, the authors emphasized issues of seasonal dependence of correlation among pollutants, multicolinearity among pollutants, and instability of coefficients for $PM_{2.5}$ and $PM_{10-2.5}$.

Lipfert et al. (2000a), using data for Philadelphia and the seven-county Philadelphia metropolitan area from 1992 to 1995, regressed twelve mortality variables (as categorized by area, age, and cause) on 29 pollution variables (PM components, O_3, SO_2, NO_2, CO, and by subareas), yielding 348 regression results. Both dependent and explanatory variables were prefiltered using the 19-day-weighted average filter prior to OLS regression. Covariates were selected from filtered temperature (several lagged and averaged values), indicator variables for

hot and cold days and day-of-week using stepwise procedure, and the average of current and previous days' pollution levels were used. Significant associations were reported for a wide variety of particulate and gaseous pollutants, especially for peak O_3. No systematic differences were seen according to particle size or chemistry. Mortality for one part of the metropolitan area could be associated with air quality from another, not necessarily neighboring part.

Clyde (1999) employed Bayesian model averaging (BMA) techniques, more often used in other fields but relatively newly applied in some air pollution epidemiology studies, to evaluate PM_{10} effects on total (nonaccidental) mortality among the elderly (> 65 years old) in the city of Chicago and Cook County, Illinois. The BMA approach (discussed later in Section 8.4.1) provides an approach for taking into account model uncertainty, uses a set of models rather than one, and each model contributes to the overall BMA outcome in proportion to the support received from observed data. The Clyde (1999) analyses included 24-h PM_{10} values derived from one daily monitoring site and daily averages of every-six-day data from a subset of six of 20 other monitoring stations during 1985-1990 and a number of other meteorological variables. Clyde (1999) reported a posterior probability close to 1.0, indicating a very high probability of a particulate matter effect, and went on to estimate a 5 to 16% increase in mortality compared to the average level of PM_{10}. She further indicated that, based on the results of the model with the linear term for PM_{10}, 95% posterior probability intervals for the expected decrease in mortality per 10 $\mu g/m^3$ PM_{10} decrement would be 0.25 to 0.82 deaths/day or roughly 91 to 300 deaths per year in the > 65 year old population in Cook County. Clyde (1999) noted, however, that these were preliminary results that are subject to a number of caveats (e.g., if the PM_{10} measurements were not representative of the outdoor exposure of the population, then the effect may have been over- or under-estimated).

Moolgavkar (2000a) evaluated (using GAM with default convergence criteria) associations between short-term measures of major air pollutants and daily deaths in three large U.S. urban areas (Cook Co., IL, encompassing Chicago; Los Angeles Co., CA; and Maricopa Co., AZ, encompassing Phoenix) during a 9-year period (1987 to 1995). Moolgavkar (2003) reanalyzed the data for Cook Co. and Los Angeles Co. (but not Maricopa Co.), using GAM with stringent convergence criteria as well as GLM with natural splines. Ozone was analyzed in the original

analysis but not in the reanalyses (it was only positive and significant in Cook county in the original analysis). This section describes the results from the reanalyses. Total nonaccidental deaths, deaths from cardiovascular disease (CVD) and chronic obstructive lung disease (COPD) were analyzed in relation to 24-h readings for PM, CO, NO_2, and SO_2 averaged over all monitors in a given county. Cerebrovascular mortality was analyzed in the original analysis but not in the reanalyses (its association with air pollution was weak in the original analysis). The results of cause-specific mortality analyses are described in a later section. Daily readings were available for each of the gaseous pollutants in both Cook Co. and Los Angeles Co., as were PM_{10} values for Cook Co. However, PM_{10} and $PM_{2.5}$ values were only available every sixth day in Los Angeles Co. PM values were highest in summer in Cook Co. and in the winter and fall in Los Angeles Co.; whereas the gases (except for O_3) were highest in winter in both counties. The PM indices were moderately correlated ($r = 0.30$ to 0.73) with CO, NO_2, and SO_2 in Cook Co. and Los Angeles Co. Total nonaccidental, CVD, and COPD deaths were all highest during winter in both counties. Adjusting for temperature and relative humidity effects in separate analyses for each mortality endpoint for these two counties, varying patterns of results were found (as noted in Appendix A, Table 8A-1). Moolgavkar (2003) also reported sensitivity of results to different degrees of freedom (df) for smoothing of temporal trends (30 df and 100 df).

As for Cook Co., PM_{10} was significantly associated with total nonaccidental mortality at lag 0 (most significant) and 1 day in GAM models with both 30 df and100 df for smoothing of temporal trends, as well as in a GLM model with 100 df for smoothing of temporal trends. The gaseous pollutants were also significantly associated with total nonaccidental mortality at various lags (wider lags than PM_{10}), but were most significant at lag 1 day. These associations did not appear to be sensitive to the extent of smoothing for temporal trends, at least at their most significant lags. In two pollutant models (results were not shown in tables but described in text), the PM_{10} association remained "robust and statistically significant" at lag 0 day; whereas the coefficients for the gases became nonsignificant. However, at lag 1 day, the PM_{10} association became nonsignificant and the gases remained significant. Thus, some extent of "sharing" of the association is apparent, and whichever pollutant is more strongly associated than the other at that lag tended to prevail in the two pollutant models in this data set.

For Los Angeles Co., CO was more significantly associated (positive and significant at lag 0 through 3 days) with mortality than PM_{10} (positive and significant at lag 2) or $PM_{2.5}$ (positive and significant at lag 1). In two pollutant models in which CO and PM indices were included simultaneously at PM indices = "best" lags, CO remained significant, whereas PM coefficients became nonsignificant (and negative for cases with 30 df for temporal smoothing). For Los Angeles data, the PM coefficients appeared to be more sensitive to the choice of the degrees of freedom than to the default versus stringent convergence criteria. GLM models tended to produce smaller risk estimates than GAM models. Moolgavkar also reported that these associations were robust to varying the extent of smoothing for weather covariates.

The results for these two cities do not reflect a common pattern. In Cook Co., all the pollutants were associated with mortality, and their relative importance varied depending on the lag day, whereas CO appeared to show the strongest mortality associations in Los Angeles. Moolgavkar concluded that, considering the substantial differences that can result from different analytic strategies, no particular numeric estimates were too meaningful, although the patterns of associations appeared to be robust.

Ostro et al. (2000; reanalyzed Ostro et al., 2003) conducted a study in Coachella Valley, CA, using (a) PM_{10} data collected from 1989-1998 and (b) $PM_{2.5}$ and $PM_{10-2.5}$ data collected during the last 2.5 years of the study period. Both $PM_{2.5}$ and $PM_{10-2.5}$ were also estimated for the earlier remaining years to increase the power of the analyses, but only $PM_{10-2.5}$ could be reliably estimated; so, predicted $PM_{2.5}$ data were not used. Original analyses used GAMs, with smoothing functions for time and indicators for day of week. Different lags for temperature, humidity and dewpoint were tested for use in the models; and then pollutants were added individually and next in combination. In the reanalyses, more stringent convergence criteria and natural splines were used, but the reanalyses were only done for cardiovascular mortality. For such cause-specific mortality, significant associations were found for $PM_{10-2.5}$ and PM_{10}, but not for $PM_{2.5}$ (possibly due to the low range of $PM_{2.5}$ concentrations and reduced sample size for $PM_{2.5}$ data) and PM risk estimates were higher for multi-day averages. The PM risk estimates were slightly reduced in the reanalyses using GAM with stringent convergence criteria

or using GLM; but sensitivity analyses showed that results were not sensitive to alternative degrees of freedom for temporal trends and temperature.

In another study, total, cardiovascular, and respiratory deaths in Santa Clara Co., CA were regressed on PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, CoH, nitrate, sulfate, O_3, CO, NO_2, adjusting for time trend, season, and minimum and maximum temperature, using a Poisson GAM model (Fairley, 1999; reanalyzed Fairley, 2003). Reanalyses included use of GAM with stringent convergence criteria, as well as natural splines and an additional indicator for O_3 (daily number of hours exceeding 60 ppb). In the reanalyses, the PM coefficients were either unchanged or only slightly decreased or increased; and the original findings, including the pattern in two-pollutant models, were unchanged. $PM_{2.5}$ and nitrate were most significantly associated with mortality, but significant associations were reported for all pollutants except $PM_{10-2.5}$ in single-pollutant models. In two- and four-pollutant models, $PM_{2.5}$ or nitrate remained significant for total mortality, but the other pollutants did not. The $PM_{2.5}$ risk estimates for respiratory deaths were larger than those for total or cardiovascular deaths but the associations were only significant for total mortality.

Mar et al. (2000; reanalyzed Mar et al., 2003) evaluated associations between air pollutants and total (nonaccidental) and cardiovascular deaths in Phoenix for only those who resided in the zip codes located near the air pollution monitor. GAM Poisson models were used, adjusting for season, temperature, and relative humidity, and a variety of air pollution variables were used, including O_3, SO_2, NO_2, CO, TEOM PM_{10}, TEOM $PM_{2.5}$, TEOM $PM_{10-2.5}$, DFPSS $PM_{2.5}$, S, Zn, Pb, soil, soil-corrected K (KS), nonsoil PM, OC, EC, and TC. Lags 0 to 4 days were evaluated. Factor analysis was also conducted on chemical components of DFPSS $PM_{2.5}$ (Al, Si, S, Ca, Fe, Zn, Mn, Pb, Br, KS, OC, and EC); and factor scores were included in the mortality analyses. Reanalyses were done using stringent convergence criteria as well as natural splines only for cardiovascular mortality. In the reanalyses, small reductions were seen in risk estimates for PM mass concentration indices using GAM/stringent convergence criteria or GLM/natural splines. For source factors, there were moderate reductions in risk estimates for the motor vehicle factor and slight increases for the regional sulfate factor and slight reductions in the coefficients for EC and OC; but the estimates remained unchanged for the vegetative burning factor. Cardiovascular mortality was significantly associated with CO, NO_2, SO_2, $PM_{2.5}$, PM_{10}, $PM_{10-2.5}$, OC and EC.

Vehicular traffic factors and regional sulfate factors were also associated with cardiovascular mortality. Soil-related factors, as well as individual variables that are associated with soil were negatively associated with total mortality. However, soil in $PM_{2.5}$ was positively and significantly associated with total mortality during the third year of the study when a WINS impactor (with sharper cut) was used instead of a cyclone sampler.

In all of the studies discussed above, some statistically significant associations between mortality and PM indicators, especially PM_{10} and $PM_{2.5}$ were found. In multipollutant models, PM coefficients were often robust to inclusion of gaseous pollutants, but sometimes reduced for specific co-pollutants (see also the co-pollutant model discussion in Section 8.4).

8.2.2.5 The Role of Particulate Matter Components

Delineation of the roles of specific ambient PM components in contributing to associations between short-term PM exposures and mortality requires evaluation of several factors, e.g., size, chemical composition, surface characteristics, and the presence of gaseous co-pollutants. While possible combinations of these factors can in theory be limitless, the actual data tend to cover definable ranges of aerosol characteristics and co-pollutant environments due to typical source characteristics (e.g., fine particles tend to be combustion products in most cities). Newly available studies conducted in the last few years have begun to provide more extensive information on the roles of PM components; and their results are discussed below in relation to three topics: (1) PM particle size (e.g., $PM_{2.5}$ versus $PM_{10-2.5}$); (2) chemical components; and (3) source oriented evaluations.

The ability to compare the relative roles of different PM size fractions and various PM constituents is restricted by the limitations of the available studies. Comparisons nevertheless can be attempted, using such information as the relative level of significance and/or the strength of correlation between component estimate and health outcome. The relative significance across cities/studies is influenced by the sample size and the level of the pollutants. The width of the confidence band also needs to be taken into account, according more weight for studies with narrower confidence bands. Caution in interpretation of such information, however, is warranted

because of potential measurement error and possible high correlations between indices being compared. Additionally, limitations of single-city studies must be recognized.

8.2.2.5.1 Particulate Matter Particle Size Evaluations

With regard to the relative importance of the fine and coarse fractions of inhalable PM_{10} particles capable of reaching thoracic regions of the respiratory tract, at the time of the 1996 PM AQCD only one acute mortality study (Schwartz et al., 1996a) had examined this issue. That study (which used GAM with default convergence criteria in analyzing Harvard Six-City Study data) suggested that fine particles ($PM_{2.5}$), distinctly more so than thoracic coarse-fraction ($PM_{10-2.5}$) particles, were associated with daily mortality. Recent reanalyses using GAM with more stringent convergence criteria have yielded only slightly smaller $PM_{2.5}$ effect-size estimates (Schwartz, 2003a). It should also be noted that (a) the Klemm et al. (2000) reanalysis reconstructed the data and replicated the original analyses (using GAM with default convergence criteria) and (b) the Klemm and Mason (2003) reanalysis, using GAM with stringent convergence criteria and GLM with parametric smoothers, also essentially reproduced the original investigators' results.

Since the 1996 PM AQCD, several new studies have used size-fractionated PM data to investigate the relative importance of fine ($PM_{2.5}$) versus coarse ($PM_{10-2.5}$) fraction particles. Table 8-2 provides synopses of those studies with regard to the relative importance of the two size fractions, as well as some characteristics of the data. The average levels of $PM_{2.5}$ ranged from about 13 to 30 $\mu g/m^3$ in the U.S. cities, but much higher average levels were measured in Santiago, Chile (64.0 µg/m3). As can be seen in Table 8-2, in the northeastern U.S. cities (Philadelphia, PA and Detroit, MI), there was more $PM_{2.5}$ mass than $PM_{10-2.5}$ mass on the average; whereas in the western U.S. (Phoenix, AZ; Coachella Valley, CA; Santa Clara County, CA) the average $PM_{10-2.5}$ levels were higher than $PM_{2.5}$ levels. It should be noted that the three Phoenix studies in Table 8-2 used much the same data set; all used fine and coarse particle data from EPA's 1995-1997 platform study. Seasonal differences in PM component levels should also be noted. For example, in Santa Clara County and in Santiago, Chile, winter $PM_{2.5}$ levels averaged twice those during summer. The temporal correlation between $PM_{2.5}$ and $PM_{10-2.5}$

TABLE 8-2. SYNOPSIS OF SHORT-TERM MORTALITY STUDIES THAT EXAMINED RELATIVE IMPORTANCE OF $PM_{2.5}$ AND $PM_{10-2.5}$

Author, City	Means ($\mu g/m^3$); Ratio of $PM_{2.5}$ to PM_{10}; and Correlation Between $PM_{2.5}$ and $PM_{10-2.5}$	Results Regarding Relative Importance of $PM_{2.5}$ versus $PM_{10-2.5}$ and Comments
Fairley (1999, 2003)* Santa Clara County, CA	$PM_{2.5}$ mean = 13; $PM_{2.5}/PM_{10}$ = 0.38; r = 0.51.	Of the various pollutants (including PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, sulfates, nitrates, CoH, CO, NO_2, and O_3), the strongest associations were found for ammonium nitrate and $PM_{2.5}$. $PM_{2.5}$ was significantly associated with mortality, but $PM_{10-2.5}$ was not, separately and together in the model. Winter $PM_{2.5}$ level is more than twice that in summer. The daily number of O_3 ppb-hours above 60 ppb was also significantly associated with mortality.
Ostro et al. (2000, 2003)* Coachella Valley, CA	$PM_{2.5}$ (Palm Springs and Indio, respectively) mean = 12.7, 16.8; $PM_{2.5}/PM_{10}$ = 0.43, 0.35; r = 0.46, 0.28.	Coarse particles dominate PM_{10} in this locale. $PM_{2.5}$ was available only for the last 2.5 years, and a predictive model could not be developed; so that a direct comparison of $PM_{2.5}$ and $PM_{10-2.5}$ results is difficult. Cardiovascular mortality was significantly associated with PM_{10} (and predicted $PM_{10-2.5}$), whereas $PM_{2.5}$ was mostly negatively associated (and not significant) at the lags examined.
Mar et al. (2000, 2003)* Phoenix, AZ 1995 to 1997	$PM_{2.5}$ (TEOM) mean = 13.0; $PM_{2.5}/PM_{10}$ = 0.28; r = 0.42.	Cardiovascular mortality was significantly associated with both $PM_{2.5}$ (lags 1, 3, and 4) and $PM_{10-2.5}$ (lag 0). Of all the pollutants (SO_2, NO_2, and elemental carbon were also associated), CO was most significantly associated with cardiovascular mortality.
Smith et al. (2000) Phoenix, AZ	Not reported, but likely same as Clyde's or Mar's data from the same location.	In linear PM effect model, a statistically significant mortality association with $PM_{10-2.5}$ was found, but not with $PM_{2.5}$. In models allowing for a threshold, indications of a threshold for $PM_{2.5}$ (in the range of 20-25) were found, but not for $PM_{10-2.5}$. A seasonal interaction in the $PM_{10-2.5}$ effect was also reported: the effect being highest in spring and summer when the contributions of Fe, Cu, Zn, and Pb to $PM_{10-2.5}$ were lowest.
Clyde et al. (2000) Phoenix, AZ	$PM_{2.5}$ mean = 13.8; $PM_{2.5}/PM_{10}$ = 0.30; r = 0.65.	Using Bayesian Model Averaging that incorporates model selection uncertainty with 29 covariates (lags 0- to 3-day), the effect of coarse particles (most consistent at lag 1 day) was stronger than that for fine particles. The association was for mortality defined for central Phoenix area where fine particles ($PM_{2.5}$) are expected to be uniform.
Lippmann et al. (2000); Ito, (2003)* Detroit, MI 1992 to 1994	$PM_{2.5}$ mean = 18; $PM_{2.5}/PM_{10}$ =0.58; r = 0.42.	Both $PM_{2.5}$ and $PM_{10-2.5}$ were positively (but not significantly) associated with mortality outcomes to a similar extent. Simultaneous inclusion of $PM_{2.5}$ and $PM_{10-2.5}$ also resulted in comparable effect sizes. Similar patterns were seen in hospital admission outcomes.
Lipfert et al. (2000a) Philadelphia, PA 1992 to 1995.	$PM_{2.5}$ mean = 17.3; $PM_{2.5}/PM_{10}$ = 0.72.	The authors conclude that no systematic differences were seen according to particle size or chemistry. However, when $PM_{2.5}$ and $PM_{10-2.5}$ were compared, $PM_{2.5}$ (at lag 1 or average of lag 0 and 1) was more significantly and precisely associated with cardiovascular mortality than $PM_{10-2.5}$.

TABLE 8-2 (cont'd). SYNOPSIS OF SHORT-TERM MORTALITY STUDIES THAT EXAMINED RELATIVE IMPORTANCE OF $PM_{2.5}$ AND $PM_{10-2.5}$

Author, City	Means ($\mu g/m^3$); Ratio of $PM_{2.5}$ to PM_{10}; and Correlation Between $PM_{2.5}$ and $PM_{10-2.5}$	Results Regarding Relative Importance of $PM_{2.5}$ versus $PM_{10-2.5}$ and Comments
Klemm and Mason (2000) Atlanta, GA	$PM_{2.5}$ mean = 19.9; $PM_{2.5}/PM_{10}$ = 0.65	No significant associations were found for any of the pollutants examined, possibly due to a relatively short study period (1-year). The coefficient and t-ratio were larger for $PM_{2.5}$ than for $PM_{10-2.5}$.
Schwartz (2003a) 6 U.S. cities	Not specified in Schwartz (2003a) paper; but see values below for same 6 cities.	Schwartz (2003a) reanalysis of Schwartz et al. (1996a) Harvard Six City time-series analyses confirmed original study findings of significant associations between total mortality and $PM_{2.5}$ across the six U.S. cities, but not with $PM_{10-2.5}$ (except in one city, Steubenville).
Klemm et al. (2000); Klemm and Mason (2003)* 6 U.S. cities	Mean ranged from 11.3 to 29.6; Mean $PM_{10-2.5}$ ranged from 6.6 to 16.1; Mean $PM_{2.5}/PM_{10}$ ranged from 0.50 to 0.66 in the six cities.	This reanalysis of the Harvard Six-Cities time-series analysis by Schwartz et al. (1996a) found significant associations between total mortality and $PM_{2.5}$ in 3 cities and in pooled effect, but no significant association with $PM_{10-2.5}$ in the reanalysis of the replication study for any city. These results essentially confirmed the findings of the original study by Schwartz et al. (1996a).
Chock et al. (2000) Pittsburgh, PA	Data distribution not reported. $PM_{2.5}/PM_{10}$ = 0.67	Seasonal dependence of correlation among pollutants, multicolinearity among pollutants, and instability of coefficients were all emphasized in discussion and conclusion. These considerations and the small size of the data set (stratified by age group and season) limit confidence in finding of no consistently significant associations for any size fractions.
Burnett et al. (2000); Burnett and Goldberg (2003)* 8 Canadian cities	$PM_{2.5}$ mean = 13.3; $PM_{2.5}/PM_{10}$ = 0.51; r = 0.37.	Both $PM_{2.5}$ and $PM_{10-2.5}$ were significantly associated with total nonaccidental mortality. Results using varying extent of smoothing of mortality temporal trends show that there is no consistent pattern of either PM mass index being more important. The authors note that $PM_{10-2.5}$ was more sensitive to the type of smoother and amount of smoothing.
Cifuentes et al. (2000) Santiago, Chile 1988 to 1996	$PM_{2.5}$ mean = 64.0; $PM_{2.5}/PM_{10}$ = 0.58; r = 0.52.	In GLM results for the whole years, $PM_{2.5}$ and NO_2 were more consistently significantly associated with total nonaccidental mortality than $PM_{10-2.5}$.

Note: * next to author name indicates that the study was originally analyzed using GAM models only with default convergence criteria using at least two nonparametric smoothing terms.

ranged between 0.30 and 0.65. Such differences in ambient PM mix features from season to season or from location to location complicates assessment of the relative importance of $PM_{2.5}$ and $PM_{10-2.5}$.

To facilitate a quantitative overview of the effect size estimates and their corresponding uncertainties from these studies, the percent excess risks are plotted in Figure 8-5. These excluded the Smith et al. study (which did not present linear term RRs for $PM_{2.5}$ and $PM_{10-2.5}$) and the Clyde et al. study (for which the model specification did not obtain RRs for $PM_{2.5}$ and $PM_{10-2.5}$ separately). Note that, in most of the original studies, the RRs were computed for comparable distributional features (e.g., interquartile range, mean, 5th -to-95th percentile, etc.). However, the increments derived and their absolute values varied across studies; therefore, the RRs used in deriving the excess risk estimates delineated in Figure 8-5 were re-computed for consistent increments of 25 $\mu g/m^3$ for both $PM_{2.5}$ and $PM_{10-2.5}$. Note also that re-computing the RRs per 25 $\mu g/m^3$ in some cases changed the relative effect size between $PM_{2.5}$ and $PM_{10-2.5}$, but it did not affect the relative significance.

All of the studies found positive associations between both the fine and coarse PM indices and increased mortality risk, however, most of the studies did not have large enough sample sizes to separate out what often appear to be relatively small differences in effect size estimates. However, three studies do show distinctly larger mortality associations with $PM_{2.5}$ than for nonsignificant $PM_{10-2.5}$ effects. For example, the Klemm et al. (2000) and Klemm and Mason's (2003) recomputations of the Harvard Six Cities time-series study data reconfirmed the original Schwartz et al. (1996a) finding that $PM_{2.5}$ was significantly associated with excess total mortality, but $PM_{10-2.5}$ across all cities was not (although the Schwartz [2003a] reanalyses also reconfirmed their original findings of a statistically significant $PM_{10-2.5}$-mortality relationship in one city, i.e., Steubenville, OH). Similar findings of $PM_{2.5}$ being significantly associated with total mortality were obtained in Santa Clara County (Fairley, 1999; Fairley 2003), and Mar et al. (2000, 2003) reported much larger $PM_{2.5}$ associations with cardiovascular mortality than for $PM_{10-2.5}$ (although both were statistically significant at $p < 0.05$). There were several other studies in which the importance of $PM_{2.5}$ and $PM_{10-2.5}$ were considered to be similar or, at least, not distinguishable: Philadelphia, PA (Lipfert et al., 2000a); Detroit, MI (Lippmann et al., 2000; reanalysis by Ito 2003); Eight Canadian cities (Burnett at al., 2000; reanalysis by Burnett and Goldberg, 2003); and Santiago, Chile (Cifuentes et al., 2000). Some other studies suggested

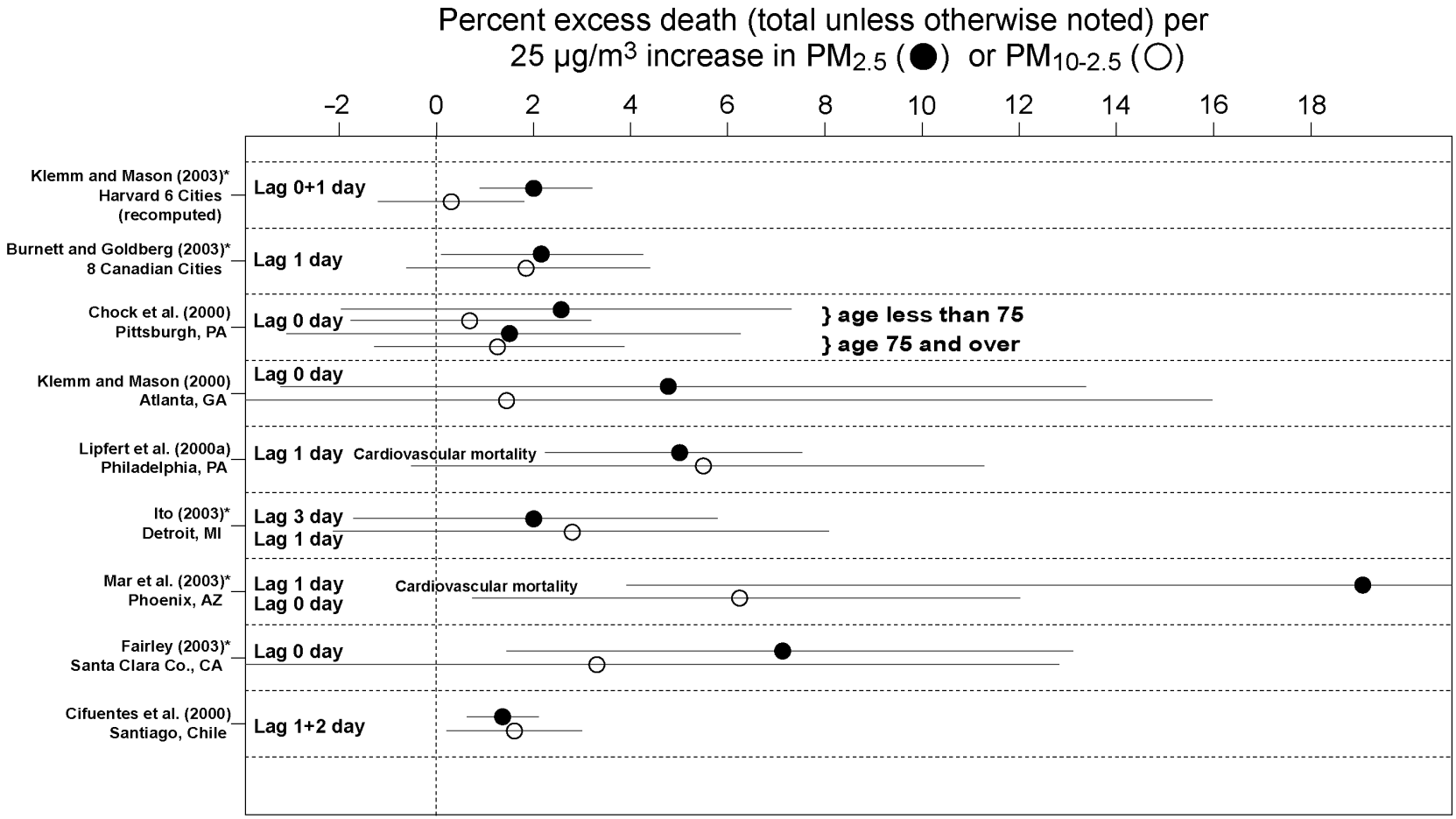

Figure 8-5. Percent excess risks estimated per 25 µg/m^3 increase in $PM_{2.5}$ or $PM_{10-2.5}$ from new studies that evaluated both $PM_{2.5}$ and $PM_{10-2.5}$, based on single pollutant (PM only) models. The asterisk next to reference indicates reanalysis of data using GLM with natural splines. Other studies used GLM or OLS.

that $PM_{10-2.5}$ was more important than $PM_{2.5}$: Coachella Valley, CA (Ostro et al., 2000 & 2003) and Phoenix, AZ (Smith et al., 2000, and Clyde et al., 2000).

In the reanalysis (Burnett and Goldberg, 2003) of the Canadian 8-city study (Burnett et al., 2000), the relative importance of $PM_{2.5}$ and $PM_{10-2.5}$ was not clear, with both PM indices being significant in single pollutant models. In GAM models (stringent convergence criteria) with LOESS smoothers, $PM_{2.5}$ was more significant and showed larger risk estimates than $PM_{10-2.5}$. However, in sensitivity analysis in which varying degrees of freedom for mortality temporal trends were applied in GLM models, the effect size and significance for these PM indices were often comparable. The authors commented that $PM_{10-2.5}$ coefficient was more sensitive to the extent of temporal smoothing than $PM_{2.5}$.

The Lippmann et al. (2000) results and reanalyses (Ito, 2003) for Detroit are also noteworthy in that additional PM indices were evaluated besides those depicted in Figure 8-5, and the overall results obtained may be helpful in comparing fine- versus coarse-mode PM effects. In analyses of 1985 to 1990 data, PM-mortality relative risks and their statistical significance were generally in descending order: PM_{10}, TSP-SO_4^{2-}, and TSP-PM_{10}. For the 1992 to 1994 period, relative risks for equivalent distributional increment (e.g., IQR) were comparable among PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ for both mortality and hospital admissions categories; and SO_4^{2-} was more strongly associated with most outcomes than H^+. Consideration of the overall pattern of results led the authors to state that the mass of the smaller size index could explain a substantial portion of the variation in the larger size indices. In these data, on average, $PM_{2.5}$ accounted for 60% of PM_{10} (up to 80% on some days) and PM_{10} for 66% of TSP mass. The temporal correlation between TSP and $PM_{2.5}$ was $r = 0.63$, and that for $PM_{2.5}$ and PM_{10} was $r = 0.90$, suggesting that much of the apparent larger particle effects may well be mainly driven by temporally covarying smaller $PM_{2.5}$ particles. The stronger associations for sulfates than H^+, suggestive of nonacid fine particle effects, must be caveated by noting the very low H^+ levels present (often at or near the detection limit).

Three research groups, using different methods, have utilized the same U.S. EPA research platform aerometric data to evaluate ambient PM-mortality associations in the Phoenix, AZ area. Although these groups used somewhat different approaches, there is some consistency across

their results in that $PM_{10-2.5}$ emerged in all three as a likely important predictor of mortality. The Mar et al. (2000, 2003) analyses evaluated total and cardiovascular mortality among people residing in zip code areas proximal to the one containing the EPA monitoring platform yielding PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$ and compositional data used in their analyses. In the Mar et al. (2000 & 2003) analyses, PM_{10} was significantly associated with total mortality, whereas $PM_{2.5}$ and $PM_{10-2.5}$ were positively (but not quite significantly) associated. However, cardiovascular mortality (CVM) was significantly associated with both $PM_{2.5}$ and $PM_{10-2.5}$, as well as being significantly associated with several source categories (as shown by factor analyses discussed later). The Smith et al. (2000) analyses related mortality in Phoenix to the EPA $PM_{2.5}$ data, but used mortality data from surrounding areas (Tempe, Scottsdale, etc.) within 50 miles of Phoenix in analyses of $PM_{10-2.5}$ effects. Based on a linear PM effect, Smith et al. found $PM_{10-2.5}$ to be significantly associated with total mortality, but not $PM_{2.5}$. However, Smith et al.'s additional finding that $PM_{2.5}$ may have a threshold effect further complicates a simple comparison of the two size-fractionated mass concentration indices. In the Clyde et al. (2000) analysis, PM-mortality associations were found only for the geographic area where $PM_{2.5}$ was considered uniformly distributed, but the association was stronger for $PM_{10-2.5}$ than for $PM_{2.5}$. That is, whereas the posterior probability for $PM_{2.5}$ effect was ~0.91, the highly ranked models (based on the Bayes Information Criterion) consistently included 1-day lagged $PM_{10-2.5}$. The $PM_{2.5}$ in Phoenix is mostly generated from motor vehicles, whereas $PM_{10-2.5}$ consists mainly of two types of particles: (a) crustal particles from natural (wind blown dust) and anthropogenic (construction and road dust) processes, and (b) organic particles from natural biogenic processes (e.g., the soil-dwelling *Coccidioides immitis* fungus in windblown dust, as discussed in Appendix 7B) and anthropogenic (sewage aeration) processes. The crustal particles may also be contaminated with metals secondarily deposited over many years as the result of emissions from smelters operating until recently in the Phoenix area.

In summary, issues regarding the relative importance of $PM_{2.5}$ and $PM_{10-.25}$ have not yet been fully resolved. Caution in interpreting size-fraction PM studies is warranted due to (a) problems with measurement and exposure error (likely higher for $PM_{10-2.5}$) and (b) the correlation between the two size fractions. Limitations of single-city studies have also been

noted. While limited sample sizes typically prevented clear statistical distinction between relative roles played by $PM_{2.5}$ and $PM_{10-.25}$, recent studies show mixed results, with some studies suggesting coarse particle effects. The relative importance may also vary depending on the chemical constituents in each size fraction, which may vary from city to city. Nevertheless, a number of studies published since the 1996 PM AQCD do appear to substantiate associations between $PM_{2.5}$ and increased total and/or CVD mortality. Consistent with the 1996 PM AQCD findings, effect-size estimates from the new studies generally fall within the range of ~1.5 to 6.5% excess total mortality per 25 $\mu g/m^3$ $PM_{2.5}$. The coarse particle ($PM_{10-2.5}$) effect-size estimates also tend to fall in about the same range, mainly from ~0.5 to 6.0%.

Crustal Particle Effects

Since the 1996 PM AQCD, several studies have yielded interesting new information concerning possible roles of crustal wind-blown particles or crustal particles within the fine particle fraction (i.e., $PM_{2.5}$) in contributing to observed PM-mortality effects.

Schwartz et al. (1999), for example, investigated the association of coarse particle concentrations with nonaccidental deaths in Spokane, WA, where dust storms elevate coarse PM concentrations. During the 1990 to 1997 period, 17 dust-storm days were identified. The PM_{10} levels during those storms averaged 263 $\mu g/m^3$, compared to 39 $\mu g/m^3$ for the entire period. The coarse particle domination of PM_{10} data on those dust-storm days was confirmed by a separate measurement of PM_{10} and $PM_{1.0}$ during a dust storm in August, 1996: the PM_{10} level was 187 $\mu g/m^3$, while $PM_{1.0}$ was only 9.5 $\mu g/m^3$. The deaths on the day of a dust storm were contrasted with deaths on control days (n = 95 days in the main analysis and 171 days in the sensitivity analysis), which are defined as the same day of the year in other years when dust storms did not occur. The relative risk for dust-storm exposure was estimated using Poisson regressions, adjusting for temperature, dewpoint, and day of the week. Various sensitivity analyses considering different seasonal adjustment, year effects, and lags were conducted. The expected relative risk for these storm days with an increment of 221 $\mu g/m^3$ would be about 1.04, based on PM_{10} relative risk from past studies, but the estimated RR for high PM_{10} days was found to be only 1.00 (CI: 0.95, 1.05) per 50 $\mu g/m^3$ PM_{10} change in this study. Schwartz et al.

concluded that there was no evidence to suggest that coarse (presumably crustal) particles were associated with daily mortality.

Ostro et al. (2000 & 2003) also analyzed Coachella Valley, CA data for 1989-1998. This desert valley, where coarse particles of geologic origin comprise ~50-60% of annual-average PM_{10} (> 90% during wind episodes throughout the year), includes the cities of Palm Springs and Indio, CA. Cardiovascular deaths were analyzed using GAM (with stringent convergence criteria) and GLM Poisson models adjusting for temperature, humidity, day-of-week, season, and time. Actual $PM_{2.5}$ and $PM_{10-2.5}$ data were only available for the last 2.5 years of the 10-year study period. So, predictive models were developed for estimating $PM_{2.5}$ and $PM_{10-2.5}$ concentrations for earlier years, but the model for $PM_{2.5}$ was not considered successful and, therefore, was not used. Thus, a strict comparison of relative strength of risk estimates for $PM_{2.5}$ and $PM_{10-2.5}$ in this data set is difficult. Cardiovascular mortality was reported to be positively associated with both PM_{10} and $PM_{10-2.5}$ at multiple lags between 0 and 2 day lags; whereas the $PM_{2.5}$ coefficient was positive only at lag 4 day, based on analyses involving far fewer observations for $PM_{2.5}$ (only over a 2 year period versus 10 years for PM_{10} and $PM_{10-2.5}$). These results hint at crustal particle effects possibly being important in this desert situation, but use of estimated values for $PM_{10-2.5}$ lessens the credibility of the reported $PM_{10-2.5}$ findings. Also, the ability to discern more clearly the role of fine particles would likely be improved by analyses of more years of actual data for $PM_{2.5}$.

In two other studies, Laden et al. (2000) and Schwartz (2003b) analyzed Harvard Six-Cities Study data and Mar et al. (2000) analyzed the Phoenix data to investigate the influence on daily mortality of crustal particles in $PM_{2.5}$ samples. These studies are discussed in more detail in Section 8.2.2.4.3 on the source-oriented evaluation of PM; and only the basic results regarding crustal particles are mentioned here. The elemental abundance data, from X-ray fluorescence (XRF) spectroscopy analysis of daily filters, were analyzed to estimate the concentration of crustal particles in $PM_{2.5}$ using factor analysis. Then the association of mortality with fine crustal mass was estimated using Poisson regression (regressing mortality on factor scores for "crustal factor"), adjusting for time trends and weather. No positive association was found between the fine crustal mass factor and mortality. However, the soil component of $PM_{2.5}$ was

positively and significantly associated with total mortality when only the third year of data (when a WINS impactor was used instead of a cyclone) was analyzed.

The above results, overall, mostly suggest that crustal particles (coarse or fine) per se are not likely associated with daily mortality. However, as noted in the previous section, three analyses of Phoenix, AZ data do suggest that $PM_{10-2.5}$ was associated with mortality. The results from one of the three studies (Smith et al., 2000) indicate that coarse particle-mortality associations are stronger in spring and summer, when the anthropogenic metal (Fe, Cu, Zn, and Pb) contribution to $PM_{10-2.5}$ is lowest as determined by factor analysis. However, during spring and summer, biogenic processes (e.g., wind-blown pollen fragments, fungal materials, endotoxins, and glucans) may contribute more to the $PM_{10-2.5}$ fraction in the Phoenix area, clouding any attribution of observed $PM_{10-2.5}$ effects there to crustal particles alone, per se. (See the discussion of bioaerosols in Chapter 7 and, also in Section 8.4.3 of this chapter).

Ultrafine Particle Effects

Wichmann et al. (2000) evaluated the attribution of PM effects to specific size fractions, including both the number concentration (NC) and mass concentration (MC) of particles in a given size range. To respond to the GAM convergence issues, Stolzel et al. (2003) reanalyzed the data, using GAM with stringent convergence criteria and GLM with natural splines. The study was carried out in the former German Democratic Republic city of Erfurt (pop. 200,000) German. Erfurt was heavily polluted by particles and SO_2 in the 1980s, and excess mortality was attributed to high levels of TSP by Spix et al. (1993). Ambient PM and SO_2 concentrations have markedly dropped since then. The present study provides a more detailed look at potential health effect associations with ultrafine particles (diameter < 0.1 μm) than earlier studies, including examination of effects in relation to number counts for fine and ultrafine particles as well as for their mass. This was made possible by use of the Mobile Aerosol Spectrometer (MAS), developed by Gessellschaft für Strahlenforschung (GSF), which measures number and mass concentrations in three ultrafine size classes (0.01 to 0.1 μm) and three size classes of larger fine particles (0.1 μm to 2.5 μm). The mass concentration $MC_{0.01-2.5}$ is well correlated with gravimetric $PM_{2.5}$, and the number concentration $NC_{0.01-2.5}$ is well correlated with total particle

counts from a condensation particle counter (CPC). Mortality data were coded by cause of death, with some discrimination between underlying causes and prevalent conditions of the deceased.

In the reanalysis by Stolzel et al. (2003), daily mortality data were fitted using a Poisson GAM (with stringent convergence criteria) and GLM, with adjustments for weather variables, time trends, day of week, and particle indices. Weekly data for all of Germany on influenza and similar diseases were also included in the model. In the original study, two types of models were fitted; one used the best single-day lag for air pollution and a second the best polynomial distributed lag (PDL) model for air pollution. Both linear (i.e., raw) and log-transformed pollution indices were examined. PDL models in the original analysis generally had larger and more significant PM effects than single-day lag models, but the reanalysis by Stolzel et al. (2003) focused on single-day lag results only. Therefore, the numerical results in the following discussion only include the single day lag results from the reanalysis. It should be noted that, unlike most of the recent reanalyses that have been conducted to address the GAM conversion issue, the reanalysis results from this study were virtually unchanged from the original results.

Both mass and number concentrations at the size ranges examined were mostly positively associated with total nonaccidental mortality. The best single-day lags reported were mostly 0 or 1 day lag for mass concentrations and the 4 day lag for number concentrations. For example, the estimated excess risk for $MC_{0.01\text{-}2.5}$ at lag 1 day was about 3.9% (CI: 0, 7.7) per 25 $\mu g/m^3$. The corresponding number for smaller fine particles, $MC_{0.01\text{-}1.0}$, was 3.5% (CI: −0.4, 7.7). For number concentration, the estimated excess risk for $NC_{0.01\text{-}2.5}$ at lag 4 day was about 4.1% (CI: −0.9, 9.3) per IQR (13,269 particles/cm^3). The corresponding number for smaller fine particles, $NC_{0.01\text{-}1.0}$, was 4.6% (CI: −0.3, 9.7) per IQR (12,690 particles/cm^3). An examination of all the results for $MC_{0.01\text{-}2.5}$ and $NC_{0.01\text{-}0.1}$ shown for lags 0 through 5 days indicates that the associations were mostly positive for these mass and number concentrations, except for the "dip" around 2 or 3 day lags.

The estimated excess risks are reduced, sometimes drastically, when co-pollutants (especially SO_2 and NO_2) are included in a two-pollutant model. This is not surprising, as the number and mass concentrations of various ultrafine and fine particles in all size ranges are

rather well correlated with gaseous co-pollutants, except for the intermodal size range $MC_{1.0\text{-}2.5}$. The number correlations range from 0.44 to 0.62 with SO_2, from 0.58 to 0.66 with NO_2, and from 0.53 to 0.70 with CO. The mass correlations range from 0.53 to 0.62 with SO_2, from 0.48 to 0.60 with NO_2, and from 0.56 to 0.62 with CO. The authors found that ultrafine particles, CO and NO_2 form a group of pollutants strongly identified with motor vehicle traffic. Immediate and delayed effects seemed to be independent in two-pollutant models, with single-day lags of 0 to 1 days and 4 to 5 days giving 'best fits' to data. The delayed effect of ultrafine particles was stronger than that for NO_2 or CO. The large decreases in excess risk for number concentration, particularly when NO_2 is a co-pollutant with $NC_{0.01\text{-}0.1}$, clearly involves a more complex structure than simple correlation. The large decrease in excess risk when SO_2 is a co-pollutant with $MC_{0.01\text{-}2.5}$ is not readily explained and is discussed in some detail in Wichmann et al. (2000).

Sulfur dioxide is a strong predictor of excess mortality in this study; and its estimated effect is little changed when different particle indicators are included in a two-pollutant model. The authors noted ". . .the [LOESS] smoothed dose response curve showed most of the association at the left end, below 15 $\mu g/m^3$, a level at which effects were considered biologically implausible. . ." Replacement of sulfur-rich surface coal has reduced mean SO_2 levels in Erfurt from 456 $\mu g/m^3$ in 1988 to 16.8 $\mu g/m^3$ during 1995 to 1998 and to 6 $\mu g/m^3$ in 1998. The estimated concentration-response functions for SO_2 are very different for these time periods, comparing Spix et al. (1993) versus Wichmann et al. (2000) results. Wichmann et al. concluded "These inconsistent results for SO_2 strongly suggested that SO_2 was not the causal agent but an indicator for something else." The authors offered no specific suggestions as to what the "something else" might be, but they did finally conclude that their studies from Germany strongly supported PM air pollution as being more relevant than SO_2 to observed mortality outcomes. However, the HEI committee also did not agree with the investigators' interpretation that the association of SO_2 with mortality was an artifact, given the similar magnitude of effect sizes between PM and SO_2 and the persistence of an SO_2 effect in the two-pollutant analyses.

8.2.2.5.2 Chemical Components

Several new studies from the United States, Canada, and The Netherlands examined mortality associations with specific chemical components of ambient PM. Table 8-3 shows the chemical components examined in these studies; the mean concentrations for Coefficient of Haze (CoH), sulfate, and H^+; and indications of those components found to be associated with increased mortality.

Coefficient of Haze, Elemental Carbon, and Organic Carbon

CoH is highly correlated with elemental carbon (EC) and is often considered as a good PM index for motor vehicle sources, although other combustion processes such as space heating likely also contribute to CoH levels. Several studies (Table 8-3) examined CoH; and, in most cases, positive and significant associations with mortality outcomes were reported. In terms of relative significance of CoH in comparison to other PM components, CoH was not the clearly most significant PM component in most of these studies. The average level of CoH in these studies ranged from 0.24 (Montreal, Quebec) to 0.5 (Santa Clara County, CA) 1000 linear feet. The correlations between CoH and NO_2 or CO in these studies (8 largest Canadian cities; Santa Clara County, CA) were moderately high (r .0.7 to 0.8) and suggested a likely motor vehicle contribution. Both EC and OC were significant predictors of cardiovascular mortality in the Phoenix study; their effect sizes per IQR were comparable to those for PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$. Also, both EC and OC represented major mass fractions of $PM_{2.5}$ (11% and 38%, respectively) and were correlated highly with $PM_{2.5}$ (r = 0.84 and 0.89, respectively). They were also highly correlated with CO and NO_2 (r = 0.8 to 0.9), indicating their associations with an "automobile" factor. Thus, the CoH and EC/OC results from the Mar et al. (2000 and 2003) study suggest that PM components from motor vehicle sources are likely associated with mortality. In a recent study in Montreal, Quebec, by Goldberg et al. (2000 and 2003), CoH appeared to be correlated with the congestive heart failure mortality (as classified based on medical records) more strongly than other PM indices such as the visual-range derived extinction coefficient (considered to be a good indicator of sulfate). However, the main focus of the study was on the role of cardiorespiratory risk factors for air pollution, and the investigators warned against comparing

TABLE 8-3. NEWLY AVAILABLE STUDIES OF MORTALITY RELATIONSHIPS TO PM CHEMICAL COMPONENTS

Author, City	Mean CoH (1000ft)	Mean $SO_4^=$ (ug/m^3)	Mean H^+ ($nmol/m^3$)	Other PM Components Analyzed	Specific PM Components Found to be Associated with Mortality (Comments)
Burnett et al. (2000); Burnett and Goldberg (2003)* 8 largest Canadian cities, 1986-1996.	0.26	2.6		PM_{10}, $PM_{2.5}$, $PM_{10-.5}$, and 47 trace elements	PM_{10}, $PM_{2.5}$, CoH, sulfate, Zn, Ni, and Fe were significantly associated with total mortality in the original analysis. The reanalysis only analyzed mass concentration indices.
Fairley (1999 & 2003)*; Santa Clara County, CA.	0.5	1.8		PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, and nitrate	CoH, sulfate, nitrate, PM_{10}, and $PM_{2.5}$ were associated with mortality. $PM_{2.5}$ and nitrate most significant.
Goldberg et al. (2000); Goldberg and Burnett (2003); Goldberg et al. (2003)* Montreal, Quebec, Canada. 1984-1993.	0.24	3.3		Predicted $PM_{2.5}$, and extinction coefficient (visual- range derived).	CoH and extinction coefficient were associated with the deaths that were classified as having congestive heart failure before death based on medical records. Associations were stronger in warm season.
Lipfert et al., (2000a) Philadelphia, PA. 1992-1995.	0.28	5.1	8.0	Nephelometry, NH_4^+, TSP, PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$	Essentially all PM components were associated with mortality.
Lippmann et al. (2000); Ito (2003)* Detroit, MI. 1992-1994.		5.2	8.8	PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$	PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ were more significantly associated with mortality outcomes than sulfate or H^+.
Klemm and Mason (2000) Atlanta, GA 1998-1999		5.2	8.8	Nitrate, EC, OC, oxygenated HC, PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$	"Interim" results based on one year of data. No statistically significant associations for any pollutants. Those with t-ratio of at least 1.0 were H^+, PM_{10}, and $PM_{2.5}$.
Mar et al. (2000 & 2003)* Phoenix, AZ. 1995-1997.				EC, OC, TC, PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$	EC, OC, TC, PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ were associated with cardiovascular mortality.
Tsai et al. (2000). Newark, Elizabeth, and Camden, NJ. 1981-1983.		12.7		PM_{15}, $PM_{2.5}$, cyclohexane-solubles (CX), dichloromethane-solubles (DCM), and acetone-solubles (ACE).	PM_{15}, PM2.5, sulfate, CX, and ACE were significantly associated with total and/or cardiovascular mortality in Newark and/or Camden.
Hoek (2003)* the Netherlands. 1986-1994.		3.8 (median)		PM_{10}, BS, and nitrate	Sulfate, nitrate, and BS were more consistently associated with total mortality than was PM_{10}.

*Note: The study was originally analyzed by GAM models only using default convergence criteria and at least two nonparametric smoothing terms and was recently reanalyzed by GAM using stringent convergence criteria and/or other non-GAM analyses.

the relative strength of associations among PM indices, pointing out complications such as likely error involved in the visual range measurements. Additionally, the estimated $PM_{2.5}$ values were predicted from other PM indices, including CoH and extinction coefficient, making it difficult to compare straightforwardly the relative importance of PM indices.

Sulfate and Hydrogen Ion

Sulfate and H^+, markers of acidic components of PM, have been hypothesized to be especially harmful components of PM (Lippmann et al., 1983; Lippmann and Thurston, 1996). The newly available studies that examined sulfate are shown in Table 8-3; two of them also analyzed H^+ data. The sulfate concentrations ranged from 1.8 $\mu g/m^3$ (Santa Clara County, CA) to 12.7 $\mu g/m^3$ (three NJ cities). Aside from the west versus east coast contrast, the higher levels observed in the three NJ cities are likely due to their study period coverage of the early 1980s, when sulfate levels were higher. Sulfate explained 25 to 30% of $PM_{2.5}$ mass in eastern U.S. and Canadian cities, but it was only 14% of $PM_{2.5}$ mass in Santa Clara County, CA. The H^+ levels measured in Detroit and Philadelphia were low. The mean H^+ concentration for Detroit, MI (the H^+ was actually measured in Windsor, a Canadian city a few miles from downtown Detroit), 8.8 $nmol/m^3$, was low as compared to the reported detection limit of 15.1 $nmol/m^3$ (Brook et al., 1997) for the measurement system used in the study. Note that the corresponding detection limit for sulfate was 3.6 $nmol/m^3$ (or 0.34 $\mu g/m^3$); and the mean sulfate level for Detroit was 54 $nmol/m^3$ (or 5.2 $\mu g/m^3$), so that the signal-to-noise ratio is expected to be higher for sulfate than for H^+. Thus, the ambient levels and possible relative measurement errors for these data should be considered in interpreting the relative strength of mortality associations in these data.

Sulfate was a statistically significant predictor of mortality, at least in single pollutant models, in: Santa Clara County, CA; Philadelphia, PA; Newark, NJ; and Camden, NJ, but not in Elizabeth, NJ; Detroit, MI; or Montreal, CN. However, it should be noted that the relative significance across the cities is influenced by the sample size (both the daily mean death counts and number of days available), as well as the range of sulfate levels and should be interpreted with caution. Figure 8-6 shows the excess risks (± 95% CI) estimated per 5 $\mu g/m^3$ increase in 24-h sulfate reported in these studies compared to the reanalysis results of the earlier Six Cities Study by Klemm and Mason (2003). The largest estimate was seen for Santa Clara County, CA;

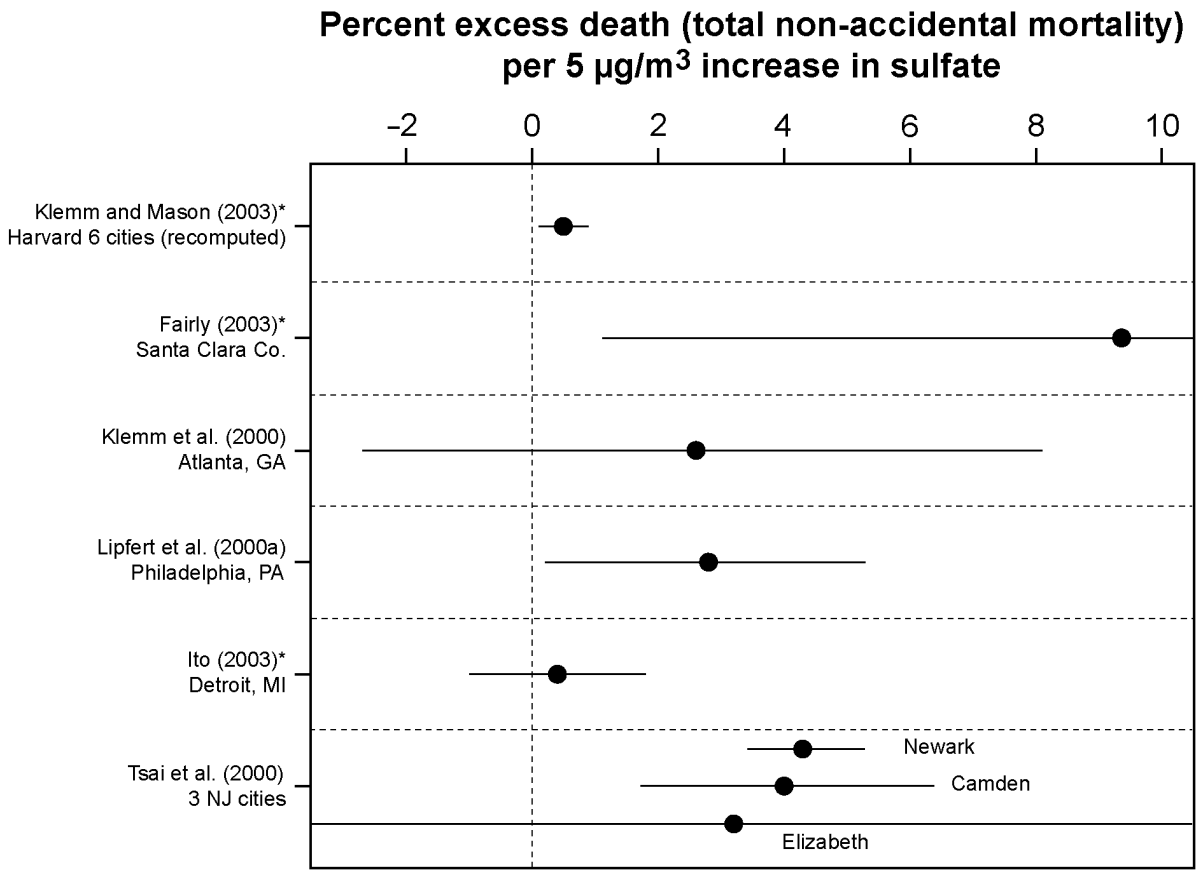

Figure 8-6. Excess risks estimated per 5 µg/m^3 increase in sulfate, based on U.S. studies for which both $PM_{2.5}$ and $PM_{10-2.5}$ data were available.

but the wide confidence band (possibly due to the small variance of the sulfate, because its levels were low) should be taken into account. In addition, the sulfate effect in the Santa Clara County analysis was eliminated once $PM_{2.5}$ was included in the model, perhaps being indicative of sulfate mainly serving as a surrogate for fine particles in general there. In any case, more weight should be accorded to estimates from other studies with narrower confidence bands. In the other studies, effect size estimates mostly ranged from ~1 to 4% per 5 µg/m^3 increase in 24-h sulfate.

The relative significance of sulfate and H^+ compared to other PM components is not clear in the existing small number of publications. Because each study included different combinations of co-pollutants that had different extents of correlation with sulfate and because

multiple mortality outcomes were analyzed, it is difficult to assess the overall importance of sulfate across the available studies. The fact that the Lippmann et al. (2000) study and the reanalysis by Ito (2003) found that Detroit, MI data on H^+ and sulfate were less significantly associated with mortality than the size-fractionated PM mass indices may be due to acidic aerosols levels being mostly below the detection limit in that data. In this case, it appears that the Detroit PM components show mortality effects even without much acidic input.

In summary, assessment of new study results for individual chemical components of PM suggest that an array of PM components (mainly fine particle constituents) are associated with mortality outcomes, including CoH, EC, OC, sulfate, and nitrate. The variations seen with regard to the relative significance of these PM components across studies may be in part due to differences in their concentrations from locale to locale. This issue is further discussed below as part of the assessment of new studies involving source-oriented evaluation of PM components.

8.2.2.5.3 Source-Oriented Evaluations

Several new studies have conducted source-oriented evaluation of PM components. In these studies, daily concentrations of PM components (i.e., trace elements) and gaseous co-pollutants were analyzed using factor analysis to estimate daily concentrations due to underlying source types (e.g., motor vehicle emissions, soil, etc.), which are weighted linear combinations of associated individual variables. The mortality outcomes were then regressed on those factors (factor scores) to estimate the effect of source types rather than just individual variables. These studies differ in terms of specific objectives/focus, the size fractions from which trace elements were extracted, and the way factor analysis was used (e.g., rotation). The main findings from these studies regarding the source-types identified (or suggested) and their associations with mortality outcomes are summarized in Table 8-4.

The Laden et al. (2000) analysis of Harvard Six Cities data for 1979-1988 (reanalyzed by Schwartz, 2003a) aimed to identify distinct source-related fractions of $PM_{2.5}$ and to examine each fraction's association with mortality. Fifteen elements in the fine fraction samples routinely found above their detection limits were included in the data analysis. For each of the six cities, up to 5 common factors were identified from among the 15 elements, using specific rotation

TABLE 8-4. SUMMARY OF SOURCE-ORIENTED EVALUATIONS OF PM COMPONENTS IN RECENT STUDIES

Author, City	Source Types Identified (or Suggested) and Associated Variables	Source Types Associated with Mortality (Comments)
Laden et al., (2000); Schwartz (2003a)* Harvard Six Cities. 1979-1988.	*Soil and crustal material*: Si *Motor vehicle emissions*: Pb *Coal combustion*: Se *Fuel oil combustion*: V *Salt*: Cl Note: the trace elements are from $PM_{2.5}$ samples	Strongest increase in daily mortality was associated with the mobile source factor. Coal combustion factor was also positively associated with mortality. Crustal factor from fine particles not associated (negative but not significant) with mortality. Coal and mobile sources account for the majority of fine particles in each city.
Mar et al. (2000 & 2003)* Phoenix, AZ. 1995-1997.	***$PM_{2.5}$ (from DFPSS) trace elements:*** *Motor vehicle emissions and re-suspended road dust*: Mn, Fe, Zn, Pb, OC, EC, CO, and NO_2 *Soil*: Al, Si, and Fe *Vegetative burning*: OC, and KS (soil-corrected potassium) *Local SO_2 sources*: SO_2 *Regional sulfate*: S	*$PM_{2.5}$ factors results*: Motor vehicle factor (1 day lag), vegetative burning factor (3 day lag), and regional sulfate factor (0 day lag) were significantly positively associated with cardiovascular mortality.
	$PM_{10-2.5}$ (from dichot) trace elements: *Soil*: Al, Si, K, Ca, Mn, Fe, Sr, and Rb *A source of coarse fraction metals*: Zn, Pb, and Cu *A marine influence*: Cl	Factors from dichot $PM_{10-2.5}$ trace elements not analyzed for their associations with mortality because of the small sample size (every 3rd-day samples from June 1996).
Tsai et al. (2000). Newark, Elizabeth, and Camden, NJ. 1981-1983.	*Motor vehicle emissions*: Pb, CO *Geological (Soil)*: Mn, Fe *Oil burning*: V, Ni *Industrial*: Zn, Cu, Cd (separately) *Sulfate/secondary aerosol*: sulfate Note: the trace elements are from PM_{15} samples	Oil burning, industry, secondary aerosol, and motor vehicle factors were associated with mortality.

*Note: The study was originally analyzed using GAM models only with default convergence criteria using at least two nonparametric smoothing terms, but was later reanalyzed using more stringent convergence criteria and/or other approaches.

factor analysis. Using the Procrustes rotation (a type of oblique rotation), the projection of the single tracer for each factor was maximized. This specification of the tracer element was based on (a) knowledge from previous source apportionment research; (b) the condition that the regression of total fine mass on that element must result in a positive coefficient; and (c) the identifications of additional local source factors that positively contributed to total fine mass

regression. Three source factors were identified in all six cities: (1) a soil and crustal material factor with Si as a tracer; (2) a motor vehicle exhaust factor with Pb as a tracer; and (3) a coal combustion factor with Se as a tracer. City-specific analyses also identified a fuel combustion factor (V), a salt factor (Cl), and selected metal factors (Ni, Zn, or Mn). In the original analysis by Laden et al., a GAM Poisson regression model (with default convergence criteria), adjusting for trend/season, day-of-week, and smooth function of temperature/dewpoint, was used to estimate impacts of each source type (using absolute factor scores) simultaneously for each city. In the reanalysis reported by Schwartz (2003a), GAM models with LOESS smoothers were replaced with penalized splines. Summary estimates across cities were obtained by combining the city-specific estimates, using inverse-variance weights. The identified factors and their tracers are listed in Table 8-4. The reanalysis using penalized splines changed somewhat the risk estimates for source-apportioned mass concentrations in each city compared to those in the original GAM results (increasing estimates in some cities and reducing them in others), but the combined estimates across the six cities did not change substantially. The combined estimates indicated that the largest increase in daily mortality was associated with the mobile source associated fine mass concentrations, with an excess risk increase of 9.3% (CI: 4.0, 14.9) per 25 $\mu g/m^3$ source-apportioned $PM_{2.5}$ (average of 0 and 1 day lags). The corresponding value for the $PM_{2.5}$ mass apportioned for the coal combustion factor was 2.0% (CI: −0.3, 4.4). The crustal factor was not associated with mortality (−5.1%; CI: −13.9, 4.6).

Mar et al. (2000) analyzed PM_{10}, $PM_{10-2.5}$, $PM_{2.5}$ measured by two methods, and various sub-components of $PM_{2.5}$ for their associations with total (nonaccidental) and cardiovascular deaths in Phoenix, AZ during 1995-1997, using both individual PM components and factor analysis-derived factor scores. In the original analysis, GAM Poisson models (with default convergence criteria) were used and adjusted for season, temperature, and relative humidity. In the reanalysis (Mar et al., 2003), GAM models with stringent convergence criteria and GLM models with natural splines were used. Only cardiovascular mortality was analyzed in the reanalysis; and the results for that category are summarized here. The evaluated air pollution variables included O_3, SO_2, NO_2, CO, TEOM PM_{10}, TEOM $PM_{2.5}$, TEOM $PM_{10-2.5}$, DFPSS $PM_{2.5}$, S, Zn, Pb, soil, soil-corrected K (KS), nonsoil PM, OC, EC, and TC. Lags 0 to 4 days were

evaluated. A factor analysis conducted on the chemical components of DFPSS $PM_{2.5}$ (Al, Si, S, Ca, Fe, Zn, Mn, Pb, Br, KS, OC, and EC) identified factors for motor vehicle emissions/re-suspended road dust; soil; vegetative burning; local SO_2 sources; and regional sulfate (see Table 8-4). The results of mortality regression with these factors suggested that the motor vehicle factor (lag 1 day), vegetative burning factor (3 day lag), and regional sulfate factor (0 day lag) each had significant positive associations with cardiovascular mortality. The $PM_{2.5}$ mass was not apportioned to these factors in this study; so information on the excess-deaths estimate per source-apportioned $PM_{2.5}$ concentrations was not available. The authors also analyzed elements from dichot $PM_{10-2.5}$ samples and identified soil, coarse fraction metals, and marine influence factors. However, these factors were not analyzed for their associations with mortality outcomes due to the short measurement period (starting in June 1996 with every third-day sampling).

It should be noted here that the Smith et al. (2000) analysis of Phoenix data also included factor analysis on the elements from the coarse fraction and identified essentially the same factors (the "coarse fraction metals" factor in Mar et al.'s study was called "the anthropogenic elements" in Smith et al.'s study). While Smith et al. did not relate these factors to mortality (due to a small sample size), they did show that the anthropogenic elements were low in summer and spring, when the $PM_{10-2.5}$ effect was largest. These results suggest that the $PM_{10-2.5}$ effects may not necessarily be due to anthropogenic components of the coarse particles, biogenically-contaminated coarse particles perhaps being key during the warmer months (as noted in Chapter 7 discussions of bioaerosols).

Tsai et al. (2000) conducted an exploratory analysis of mortality in relation to specific PM source types for three New Jersey cities (Camden, Newark, and Elizabeth) using factor analysis - Poisson regression techniques. During the three-year study period (1981 to 1983), extensive chemical speciation data were available, including nine trace elements, sulfate, and particulate organic matter. Total (excluding accidents and homicides), cardiovascular, and respiratory mortality were analyzed. A factor analysis of trace elements and sulfate was first conducted and identified several major source types: motor vehicle (Pb, CO); geological (Mn, Fe); oil burning (V, Ni); industrial (Zn, Cu); and sulfate/secondary aerosols (sulfate). In addition to Poisson

regression of mortality on these factors, an alternative approach was also used, in which the inhalable particle mass (IPM, $D_{50} < 15$ μm) was first regressed on the factor scores of each of the source types to apportion the PM mass and then the estimated daily PM mass for each source type was included in Poisson regression, so that RR could be calculated per mass concentration basis for each PM source type. Oil burning (V, Ni), various industrial sources (Zn, Cd), motor vehicle (Pb, CO), and secondary aerosols, as well as the individual PM indices IPM, FPM ($D_{50} < 3.5$ μm), and sulfates, were all associated with total and/or cardiorespiratory mortality in Newark and Camden, but not in Elizabeth. In Camden, the RRs for the source-oriented PM were higher (1.10) than those for individual PM indices (1.02).

In summary, these source-oriented factor analyses studies suggest that a number of source types are associated with mortality, including motor vehicle emissions, coal combustion, oil burning, and vegetative burning. The crustal factor from fine particles was not associated with mortality in the Harvard Six Cities data. In Phoenix, where coarse particles were reported to be associated with mortality, the associations between the factors related to coarse particles (soil, marine influence, and anthropogenic elements) and mortality could not be evaluated due to the small sample size. Thus, although unresolved issues do remain (mainly due to the lack of sufficient data), the limited results from the source-oriented evaluation approach (using factor analysis) thus far seem to implicate ambient fine particles of anthropogenic origin from several sources as likely being important in contributing to increased mortality risks.

8.2.2.6 New Assessments of Cause-Specific Mortality

Consistent with similar findings described in the 1996 PM AQCD, most of the newly available studies summarized in Tables 8-1 and 8A-1 that examined nonaccidental total, circulatory, and respiratory mortality categories (e.g., the NMMAPS analyses reported by Samet) have continued to find significant PM associations with both cardiovascular and/or respiratory-cause mortality. Several studies (e.g., Fairley, 1999; his reanalysis, 2003; Wordley et al., 1997; Prescott et al., 1998) reported estimated PM effects that were generally higher for respiratory deaths than for circulatory or total deaths.

The NMMAPS 90-cities analyses not only examined all-cause mortality (excluding accidents), but also evaluated cardiorespiratory and other remaining causes of deaths (Samet et al., 2000a,b; reanalysis by Dominici et al., 2002 and 2003). Results were presented for all-cause, cardiorespiratory, and "other" mortality for lag 0, 1, and 2 days. The investigators commented that, compared to the result for cardiorespiratory deaths showing 1.6% (CI: 0.8, 2.4) increase per 50 $\mu g/m^3 PM_{10}$ in a GLM model (versus 1.1% for total nonaccidental mortality using GLM), there was less evidence for noncardiorespiratory deaths. However, the estimates for "other" mortality, although less than half the size of those for cardiorespiratory mortality, were nevertheless positive, with a fairly high posterior probability (e.g., 0.92 at lag 1 day) that the overall effects were greater than zero. It should be noted that the "other" (other than cardiorespiratory) category for underlying cause of mortality may at times include some deaths influenced by cardiovascular or respiratory causes. For example, Lippmann et al. (2000) noted that the "other" (noncirculatory and nonrespiratory) mortality in their study showed seasonal cycles and apparent influenza peaks, suggesting that this series may have also been influenced by respiratory contributing causes. Thus, interpretation of the observed associations between PM and broad "specific" categories (e.g., other) of underlying causes of death may not be straightforward.

As also mentioned earlier in the multicities results section, Schwartz (2003b) reanalyzed data from Braga et al. (2001a) to examine the lag structure of PM_{10} associations with specific causes of mortality in ten U.S. cities. The pattern of larger PM_{10} excess risk estimates for respiratory categories than for cardiovascular categories found in this study was similar to that in the Hoek et al. analyses noted above. For example, the combined risk estimates across 10 cities per 50 $\mu g/m^3$ increase in PM_{10} (2-day mean) were 4.1% (CI: 2.5, 5.6), 7.7% (CI: 4.1, 11.5), and 11.0% (CI: 7, 15.1) for cardiovascular, COPD, and pneumonia, respectively, using GAM with stringent convergence criteria. These values were even larger for unconstrained distributed lag models.

Another U.S. study, that of Moolgavkar (2000a), evaluated possible PM effects on cause-specific mortality across a broad range of lag times (0-5 days) in Cook Co., IL; Los Angeles Co., CA; and Maricopa Co., AZ. In addition to total nonaccidental mortality, deaths related to all

cardiovascular disease (CVD), cerebrovascular disease (CRV), and chronic obstructive lung disease (COPD) were analyzed in the original study. The data for Cook Co. and Maricopa Co. were reanalyzed using GAM model with stringent convergence criteria and GLM model with natural splines (Moolgavkar, 2003). Cerebrovascular disease mortality was not reanalyzed because there was little evidence of association for PM with this category at any lag in any of the three counties analyzed. Moolgavkar reported varying patterns of results for PM indices in evaluations of daily deaths related to CVD and COPD in the two counties. In the Cook Co. (Chicago) area, the association of PM_{10} with CVD mortality was statistically significant at a lag of 3 days based on a single-pollutant analysis and continued to be significantly associated with CVD deaths with a 3-day lag in two pollutant models including one or another of CO, NO_2, SO_2, or O_3. In Los Angeles single-pollutant analyses, CVD mortality was significantly associated with PM_{10} (2 day lag) and $PM_{2.5}$ (0 and 1 day lag). Their percent excess risk estimates were up to twice those for total nonaccidental mortality. In a two-pollutant model with CO (most strongly positively associated with mortality in Los Angeles Co. among the pollutants), PM_{10} risk estimates were reduced. However, $PM_{2.5}$ excess risk estimates in the two-pollutant model with CO nearly doubled (2.5% per 25 $\mu g/m^3$ increase in $PM_{2.5}$ to 4.8% using GLM); whereas that for CO became significantly negative. Obviously, given that CO and $PM_{2.5}$ were fairly well correlated ($r \approx 0.58$), the estimated associations were most likely confounded between these two pollutants in this locale. With regard to COPD deaths, PM_{10} was significantly associated with COPD mortality (lag 2 days) in Cook Co., but in Los Angeles Co., both PM_{10} and (especially) $PM_{2.5}$ showed erratic associations with COPD mortality at varying lags, alternating positive and negative (significantly, at lag 3 day) coefficients. The combination of the every sixth day PM data in Los Angeles (versus daily PM_{10} in Cook Co.) and relatively small daily counts for COPD (median = 6/day versus 57/day for CVD) in Los Angeles makes the effective sample size of COPD mortality analysis small and the results unstable for that county.

The Goldberg et al. (2000; 2001a,b,c,d) study, and its reanalyses (Goldberg et al., 2003; Goldberg and Burnett, 2003) in Montreal, CN, investigated the role of comorbidity prior to deaths in PM-mortality associations for various subcategories, including cancer, acute lower respiratory disease, chronic coronary artery disease, and congestive heart failure (CHF). They

could classify deaths into these subcategories using medical records from the universal Quebec Health Insurance Plan (QHIP). This way of classifying deaths would presumably take into account more detailed information on the disease condition prior to death than the "underlying cause" in the death records. Thus, the PM-mortality associations could be compared by using subcategories defined by underlying cause of health (from death records versus those deaths for which patient records from QHIP could be used to identify the comorbidity conditions). The Goldberg and Burnett (2003) reanalysis found that total nonaccidental mortality (which was significantly associated with PM indices in the original report using GAM with default convergence criteria) was not associated with PM indices in GLM models. They reported that the associations between PM and nonaccidental mortality were rather sensitive to weather model specification and did not find significant PM associations with most of the subcategories as defined from either QHIP or underlying cause. However, they did find significant associations between CoH, NO_2, and SO_2 and the CHF deaths as defined from QHIP, but not the CHF deaths as defined from underlying cause. The association was even stronger in warm seasons. It should be noted, however, that while the period for this study was relatively long (~10 years) and the counts for the total nonaccidental deaths were not small (median = 36 deaths per day), the counts for various subcategories were quite small (e.g., CHF underlying cause mortality mean = 0.75 per day).

Zmirou et al. (1998) presented cause-specific mortality analyses results for 10 of the 12 APHEA European cities (APHEA1). Using Poisson autoregressive models parametrically adjusting for trend, season, influenza epidemics, and weather, each pollutant's relative risk was estimated for each city and "meta-analyses" of city-specific estimates were conducted. The pooled excess risk estimates for cardiovascular mortality were 1.0% (CI: 0.3, 1.7) per 25 $\mu g/m^3$increase in BS and 2.0% (CI: 0.5, 3.0) per 50 $\mu g/m^3$increase in SO_2 in western European cities. The pooled risk estimates for respiratory mortality in the same cities were 2.0% (CI: 0.8, 3.2) and 2.5% (CI: 1.5, 3.4) for BS and SO_2, respectively.

Seeking unique cause-specificity of effects associated with various pollutants has been difficult because the "cause specific" categories examined are typically rather broad (usually cardiovascular and respiratory) and overlap and because cardiovascular and respiratory

conditions tend to occur together. Examinations of more specific cardiovascular and respiratory subcategories may be necessary to test hypotheses about any specific mechanisms, but smaller sample sizes for more specific sub-categories may make a meaningful analysis difficult. The Hoek et al. (2000 and 2001) study and its reanalysis by Hoek (2003) took advantage of a larger sample size to examine cause-specific mortality. The large sample size, including the whole population of the Netherlands (mean daily total deaths ~330, or more than twice that of Los Angeles County), allowed examination of specific cardiovascular causes of deaths. The reanalysis using GAM with stringent convergence criteria as well as GLM with natural splines either did not change or even increased the effect estimates. Deaths due to heart failure, arrhythmia, and cerebrovascular causes were more strongly (~2 to 4 times larger excess risks) associated with air pollution than the overall cardiovascular deaths. The investigators concluded that specific cardiovascular causes (such as heart failure) were more strongly associated with air pollution than total cardiovascular mortality, but noted that the largest contribution to the association between air pollution and cardiovascular mortality was from ischemic heart disease (about half of all CVD deaths). The analyses of specific respiratory causes, COPD, and pneumonia yielded even larger risk estimates (e.g., ~6 to 10 times, respectively, larger than that for overall cardiovascular deaths). Estimated PM_{10} excess risks per 50 $\mu g/m^3$ PM_{10} (average of 0 through 6 day lags) were 1.2% (CI: 0.2, 2.3), 0.9% (CI: −0.8, 2.7), 2.7% (CI: −4.2, 10.1), 2.4% (CI: −2.3, 7.4), 6.1% (CI: 1, 11.4), and 10.3% (CI: 3.7, 17.2), respectively, for total nonaccidental, cardiovascular, arrhythmia, heart failure, COPD, and pneumonia, using GAM models with stringent convergence criteria. Thus, the results from this study with a large effective sample size also confirm past observations that PM risk estimates for specific causes of cardiovascular or respiratory mortality can be larger than those estimated for total nonaccidental mortality.

Another study (Gouveia and Fletcher, 2000), using data from Sao Paulo, Brazil for 1991-1993, evaluated respiratory mortality in children (age ≤ 5 years). The Poisson auto-regressive model included parametric terms (e.g., quadratic, two-piece linear temperature etc.) to adjust for weather and temporal trends. Although Gouveia and Fletcher found significant associations between air pollution and elderly mortality, they did not find statistically significant

associations between air pollution and child respiratory mortality (the PM_{10} coefficient was negative and not significant). However, it should be noted that the average daily respiratory mortality counts for this study were relatively small (~2.4/day) and the modest period of observations (3 years) short. Thus, the statistical power of the data was likely less than desirable, and there may not have been sufficient power to elucidate the range of short-term PM effects on child respiratory mortality.

Overall, then, the above assessment of newly available studies provides interesting additional new information with regard to cause-specific mortality related to ambient PM. That is, a growing number of studies continue to report increased cardiovascular- and respiratory-related mortality risks as being significantly associated with ambient PM measures at one or another varying lag times. When specific subcategories of cardiovascular disease were examined in a large population (e.g., in the Netherlands study by Hoek et al.), some of the subcategories such as heart failure were more strongly associated with PM and other pollutants than total cardiovascular mortality. Largest PM effect size estimates are most usually reported for 0-1 day lags (with some studies also now noting a second peak at 3-4 day lags). A few of the newer studies also report associations of PM metrics with "other" (i.e., noncardiorespiratory) causes, as well. However, at least some of these "other" associations may also be due to seasonal cycles that include relationships to peaks in influenza epidemics that may imply respiratory complications as a contributing cause to the "other" deaths. Alternately, the "other" category may include sufficient numbers of deaths due to diabetes or other diseases which may also involve cardiovascular complications as contributing causes. Varying degrees of robustness of PM effects are seen in the newer studies, as typified by PM estimates in multiple pollutant models containing gaseous co-pollutants. That is, some studies show little effect of gaseous pollutant inclusion on estimated PM effect sizes, some show larger reductions in PM effects to nonsignificant levels upon such inclusion, and a number also report significant associations of cardiovascular and respiratory effects with one or more gaseous co-pollutants. Thus, the newer studies both further substantiate PM effects on cardiovascular- and respiratory-related mortality, while also pointing toward possible significant contributions of gaseous pollutants to such cause-

specific mortality. The magnitudes of the PM effect size estimates are consistent with the range of estimates derived from the few earlier available studies assessed in the 1996 PM AQCD.

8.2.2.7 Salient Points Derived from Assessment of Studies of Short-Term Particulate Matter Exposure Effects on Mortality

The most salient key points to be extracted from the above discussion of newly available information on short-term PM exposures relationships to mortality can be summarized as follow:

PM_{10} effects estimates. Since the 1996 PM AQCD, there have been more than 80 new time-series PM-mortality analyses published. Estimated mortality relative risks in these studies are generally positive, statistically significant, and consistent with the previously reported PM-mortality associations. However, due to the concerns regarding the GAM convergence issue, quantitative evaluations were made here based only on the studies that either did not use GAM Poisson model with default convergence criteria or on those studies that have reanalyzed the data using more stringent convergence criteria and/or used fully parametric approaches.

Of interest are several studies that evaluated multiple cities using consistent data analytical approaches. The NMMAPS analyses for the largest 90 U.S. cities (Samet et al., 2000a,b; Dominici et al., 2002 and 2003b) derived a combined nationwide excess risk estimate of about 1.4% (1.1% using GLM) increase in total (nonaccidental) mortality per 50 $\mu g/m^3$increase in PM_{10}. Other well-conducted multicity analyses, as well as various single city analyses, obtained larger PM_{10}-effect size estimates for total nonaccidental mortality, generally falling in the range of 2 to 3.5% per 50 $\mu g/m^3$increase in PM_{10}. These estimates are consistent with and overlap the lower end of the range of PM_{10} risk estimates given in the 1996 PM AQCD. However, somewhat more geographic heterogeneity is evident among the newer multicity study results than was the case among the few studies assessed in the 1996 PM AQCD. In the NMMAPS analysis of the 90 largest U.S. cities data, for example, the risk estimates varied by U.S. geographic region, with the estimate for the Northeast being the largest (approximately twice the nation-wide estimate). The observed heterogeneity in the estimated PM risks across cities/regions could not be explained by city-specific explanatory variables, such as mean levels of pollution and weather, mortality rate, sociodemographic variables (e.g., median household income), urbanization, or variables related to measurement error. Notable apparent

heterogeneity was also seen among effects estimates for PM (and SO_2) indices in the multicity APHEA studies conducted in European cities. In APHEA2, they found that several city-specific characteristics, such as NO_2 levels and warm climate, were important effect modifiers. The issue of heterogeneity of effect estimates is discussed further in Section 8.4.

Model specification Issue: The investigations of the GAM convergence issue also led to examination of the sensitivity of the PM risk estimates to different model specifications. Of particular importance is the reemergence of model specification issues related to control for weather effects with results of reanalyses highlighting the sensitivity of modeling outcomes to kinds and numbers of weather-related variables included in base models. Related to this, several reanalyses also examined the sensitivity of results to varying the degrees of freedom for smoothing of weather and temporal trends. PM risk estimates were often reduced when more degrees of freedom were given to model temporal trends. While at present there is no consensus as to what constitutes an "adequate" extent of smoothing (from an epidemiologic viewpoint), the overall assessment of PM risk estimates should take into consideration the range of sensitivity of results to this aspect of model specification.

*Confounding and effect modification by other pollutant*s. Numerous new short-term PM exposure studies not only continue to report significant associations between various PM indices and mortality, but also between gaseous pollutants (O_3, SO_2, NO_2, and CO) and mortality. In most of these studies, simultaneous inclusions of gaseous pollutants in the regression models did not meaningfully affect the PM-effect size estimates. This was the case for the NMMAPS 90 cities study with regard to the overall combined U.S. regional and nationwide risk estimates derived for that study. The issue of confounding is discussed further in Section 8.4.

*Fine and coarse particle effect*s. Newly available studies provide generally positive (and often statistically significant) $PM_{2.5}$ associations with mortality, with effect size estimates falling in the range reported in the 1996 PM AQCD. New results from Germany appear to implicate both ultrafine (nuclei-mode) and accumulation-mode fractions of urban ambient fine PM as being important contributors to increased mortality risks. As to the relative importance of fine and coarse particles, in the 1996 PM AQCD there was only one acute mortality study (Schwartz et al., 1996a) that examined this issue. The results of that study of six U.S. cities suggested that

fine particles ($PM_{2.5}$), were associated with daily mortality, but not coarse particles ($PM_{10-2.5}$), except for in Steubenville, OH.. Now, eight studies have analyzed both $PM_{2.5}$ and $PM_{10-2.5}$ for their associations with mortality. While the results from some of these new studies (e.g., the Santa Clara County, CA analysis [Fairley, 1999]) did suggest that $PM_{2.5}$ was more important than $PM_{10-2.5}$ in predicting mortality fluctuations, other studies (e.g., Phoenix, AZ analyses [Clyde et al., 2000; Mar et al., 2000; Smith et al., 2000]) suggest that $PM_{10-2.5}$ may also be important in at least some locations. Seasonal dependence of size-related PM component effects observed in some of the studies complicates interpretations.

Chemical components of PM. Several new studies have examined the role of specific chemical components of PM. The studies conducted in U.S., Canadian, and European cities showed mortality associations with specific fine particle components of PM, including sulfate, nitrate, and CoH; but their relative importance varied from city to city, likely depending on their levels (e.g., no clear associations in those cities where H^+ and sulfate levels were very low, i.e., circa nondetection limits). The results of several studies that investigated the role of crustal particles, although somewhat mixed, overall do not appear to support associations between crustal particles and mortality (see also the discussion, below, of source-oriented evaluations).

*Source-oriented evaluation*s. Several studies conducted source-oriented evaluations of PM components using factor analysis. The results from these studies generally indicated that several combustion-related fine particle source-types are likely associated with mortality, including motor vehicle emissions, coal combustion, oil burning, and vegetative burning. The crustal factor from fine particles was not associated with total nonaccidental mortality in the Harvard Six Cities data, and the soil (i.e., crustal) factor from fine particles in the Phoenix data was not associated with cardiovascular mortality. Thus, the results of source-oriented evaluations most clearly appear to implicate fine particles of anthropogenic origin as being important in contributing to increased mortality, but not short-term exposures to crustal materials in U.S. ambient environments.

Cause-specific mortality. Findings for new results concerning cause-specific mortality comport well with those for total (nonaccidental) mortality, the former showing generally larger effect size estimates for cardiovascular, respiratory, and/or combined cardiorespiratory excess

risks than for total mortality risks. An analysis of specific cardiovascular causes in a large population (The Netherlands) suggested that specific causes of deaths (such as heart failure) were more strongly associated with ambient PM (and other pollutants) than total cardiovascular mortality.

Lags. In general, maximum effect sizes for total mortality appear to be obtained with 0-1 day lags, with some studies indicating a second peak for 3-4 days lags. There is also some evidence that, if effects distributed over multiple lag days are considered, the effect size may be larger than for any single maximum-effect-size lag day. Lags are discussed further in Section 8.4.

Threshold. Few new short-term mortality studies explicitly address the issue of thresholds. One study that analyzed Phoenix, AZ data (Smith et al., 2000) did report some limited evidence suggestive of a possible threshold for $PM_{2.5}$. Also, several different analyses of larger PM_{10} data sets across multiple cities (Dominici, et al., 2002; Daniels et al., 2000; and reanalysis by Dominici et al., 2003a) generally provide only limited, if any, support to indicate a threshold for PM_{10} mortality effects. Threshold issues are discussed further in Section 8.4.

8.2.3 Mortality Effects of Long-Term Exposure to Ambient Particulate Matter

8.2.3.1 Studies Published Prior to the 1996 Particulate Matter Criteria Document

8.2.3.1.1 Aggregate Population Cross-Sectional Chronic Exposure Studies

Mortality effects associated with chronic, long-term exposure to ambient PM have been evaluated in cross-sectional studies and, more recently, in prospective cohort studies. A number of older cross-sectional studies from the 1970s provided indications of increased mortality associated with chronic (annual average) exposures to ambient PM, especially with respect to fine mass or sulfate (SO_4^{2-}) concentrations. These cross-sectional studies were discussed in detail in Section 12.4.1.2 of the 1996 PM AQCD. However, questions unresolved at the time regarding the adequacy of statistical adjustments for other potentially important covariates (e.g., cigarette smoking, economic status, etc.) across cities tended to limit the degree of confidence that was placed by the 1996 PM AQCD (U.S. Environmental Protection Agency, 1996a) on such purely "ecological" studies or on quantitative estimates of PM effects derived from them.

Evidence comparing the toxicities of specific PM components was relatively limited, although the sulfate and acid components were discussed in detail in the 1986 PM AQCD.

8.2.3.1.2 Prospective Cohort Chronic Exposure Studies

Prospective cohort studies of mortality associated with chronic exposures to air pollution of outdoor origins have yielded especially valuable insights into the adverse health effects of long-term PM exposures. Such cohort studies using subject-specific information about relevant covariates (such as cigarette smoking, occupation, etc.) typically are capable of providing more certain findings of long-term PM exposure effects than are purely "ecological studies" (Künzli and Tager, 1997). The new, better designed cohort studies, as discussed below, have largely confirmed the magnitude of PM effect estimates derived from past cross-sectional studies.

The extensive Harvard Six-Cities Study (Dockery et al., 1993) and the initial American Cancer Society (ACS) Study (Pope et al., 1995) agreed in their findings of statistically significant positive associations between fine particles and excess mortality, although the ACS study did not evaluate the possible contributions of other air pollutants. Neither study considered multipollutant models, although the Six-City study did examine various PM and gaseous pollutant indices (including total particles, $PM_{2.5}$, SO_4^{2-}, H^+, SO_2, and O_3) and found that sulfate and $PM_{2.5}$ fine particles were most strongly associated with mortality. The excess RR estimates originally reported for total mortality in the Six-Cities study (and 95 percent confidence intervals, CI) per increments in PM indicator levels were: Excess RR = 18% (CI: 6.8%, 32%) for 20 $\mu g/m^3$ PM_{10}; excess RR = 13.0% (CI: 4.2%, 23%) for 10 $\mu g/m^3$ $PM_{2.5}$; and excess RR = 13.4% (CI: 5.1%, 29%) for 5 $\mu g/m^3$ SO_4^{2-}. The estimates for total mortality derived from the ACS study were excess RR = 6.6% (CI: 3.5%, 9.8%) for 10 $\mu g/m^3$ $PM_{2.5}$ and excess RR 3.5% (CI: 1.9%, 5.1%) for 5 $\mu g/m^3$ SO_4^{2-}. The ACS pollutant RR estimates were smaller than those from the Six-Cities study, although their 95% confidence intervals overlap.

In some cases in these studies, the life-long cumulative exposure of the study cohorts included distinctly higher past PM exposures, especially in cities with historically higher PM levels (e.g., Steubenville, OH); but more current PM measurements were used to help estimate the chronic PM exposures. In the ACS study, the pollutant exposure estimates were based on

concentrations at the start of the study (during 1979-1983). In addition, the average age of the ACS cohort was 56, which could overestimate the pollutant RR estimates and perhaps underestimate the life-shortening associated with PM associated mortality. Still, although caution must be exercised regarding use of the reported quantitative risk estimates, the Six-Cities and ACS prospective cohort studies provided consistent evidence of significant mortality associations with long-term exposure to ambient PM.

The Six-Cities cohort was preselected by the investigators to be a representative population for the U.S. midwest / eastern regions of the country heavily-impacted by both coal combustion and motor vehicle effluents. By contrast, the ACS study cohort was drawn from a large pool of volunteers who happened to live in communities where several years of fine particle and/or sulfate ambient air concentration data were available. It is important to note that the ACS had a relatively small proportion of people with less than high school education (12% versus 28% for Six-Cities) and, by inference, better diets and access to good health care than an average U.S. population. To the extent that the mortality impact is lower in the better educated portion of the population, the mortality experience of the ACS cohort likely provides an underestimate for the U.S. population as a whole.

In contrast to the Six-Cities and ACS studies, early results reported by Abbey et al. (1991) and Abbey et al. (1995a) from another prospective cohort study, the Adventist Health Study on Smog (AHSMOG), reported no significant mortality effects of previous PM exposure in a relatively young cohort of California nonsmokers. However, these analyses used TSP as the PM exposure metric, rather than more health-relevant PM metrics such as PM_{10} or $PM_{2.5}$, included fewer subjects than the ACS study, and considered a shorter follow-up time than the Six-Cities study (ten years versus 15 years for the Six-Cities study). Further, the AHSMOG study included only nonsmokers (indicated by the Six-Cities Study as having lower pollutant RR's than smokers), suggesting that a longer follow-up time than considered in the past (10 years) might be required to have sufficient power to detect significant pollution effects than would be needed in studies that include smokers (such as the Six-Cities and ACS studies). Thus, greater emphasis was placed in the 1996 PM AQCD on the results of the Six-Cities and ACS studies.

Overall, the previously available chronic PM exposure studies collectively indicated that increases in mortality are associated with long-term exposure to ambient airborne particles; and effect size estimates for total mortality associated with chronic PM exposure indices appeared to be much larger than those reported from daily mortality PM studies. This suggested that a major fraction of the reported mortality relative risk estimates associated with chronic PM exposure likely reflects cumulative PM effects above and beyond those exerted by the sum of acute exposure events (i.e., assuming that the latter are fully additive over time). The 1996 PM AQCD (Chapter 12) reached several conclusions concerning four key questions about the prospective cohort studies, as noted below:

(1) Have potentially important confounding variables been omitted?

> "While it is not likely that the prospective cohort studies have overlooked plausible confounding factors that can account for the large effects attributed to air pollution, there may be some further adjustments in the estimated magnitude of these effects as individual and community risk factors are included in the analyses." These include individual variables such as education, occupational exposure to dust and fumes, and physical activity, as well as ecological (community) variables such as regional location, migration, and income distribution. Further refinement of the effects of smoking status may also prove useful."

(2) Can the most important pollutant species be identified?

> "The issue of confounding with co-pollutants has not been resolved for the prospective cohort studies . . . Analytical strategies that could have allowed greater separation of air pollutant effects have not yet been applied to the prospective cohort studies." The ability to separate the effects of different pollutants, each measured as a long-term average on a community basis, was clearly most limited in the Six Cities study. The ACS study offered a much larger number of cities, but did not examine differences attributable to the spatial and temporal differences in the mix of particles and gaseous pollutants across the cities. The AHSMOG study constructed time- and location-dependent pollution metrics for most of its participants that might have allowed such analyses, but no results were reported.

(3) Can the time scales for long-term exposure effects be evaluated?

> "Careful review of the published studies indicated a lack of attention to this issue. Long-term mortality studies have the potential to infer temporal relationships based on characterization of changes in pollution levels over time. This potential was greater in the Six Cities and AHSMOG studies because of the greater length of the historical air pollution data for the cohort [and the availability of air pollution data throughout the study]. The chronic exposure studies, taken together, suggest that

there may be increases in mortality in disease categories that are consistent with long-term exposure to airborne particles, and that at least some fraction of these deaths are likely to occur between acute exposure episodes. If this interpretation is correct, then at least some individuals may experience some years of reduction of life as a consequence of PM exposure."

(4) Is it possible to identify pollutant thresholds that might be helpful in health assessments?

"Model specification searches for thresholds have not been reported for prospective cohort studies. . . . Measurement error in pollution variables also complicates the search for potential threshold effects. . . . The problems that complicate threshold detection in the population-based studies have a somewhat different character for the long-term studies."

8.2.3.2 New Prospective Cohort Analyses of Mortality Related to Chronic Particulate Matter Exposures

Considerable further progress has been made towards addressing the above issues. As an example, extensive reanalyses (Krewski et al., 2000) of the Six-Cities and ACS studies (sponsored by HEI) indicate that the published findings of the original investigators (Dockery et al., 1993; Pope et al., 1995) are based on substantially valid data sets and statistical analyses. The HEI reanalysis project demonstrated that small corrections in input data have very little effect on the findings and that alternative model specifications further substantiate the robustness of the originally reported findings. In addition, some of the above key questions have been further investigated by Krewski et al. (2000) via sensitivity analyses (in effect, new analyses) for the Six City and ACS studies data sets, including consideration of a much wider range of confounding variables. Newly published analyses of ACS data for more extended time periods (Pope et al., 2002) further substantiate original findings and also provide much clearer, stronger evidence for ambient PM exposure relationships with increased lung cancer risk. Newer published analyses of AHSMOG data (Abbey et al., 1999; Beeson et al., 1998) also extend the AHSMOG findings and show some analytic outcomes different from earlier analyses reported out from the study. Results from the Veterans' Administration- Washington University (hereafter called "VA") prospective cohort study are also now available (Lipfert et al., 2000b).

8.2.3.2.1 Health Effects Institute Reanalyses of the Six-Cities and ACS Studies

The overall objective of the HEI "Particle Epidemiology Reanalysis Project" was to conduct a rigorous and independent assessment of the findings of the Six Cities (Dockery et al., 1993) and ACS (Pope et al., 1995) studies of air pollution and mortality. The following description of approach, key results, and conclusions is largely extracted from the Executive Summary of the HEI final report (Krewski et al., 2000). The HEI-sponsored reanalysis effort was approached in two steps:

- *Part I: Replication and Validation*. The Reanalysis Team sought to test (a) whether the original studies could be replicated via a quality assurance audit of a sample of the original data and (b) whether the original numeric results could be validated.
- *Part II: Sensitivity Analyses*. The Reanalysis Team tested the robustness of the original analyses to alternate risk models and analytic approaches.

The Part I audit of the study population data for both the Six Cities and ACS studies and of the air quality data in the Six Cities Study revealed that data were of generally high quality with few exceptions. In both studies, a few errors were found in the data coding for and exclusion of certain subjects; but when those subjects were included in the analyses, they did not materially change the results from those originally reported. Because the air quality data used in the ACS Study could not be audited, a separate air quality database was constructed for the sensitivity analyses in Part II.

The Reanalysis Team was able to replicate the original results for both studies using the same data and statistical methods as used by the original investigators, as shown in Table 8-5. The Reanalysis Team confirmed the original point estimates. For the Six Cities Study, they reported the excess relative risk of mortality from all causes associated with an increase in fine particles of 10 $\mu g/m^3$ to be 14%, close to the 13% reported by the original investigators. For the ACS Study, they reported the relative risk of all-cause mortality associated with a 10 $\mu g/m^3$ increase in fine particles to be 7.0% in the reanalysis, close to the original 6.6% value.

The Part II sensitivity analysis applied an array of different models and variables to determine whether the original results would remain robust to different analytic assumptions and model specifications. The Reanalysis Team first applied the standard Cox model used by the original investigators and included variables in the model for which data were available from

TABLE 8-5. COMPARISON OF SIX CITIES AND AMERICAN CANCER SOCIETY (ACS) STUDY FINDINGS FROM ORIGINAL INVESTIGATORS AND HEALTH EFFECTS INSTITUTE REANALYSIS

Type of Health Effect & Location	Indicator	Mortality Risk per Increment in PM [a]	
Original Investigators' Findings		**Total Mortality Excess Relative Risk (95% CI)**	**Cardiopulmonary Mortality Excess Relative Risk (95% CI)**
Six City [b]	$PM_{2.5}$	13% (4.2%, 23%)	18% (6.0%, 32%)
Six City [b]	$PM_{15/10}$	18% (6.8%, 32%)	e
ACS Study [c]	$PM_{2.5}$	6.6% (3.5%, 9.8%)	12% (6.7%, 17%)
HEI reanalysis Phase I: Replication			
Six City Reanalysis [d]	$PM_{2.5}$	14% (5.4%, 23%)	19% (6.5%, 33%)
	PM_{15}	19% (6.1%, 34%)	20% (2.9%, 41%)
ACS Study Reanalysis [d]	$PM_{2.5}$	7.0% (3.9%, 10%)	12% (7.4%, 17%)
	PM_{15} (dichot)	4.1% (0.9%, 7.4%)	7.3% (3.0%, 12%)
	PM_{15} (SSI)	1.6% (−0.8%, 4.1%)	5.7% (2.5%, 9.0%)

[a] Estimates calculated on the basis of differences between the most-polluted and least-polluted cities, scaled to increments of 20 μg/m^3 increase for PM_{10} and 10 μg/m^3 increments for PM_{15} and $PM_{2.5}$.
[b] Dockery et al. (1993).
[c] Pope et al. (1995).
[d] Krewski et al. (2000).
[e] Results presented only by smoking category subgroup.

both original studies, but had not been used in the published analyses (e.g., physical activity, lung function, marital status). The Reanalysis Team also designed models to include interactions between variables. None of these alternative models produced results that materially altered the original findings.

Next, for both the Six Cities and ACS studies, the Reanalysis Team investigated the possible effects of fine particles and sulfate on a range of potentially susceptible subgroups of the population. These analyses did not find differences in PM-mortality associations among subgroups based on various personal characteristics (e.g., including gender, marital status, smoking status, and exposure to occupational dusts and fumes). However, estimated effects of

fine particles did vary with educational level: the association between an increase in fine particles and mortality tended to be higher for individuals without a high school education than for those with more education. The Reanalysis Team postulated that this finding could be attributable to some unidentified socioeconomic effect modifier. The authors concluded "The Reanalysis Team found little evidence that questionnaire variables had led to confounding in either study, thereby strengthening the conclusion that the observed association between fine particle air pollution and mortality was not the result of a critical covariate that had been neglected by the Original Investigators." (Krewski et al., 2000, pp. 219-220).

In the ACS Study, the Reanalysis Team tested whether the relationship between ambient concentrations and mortality was linear. They found some indications of both linear and nonlinear relationships, depending upon the analytic technique used, suggesting that the shapes of the concentration-response relationships warrant additional research in the future.

One of the criticisms of both original studies has been that neither analyzed the effects of change in pollutant levels over time. In the Six Cities Study, for which such data were available, the Reanalysis Team tested whether effect estimates changed when certain key risk factors (smoking, body mass index, and air pollution) were allowed to vary over time. In general, the reanalysis results did not change when smoking and body mass index were allowed to vary over time. The Reanalysis Team did find for the Six Cities Study, however, that when the general decline in fine particle levels over the monitoring period was included as a time-dependent variable, the association between fine particles and all-cause mortality was reduced (Excess RR = 10.4% (CI: 1.5, 20). This would be expected, because the most polluted cities would likely have the greatest decline as pollution controls were applied, and it is likely indicative of the effectiveness of control measures in reducing source emissions importantly contributing to the toxicity of ambient PM in those cities. Despite this adjustment, the $PM_{2.5}$ effect estimate continued to be positive and statistically significant.

To test the validity of the original ACS air quality data, the Reanalysis Team constructed and applied its own air quality dataset from available historical data. In particular, sulfate levels with and without adjustment were found to differ by about 10% for the Six Cities Study. Both the original ACS Study air quality data and the newly constructed data set contained sulfate

levels inflated by 50% due to artifactual sulfate. For the Six Cities Study, the relative risks of mortality were essentially unchanged with adjusted or unadjusted sulfate. For the ACS Study, adjusting for artifactual sulfate resulted in slightly higher relative risks of all-cause mortality and from cardiopulmonary disease compared with unadjusted data, while the relative risk of mortality from lung cancer was lower after the data had been adjusted. Thus, the Reanalysis Team found essentially the same results as the original Harvard Six-Cities and ACS studies, even after using independently developed pollution data sets and adjusting for sulfate artifact.

Because of the limited statistical power to conduct most model specification sensitivity analyses for the Six Cities Study, the Reanalysis Team conducted most of its sensitivity analyses using only the ACS Study data set that considered 151 cities. When a range of city-level (ecologic) variables (e.g., population change, measures of income, maximum temperature, number of hospital beds, water hardness) were included in the analyses, the results generally did not change. The only exception was that associations with fine particles and sulfate were reduced when city-level measures of population change or SO_2 were included in the model.

A major product of the Reanalysis Project is the determination that both pollutant variables and mortality appear to be spatially correlated in the ACS Study data set. If not identified and modeled correctly, spatial correlation could cause substantial errors in both the regression coefficients and their standard errors. The Reanalysis Team identified several methods for addressing this, each of which resulted in some reduction in the estimated regression coefficients. The full implications and interpretations of spatial correlations in these analyses have not been resolved and were noted to be an important subject for future research.

When the Reanalysis Team sought to take into account both underlying variation from city to city (random effects) and variation from the spatial correlation between cities, positive associations were still found between mortality and sulfates or fine particles. Results of various models, using alternative methods to address spatial autocorrelation and including different ecologic covariates, found fine particle-mortality associations that ranged from 1.11 to 1.29 (the RR reported by original investigators was 1.17) per 24.5 $\mu g/m^3$ increase in $PM_{2.5}$. With the exception of SO_2, consideration of other pollutants in these models did not alter the associations found with sulfates. The authors reported stronger associations for SO_2 than for sulfate, which

suggests that artifactual sulfate was "picking up" some of the SO_2 association, perhaps because the sulfate artifact is in part proportional to the prevailing SO_2 concentration (Coutant, 1977). The Reanalysis Team did not use data adjusted for artifactual sulfate for most alternative analyses. When they did use adjusted sulfate data, relative risks of mortality from all causes and cardiopulmonary disease increased. This suggests that more analyses with adjusted sulfate might result in somewhat higher relative risks for sulfate. The Reanalysis Team concluded:

> "it suggests that uncontrolled spatial autocorrelation accounts for 24% to 64% of the observed relation. Nonetheless, all our models continued to show an association between elevated risks of mortality and exposure to airborne sulfate" (Krewski et al., 2000, p. 230).

In summary, the reanalyses generally confirmed the original investigators' findings of associations between mortality and long-term exposure to PM, while recognizing that increased mortality may be attributable to more than one ambient air pollution component. Regarding the validity of the published Harvard Six-Cities and ACS studies, the HEI Reanalysis Report concluded that "Overall, the reanalyses assured the quality of the original data, replicated the original results, and tested those results against alternative risk models and analytic approaches without substantively altering the original findings of an association between indicators of particulate matter air pollution and mortality."

Villeneuve et al. (2002) used Poisson regression models in further analyses of the Harvard Six City study cohort to evaluate relationships between fixed-in-time and time-dependent measures of $PM_{2.5}$ and the risk of mortality among adult, Caucasian participants. The RR of mortality using the Poisson method based upon city-specific exposures that remained constant during the follow up was 1.31 (CI: 1.12, 1.52), similar to results derived from the Cox model used in the original analysis. However, the authors report that the RR of mortality due to $PM_{2.5}$ exposure decreased when time-dependent measures of air pollution were modeled (Table 8-6). Specifically, when the mean $PM_{2.5}$ level within each city during each period of follow-up was modeled, the RR was 1.16 (CI: 1.02, 1.32). The authors noted that "there were considerable variations in mortality rates across the calendar periods that were modeled," and that "the

TABLE 8-6. RELATIVE RISK[a] OF ALL-CAUSE MORTALITY FOR SELECTED INDICES OF EXPOSURE TO FINE PARTICULATE MATTER (per 18.6 μg/m^3) BASED ON MULTIVARIATE POISSON REGRESSION ANALYSIS, BY AGE GROUP, FOR HARVARD SIX CITY STUDY DATA [b]

		Age Group (years)		
Model	**$PM_{2.5}$ Exposure City Specific Index**	**Total**	**< 60**	**≥ 60**
1	Exposure to $PM_{2.5}$ remained fixed over the entire follow up period.	1.31 (1.12 – 1.52)	1.89 (1.32 – 2.69)	1.21 (1.02 – 1.43)
2	Exposure to $PM_{2.5}$ defined according to 13 calendar periods (no smoothing). [a]	1.19 (1.04 – 1.36)	1.52 (1.15 – 2.00)	1.11 (0.95 – 1.29)
3	Exposure to $PM_{2.5}$ defined according to 13 calendar periods (smoothed). [b]	1.16 (1.02 – 1.32)	1.43 (1.10 – 1.85)	1.09 (0.93 – 1.26)
4	Time dependent estimate of $PM_{2.5}$ received during the previous two years.	1.16 (1.02 – 1.31)	1.42 (1.09 – 1.82)	1.08 (0.94 – 1.25)
5	Time dependent estimate of $PM_{2.5}$ received 3 - 5 years before current year.	1.14 (1.02 – 1.27)	1.35 (1.08 – 1.87)	1.08 (0.95 – 1.22)
6	Time dependent estimate of $PM_{2.5}$ received > 5 years before current year.	1.14 (1.05 – 1.23)	1.34 (1.11 – 1.59)	1.09 (0.99 – 1.20)

[a] Relative risks were adjusted by age, gender, body mass, index, education, number of years smoked (at baseline), occupational exposures and number of cigarettes smoked weekly.
[b] For each city, exposure to $PM_{2.5}$ was estimated for 13 calendar periods using loglinear regression based on annual mean $PM_{2.5}$ levels. The calendar periods used were: 1970-1978, 1979, 1981, . . . 1989, and 1990+. $PM_{2.5}$ associations with all-cause mortality assessed for male Caucasian participants in Six Cities Study.

Source: Villeneuve et al. (2002).

magnitude of these variations in mortality rates may have dampened any real $PM_{2.5}$ effect on mortality."

Similar results were observed by Villeneuve et al. (2002) irrespective of the exposure window considered. They used various time-dependent indices that denoted (a) exposures received in the last two years of follow-up and (b) exposures lagged 3 to 4 and ≥ 5 years. Effect modification was evaluated by fitting interaction terms that consisted of $PM_{2.5}$ exposure and individual risk factors (body mass index, education, smoking, age, gender, and occupational exposure to dusts). The significance of this term was formally tested by constructing a likelihood ratio test statistic. An interaction effect between $PM_{2.5}$ exposure and age was seen ($p < 0.05$), and they therefore presented stratified analysis by age group (< 60, ≥ 60 years).

For each index of $PM_{2.5}$, the RR of all-cause mortality was more pronounced among subjects < 60 years old. There was no effect modification between $PM_{2.5}$ and the other individual risk factors. The RR for PM-associated mortality did not depend on when exposure occurred in relation to death, possibly because of little variation between the time-dependent city-specific $PM_{2.5}$ exposure indices ($r > 0.90$) and the fact that the rank ordering of the cities changed little during follow-up. Villeneuve et al. (2002) concluded that the "attenuated risk of mortality that was observed with a time-dependent index of $PM_{2.5}$ is due to the combined influence of city-specific variations in mortality rates and decreasing levels of air pollution that occurred during follow-up."

8.2.3.2.2 The ACS Study Extension

Pope et al. (2002) extended the analyses (Pope et al., 1995) and reanalyses (Krewski et al., 2000) of the ACS CPS-II cohort to include an additional nine years of follow-up data. The 2002 study has a number of advantages over the previous analyses, in that it (a) doubles the follow-up time from 7 to 16 years and triples the number of deaths; (b) expands the ambient air pollution data substantially, including two recent years of fine particle data and adding data on gaseous co-pollutants; (c) improves statistical adjustments for occupational exposure; (d) incorporates data on dietary covariates believed to be important factors in mortality, including total fat consumption, and consumption of vegetables, citrus fruit, and high-fiber grains; and (e) uses recent developments in nonparametric spatial smoothing and random effects statistical models as input to the Cox proportional hazards model. Each participant was identified with a specific metropolitan area, and mean pollutant concentrations were calculated for all metropolitan areas with ambient air monitors in the one to two years prior to enrollment. Ambient pollution during the follow-up period was extracted from the AIRS data base. There was no network of $PM_{2.5}$ monitoring in the United States between the early 1980s and the late 1990s. In an attempt to estimate the concentration during this period, the integrated average of $PM_{2.5}$ concentrations during 1999 to 2000 was averaged with the earlier 1979 to 1983 period. For the 51 cities where paired data were available, the concentrations of $PM_{2.5}$ were lower in 1999 to 2000 than in 1979 to 1983 for most cities. Mean $PM_{2.5}$ levels for the two periods were highly correlated ($r = 0.78$),

and the rank order of the cities by relative pollution levels remained nearly the same. Analyses based on the early period would likely provide the best estimate of $PM_{2.5}$-associated risks, as shown in Figures 8-8 and 8-9. Averages of daily averages of the gaseous pollutants were used except for O_3, where the average daily 1-h maximum was calculated for the whole year and for the typical peak O_3 quarter (July, August, September). Mean sulfate concentrations for 1990 were calculated from archived quartz filters, virtually eliminating the historical sulfate artifact leading to overestimation of sulfate concentrations.

The Krewski et al. (2000), Burnett et al. (2001a), and Pope et al. (2002) studies were concerned that survival times of participants in nearby locations might not be independent of each other, due to missing, unmeasured, or mis-measured risk factors or their surrogates that may be spatially correlated with air pollution, thus violating an important assumption of the Cox proportional hazards model. Thus, model fitting proceeded in two stages, the first of which was an adjusted relative risk model with a standard Cox proportional hazards model including individual-specific covariates and indicator variables for each metropolitan area, but not air pollutants. In the second stage, the adjusted log(relative risks) were fitted to fine particle concentrations or other air pollutants by a random effects linear regression model.

Models were estimated separately for each of four mortality (total, cardiopulmonary, lung cancer, and causes other than cardiopulmonary or lung cancer deaths) endpoints for the entire follow-up period and for fine particles in three time periods (1979-1983, 1999-2000, and the average of the mean concentrations in these two periods). The results are shown in Table 8-7. Figures 8-7, 8-8, and 8-9 show the results displayed in Figures 2, 3, and 5 of Pope et al. (2002). Figure 8-7 shows that a smooth nonparametric model can be reasonably approximated by a linear model for all-cause mortality, cardiopulmonary mortality, and other mortality; but the log(relative risk) model for lung cancer appears to be nonlinear, with a steep linear slope up to an annual mean concentration of about 13 $\mu g/m^3$ and a flatter linear slope at fine particle concentrations > 13 $\mu g/m^3$.

Figure 4 in Pope et al. (2002) shows results for the stratified first-stage models: ages < 60 and > 69 years are marginally significant for total mortality; ages > 70 years are significant for cardiopulmonary mortality; and ages 60 to 69 years for lung cancer mortality. Men are at

TABLE 8-7. SUMMARY OF RESULTS FROM THE EXTENDED ACS STUDY*

Cause of Death	$PM_{2.5}$, Average Over 1979-1983	$PM_{2.5}$, Average Over 1999-2000	$PM_{2.5}$, Average Over All Seven Years
All causes	4.1% (0.8, 7.5%)	5.9% (2.0, 9.9%)	6.2% (1.6, 11.0%)
Cardiopulmonary	5.9% (1.5, 10.5%)	7.9% (2.3, 14.0%)	9.3% (3.3, 15.8%)
Lung cancer	8.2% (1.1, 15.8%)	12.7% (4.1, 21.9%)	13.5% (4.4, 23.4%)
Other	0.8% (−3.0, 4.8%)	0.9% (−3.4, 5.5%)	0.5% (−4.8, 6.1%)

*Adjusted mortality excess risk ratios (95% confidence limits) per 10 μg/m^3 $PM_{2.5}$ by cause of death associated with each of the multiyear averages of fine particle concentrations. The multiyear average concentrations are used as predictors of cause-specific mortality for all of the 16 years (1982-1998) of the ACS follow-up study. The excess risk ratios are obtained from the baseline random effects Cox proportional hazards models adjusted for age, gender, race, smoking, education, marital status, BMI, alcohol consumption, occupational dust exposure, and diet. Based on Table 2 in Pope et al. (2002) and more precise data from authors (G. Thurston, personal communication, March 13, 2002).

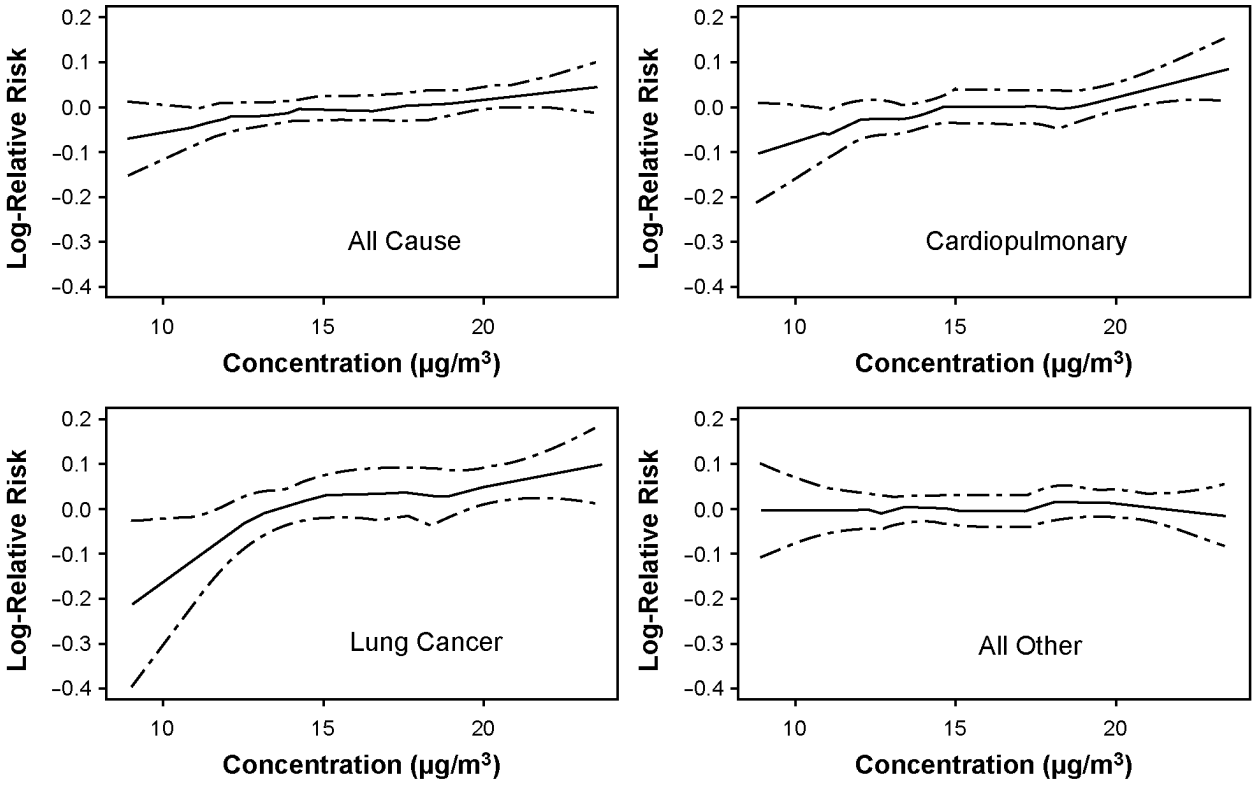

Figure 8-7. Natural logarithm of relative risk for total and cause-specific mortality per 10 μg/m^3 $PM_{2.5}$ (approximately the excess relative risk as a fraction), with smoothed concentration-response functions. Based on Pope et al. (2002) mean curve (solid line) with pointwise 95% confidence intervals (dashed lines).

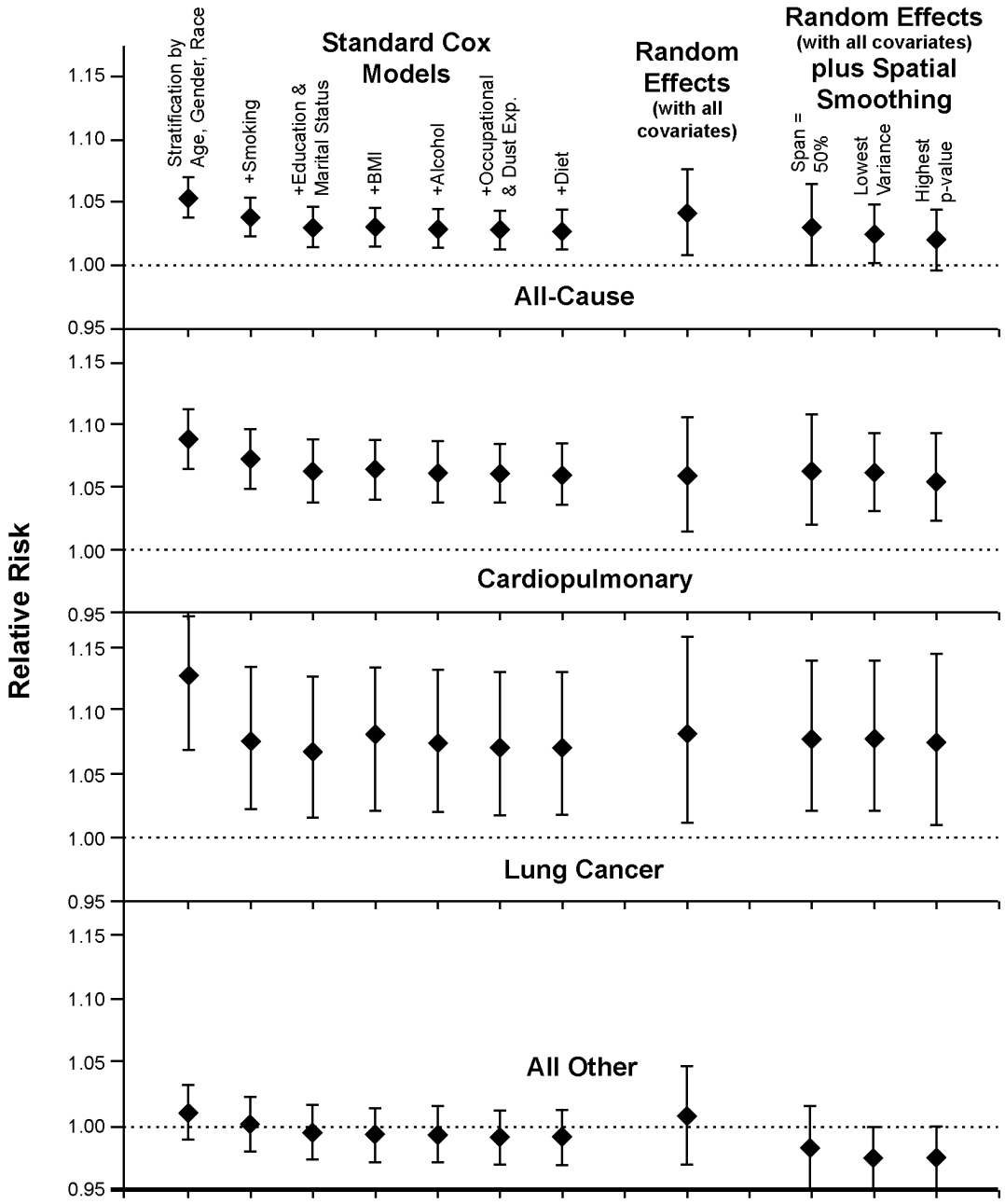

Figure 8-8. Relative risk of total and cause-specific mortality per 10 μg/m^3 $PM_{2.5}$, derived for means of 1979-1983 $PM_{2.5}$ data for various cities, using alternative statistical models. The standard Cox models are built up in a sequential stepwise manner from the baseline model stratified by age, gender, and race by adding additional covariates. The random effects model allows for additional city-to-city variation, and the spatial smoothing models show the effects of increasingly aggressive adjustment for spatial correlation.

Source: Based on Pope et al. (2002).

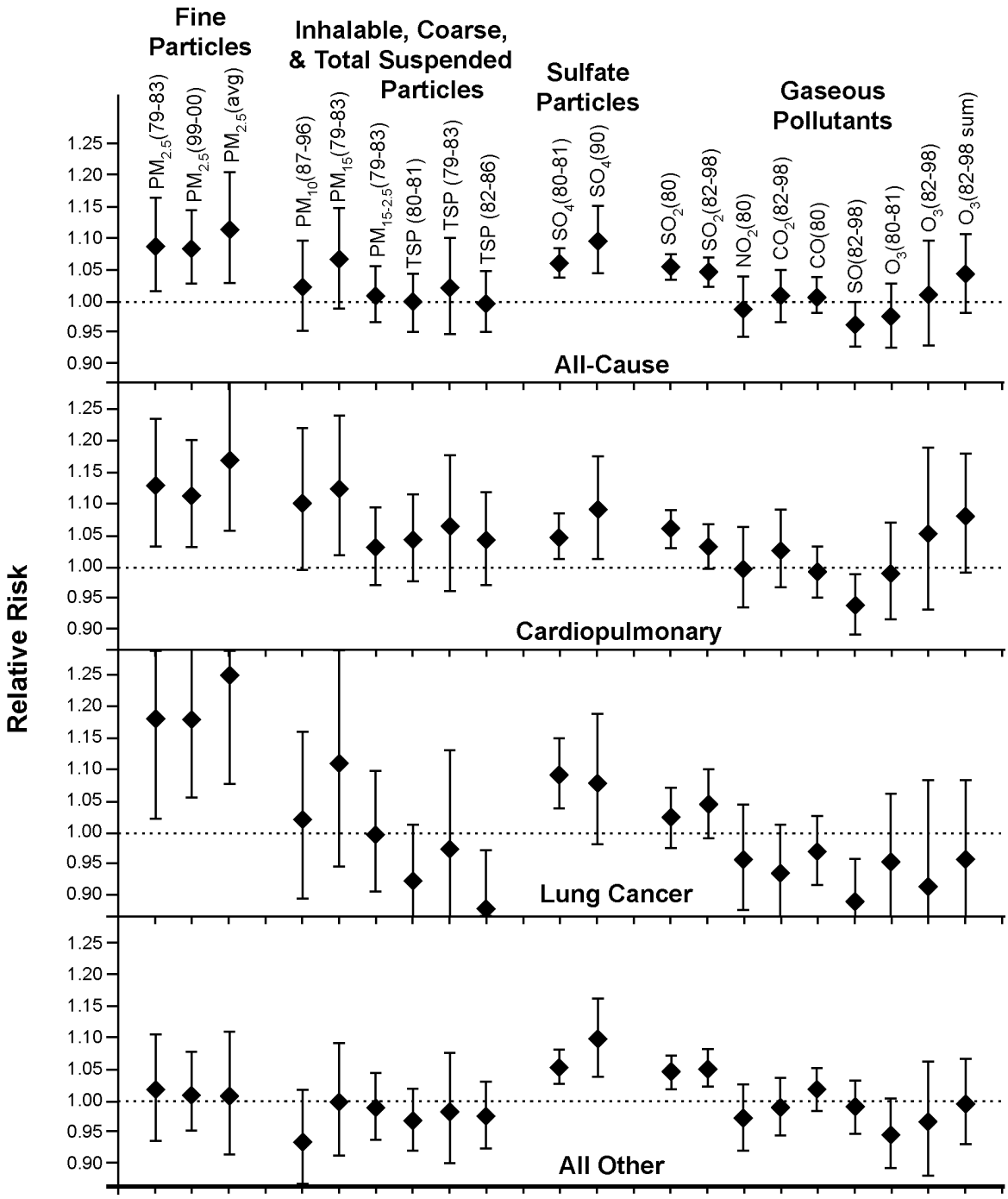

Figure 8-9. Relative risk of total and cause-specific mortality for particle metrics and gaseous pollutants over different averaging periods (years 1979-2000 in parentheses).

Source: Based on Pope et al. (2002).

significantly higher risk for total and lung cancer mortality than are women, but slightly less so for cardiopulmonary mortality (although still significant). Log (RR) decreases significantly from individuals with less than to those with more than a high school education, replicating findings in Krewski et al. (2000), but with twice the time on study. Including smoking status showed increased fine particle RR for cardiopulmonary and lung cancer mortality in never-smokers and least effect in current smokers; however, for total mortality, significant or near-significant effects occurred in both current and never-smokers, but not former smokers.

The second-stage random effects models on the right side of Figure 8-8 have much wider confidence intervals than the first-stage models, but are still statistically significant for total, cardiopulmonary, and lung cancer mortality. Spatial smoothing decreased the magnitude and significance of the fine particle effect for total mortality. For cardiopulmonary mortality, spatial smoothing increased the magnitude of the RR and its significance by reducing the width of the confidence intervals in the "50%-span" and "lowest variance" smoothing methods. For lung cancer mortality, spatial smoothing little changed the magnitude of the RR, but increased its significance by reducing the width of confidence intervals in the "50%-span" and "lowest variance" smoothing methods.

Figure 8-9 shows statistically significant relationships between fine particles and total, cardiopulmonary, and lung cancer mortality no matter which averaging span was used for $PM_{2.5}$ and slightly larger effect estimates for the average concentration of the 1979 to 1983 and 1999 to 2000 intervals. PM_{15} for 1979 to 1983 is significantly associated with cardiopulmonary mortality and marginally with total mortality; whereas 1987 to 1996 PM_{15} is not significantly associated with cardiopulmonary mortality. Coarse particles ($PM_{15-2.5}$) and TSP are not significantly associated with any endpoint, but are positively associated with cardiopulmonary mortality. Sulfate particles are very significantly associated with all endpoints, including mortality from all other causes, but only marginally for lung cancer mortality using 1990 filters. Figure 8-9 also shows highly positive significant relationships between SO_2 and total, cardiopulmonary, and other-causes mortality, but a weaker SO_2 association with lung cancer mortality. Only O_3 using only the third quarter for 1982 to 1998 showed a marginally significant relationship with cardiopulmonary mortality, but not the year-round average. The other criteria

pollutants, CO and NO_2, are neither significantly nor positively related to any mortality endpoint, unlike some findings for acute PM exposure-mortality studies.

This paper confirms that the general pattern of findings for the first seven years of the study (Pope et al., 1995; Krewski et al., 2000) can be reasonably extrapolated to the patterns that remain present with twice the length of time on study and three times the number of deaths. As shown later in Table 8-11, the excess relative risk estimate (95% CI) per 10 $\mu g/m^3$ $PM_{2.5}$ for total mortality in the original ACS study (Pope et al., 1995) was 6.6% (CI: 3.6, 9.9); in the ACS reanalysis (Krewski et al., 2000) it was 7.0% (CI: 3.9, 10); and, in the extended ACS data set (Pope et al., 2002), it was 4.1% (CI: 0.8, 7.5) using the 1979 to 1983 data and 6.2% (CI: 1.6, 11) using the average of the 1979 to 1983 and 1999 to 2000 data. The excess relative risk estimate (95% CI) per 10 $\mu g/m^3$ $PM_{2.5}$ for cardiopulmonary mortality in the original ACS study (Pope et al., 1995) was 12% (CI: 6.7, 17); in the ACS reanalysis (Krewski et al., 2000), it was 12% (CI: 7.4, 17); and, in the extended ACS data set (Pope et al., 2002), it was 5.9% (CI: 1.5, 10) using the 1979 to 1983 data and 9.3% (CI: 3.3, 16) using the average of the 1979 to 1983 and 1999 to 2000 data. Thus, the additional data and statistical analyses reported by Pope et al. (2002) yield somewhat smaller estimates than the original study (Pope et al., 1995), but are similar to estimates from the Krewski et al. (2000) reanalysis of the original ACS data set.

The Pope et al. (2002) study also considered the PM risks by subgroup characteristics. The risks were generally found (although not significantly so) to be somewhat higher for males than females. The $PM_{2.5}$ relative risks also tended to be higher for nonsmokers than smokers. This is consistent with the fact that smokers would have a much higher baseline risk, especially for lung cancer, and would tend to have lower air pollution-mortality risk when viewed relative to the much higher smoker baseline risk. $PM_{2.5}$ mortality relative risks also tended to be higher for those with less education, which may be due to related socioeconomic factors or, more likely, to the generally greater inter-state mobility of higher-educated persons. Since the MSA was assumed unchanged from that at the start of the study, this would tend to weaken the association for higher education subjects, as the MSA-based exposure information would tend to have less accuracy in that highly mobile group. This may indicate that the less-educated group RR estimates may be more indicative of the true $PM_{2.5}$ effects (i.e., as their exposure information is

likely to be more accurate) and, therefore, that the overall study $PM_{2.5}$ RR estimates (which include the highly-educated) may be biased somewhat low.

Based on the above patterns of results, the authors drew the following conclusions:

(1) The apparent association between long-term exposure to fine particle pollution and mortality persists with longer follow-up as the participants in the cohort grow older and more of them die.

(2) The estimated fine particle effect on cardiopulmonary and cancer mortality remained relatively stable even after adjustment for smoking status, although the estimated effect was larger and more significant for never-smokers versus former or current smokers. The estimates were relatively robust against inclusion of many additional covariates: education, marital status, body mass index (BMI), alcohol consumption, occupational exposure, and dietary factors. However, the data on individual risk factors were collected only at the time of enrollment and have not been updated, so that changes in these factors since 1982 could introduce risk-factor exposure mis-classification and consequent loss of precision in the estimates that might limit the ability to characterize time dependency of effects. Moreover, it is noteworthy that this study found education to be an effect modifier, with larger and more statistically significant PM effect estimates for persons with less education. This may be due to the fact that less-education is a marker for lower socioeconomic status and, hence, poorer health status and greater pollution susceptibility. These results may also reflect that the mobility of the less-educated may provide better estimates of exposure in this study (with no follow up of address changes) than for the more mobile well-educated. In either case, because this cohort has a much higher percentage of well-educated persons than the general public, the education effect modification seen suggests that the overall PM effect estimates are likely underestimated by this study cohort than are likely to be found for the general public.

(3) Additional assessments for potential spatial or regional differences not controlled in the first-stage model were evaluated. If there are unmeasured or inadequately modeled risk factors that differ across locations or are spatially clustered, then PM risk estimates may be biased. If the clustering is independent or random or independent across areas, then adding a random-effects component to the Cox proportional hazards model could address the problem. However, if location is associated with air pollution, then the spatial correlation may be evaluated using nonparametric smoothing methods. No significant spatial autocorrelation was found after controlling for fine particles. Even after adjusting for spatial correlation, estimated $PM_{2.5}$ effects were significant and persisted for cardiopulmonary and lung cancer mortality and were borderline significant for total mortality, but with much wider confidence intervals after spatial smoothing.

(4) Fine particles ($PM_{2.5}$) were associated with elevated total, cardiopulmonary, and lung cancer mortality risks, but not with other-cause mortality. PM_{10} for 1987-1996 and PM_{15} for 1979-1983 were just significantly associated with cardiopulmonary mortality, but neither $PM_{10-2.5}$ nor TSP were associated with total or any cause-specific mortality. All endpoints but lung cancer mortality were very significantly associated with sulfates,

except for lung cancer with 1990 sulfate data. All endpoints except lung cancer mortality were significantly associated with SO_2 using 1980 data, as were total and other mortality using the 1982-1998 SO_2 data; but cardiopulmonary and lung cancer mortality had only a borderline significant association with the 1982-1998 SO_2 data. None of the other gaseous pollutants showed significant positive associations with any endpoint. Thus, neither coarse thoracic particles nor TSP were significantly associated with mortality; nor were CO and NO_2 on a long-term exposure basis.

(5) The concentration-response curves estimated using nonparametric smoothers were all monotonic and nearly linear (except for lung cancer). However, the shape of the curve may become nonlinear at much higher concentrations.

(6) The excess risk from $PM_{2.5}$ exposure is much smaller than that estimated for cigarette smoking for current smokers in the same cohort (Pope et al., 1995): RR = 2.07 for total mortality, RR = 2.28 for cardiopulmonary mortality, and RR = 9.73 for lung cancer mortality. In the more polluted areas of the United States, the relative risk for substantial obesity (a known risk factor for cardiopulmonary mortality) is larger than that for $PM_{2.5}$, but the relative risk from being moderately overweight is somewhat smaller.

8.2.3.2.3 AHSMOG Analyses

The Adventist Health Study of Smog (AHSMOG), another major U.S. prospective cohort study of chronic PM exposure-mortality effects, started with enrollment in 1977 of 6,338 nonsmoking non-Hispanic white Seventh Day Adventist residents of California, ages 27 to 95 years. All had resided for at least 10 years within 5 miles (8 km) of their then-current residence locations, either within one of the three major California air basins (San Diego, Los Angeles, or San Francisco), or else were part of a random 10% sample of Adventist Health Study participants living elsewhere in California. The study has been extensively described and its initial results reported earlier (Hodgkin et al., 1984; Abbey et al., 1991; Mills et al., 1991).

In the more recent AHSMOG analyses (Abbey et al., 1999), the mortality status of subjects after ~15 years of follow-up (1977-1992) was determined by various tracing methods and 1,628 deaths (989 female, 639 male) were found in the cohort. This 50% percent increase during the follow-up period (versus previous AHSMOG reports) notably enhances the power of the latest analyses over past published ones. Of 1,575 deaths from all natural (non-external) causes, 1,029 were cardiopulmonary, 135 were nonmalignant respiratory (ICD9 codes 460-529), and 30 were lung cancer (ICD9 code 162) deaths. Abbey et al. (1999) also created another death category,

contributing respiratory causes (CRC), which included any mention of nonmalignant respiratory disease as an underlying or "contributing cause" on the death certificate. Numerous analyses were done for the CRC category, due to the large numbers and relative specificity of respiratory causes as a factor in the deaths. Education was used to index socioeconomic status, rather than income. Physical activity and occupational exposure to dust were also used as covariates. Cox proportional hazard models adjusted for a variety of covariates or stratified by sex were used. The "time" variable used in most of the models was survival time from date of enrollment, except that age on study was used for lung cancer effects due to the expected lack of short-term effects. Many covariate adjustments were evaluated, yielding results for all non-external mortality as shown in Table 8-8.

TABLE 8-8. RELATIVE RISK OF MORTALITY FROM ALL NONEXTERNAL CAUSES, BY SEX AND AIR POLLUTANT, FOR AN ALTERNATIVE COVARIATE MODEL IN THE AHSMOG STUDY

		Females			Males		
Pollution Index	**Pollution Increment**	**RR**	**LCL**	**UCL**	**RR**	**LCL**	**UCL**
PM_{10} > 100, cl/yr	30 days/yr	0.958	0.899	1.021	1.082	1.008	1.162
PM_{10} mean	20 µg/rn^3	0.95	0.873	1.033	1.091	0.985	1.212
SO_4 mean	5 µg/rn^3	0.901	0.785	1.034	1.086	0.918	2.284
0_3 > 100 ppb, b/yr	551 h/yr (IQR)	0.9	0.8	1.02	1.14	0.98	1.32
SO_2 mean	3.72 (IQR)	1	0.91	1.1	1.05	0.94	1.18

LCL = Lower *95%* confidence limit UCL Upper *95%* confidence limit

Source: Abbey et al. (1999).

As for cause-specific mortality analyses of the AHSMOG data, positive and statistically significant effects on deaths with underlying contributing respiratory causes were also found for 30 day/year > 100 µg/m^3 PM_{10} (RR = 1.14, CI: 1.03, 1.56) in models that included both sexes and adjustment for age, pack-years of smoking, and BMI. Subsets of the cohort had elevated

risks: (a) former smokers had higher RRs than never-smokers (RR for PM_{10} exceedances for never- smokers was marginally significant by itself); (b) subjects with low intake of antioxidant vitamins A, C, E had significantly elevated risk of response to PM_{10}, whereas those with adequate intake did not (suggesting that dietary factors or, possibly, other socioeconomic or life style factors for which they are a surrogate may be important covariates); and (c) there also appeared to be a gradient of PM_{10} risk with respect to time spent outdoors, with those who had spent at least 16 h/wk outside being at greater risk from PM_{10} exceedances. The extent to which time spent outdoors is a surrogate for other variables or is a modifying factor reflecting temporal variation in exposure to ambient air pollution is not clear, e.g., if the males spent much more time outdoors than the females, outdoor exposure time could be confounded with gender. When the cardiopulmonary analyses are broken down by gender (Table 8-9), the RRs for female deaths were generally smaller than that for males, but none of the risks for PM indices or gaseous pollutants were statistically significant at $p < 0.05$.

TABLE 8-9. RELATIVE RISK OF MORTALITY FROM CARDIOPULMONARY CAUSES, BY SEX AND AIR POLLUTANT, FOR AN ALTERNATIVE COVARIATE MODEL IN THE AHSMOG STUDY

		Females			Males		
Pollution Index	**Pollution Increment**	**RR**	**LCL**	**UCL**	**RR**	**LCL**	**UCL**
$PM_{10} > 100$, d/yr	30 days/yr	0.929	0.857	1.007	1.062	0.971	1.162
PM_{10} mean	20 $\mu g/rn^3$	0.933	0.836	1.042	1.082	0.943	1.212
SO_4 mean	5 $\mu g/rn^3$	0.95	0.793	1.138	1.006	0.926	1.086
$O_3 > 100$ ppb, h/yr	551 h/yr (IQR)	0.88	0.76	1.02	1.06	0.87	1.29
O_3 mean	10 ppb	0.975	0.865	1.099	1.066	0.92	1.236
SO_2 mean	3.72 (IQR)	1.02	0.9	1.15	1.01	0.86	1.18

LCL = Lower 95% confidence limit UCL = Upper 95% confidence limit

Source: Abbey et al. (1999).

The AHSMOG cancer analyses yielded very mixed results (Table 8-10) for lung cancer mortality. For example, RR's for lung cancer deaths were statistically significant for males for PM_{10} and O_3 metrics, but not for females. In contrast, such cancer deaths were significant for mean NO_2 only for females (but not for males), but lung cancer metrics for mean SO_2 were significant for both males and females. This pattern is not readily interpretable, but is reasonably attributable to the very small numbers of cancer-related deaths (18 for females and 12 for males), resulting in wide RR confidence intervals and very imprecise effects estimates.

TABLE 8-10. RELATIVE RISK OF MORTALITY FROM LUNG CANCER BY AIR POLLUTANT AND BY GENDER FOR AN ALTERNATIVE COVARIATE MODEL

			Females			Males		
Pollution Index	**Pollution Increment**	**Smoking Category**	**RR**	**LCL**	**UCL**	**RR**	**LCL**	**UCL**
PM_{10} > 100, d/yr	30 days/yr	All[1]	1.055	0.657	1.695	1.831	1.281	2.617
PM_{10} mean	20 µg/rn^3	All	1.267	0.652	2.463	2.736	1.455	5.147
NO_2 mean	19.78 (IQR)	All	2.81	1.15	6.89	1.82	0.93	3.57
0_3>l00 ppb, h/yr	551 h/yr (IQR)	All	1.39	0.53	3.67	4.19	1.81	9.69
		never smoker				6.94	1.12	43.08
		past smoker				4.25	1.5	12.07
O_3 mean	10 ppb	All	0.805	0.436	1.486	1.853	0.994	3.453
SO_2 mean	3.72 (IQR)	All	3.01	1.88	4.84	1.99	1.24	3.2
		never smoker	2.99	1.66	5.4			

[1]All = both never smokers and past smokers.
LCL = Lower 95% confidence limit. UCL = Upper 95% confidence limit.

Source: Abbey et al. (1999).

The analyses reported by Abbey et al. (1999) attempted to separate PM_{10} effects from those of other pollutants by use of two-pollutant models, but no quantitative findings from such models were reported. Abbey et al. did mention that the PM_{10} coefficient for CRC remained stable or increased when other pollutants were added to the model. Lung cancer mortality models for males evaluated co-pollutant effects in detail and indicated that NO_2 was nonsignificant in all two-pollutant models, but other pollutant coefficients were stable. The PM_{10} and O_3 effects remained stable when SO_2 was added, suggesting possible independent effects, but PM_{10} and O_3 effects were hard to separate because these pollutants were highly correlated in this study. Again, the very small number of lung cancer observations and likely great imprecision of reported effects estimates markedly limit the weight that should be accorded to these cancer results.

Other analyses, by Beeson et al. (1998), evaluated essentially the same data as in Abbey et al. (1999), but focused on lung cancer incidence (1977 to 1992). There were only 20 female and 16 male lung cancer cases among the 6,338 subjects. Exposure metrics were constructed to be specifically relevant to cancer, those being the annual average of monthly exposure indices from January, 1973 through ensuing months but ending 3 years before date of diagnosis (thus representing a 3-year lag between exposure and diagnosis of lung cancer). The covariates in the Cox proportional hazards model were pack-years of smoking and education, and the time variable was attained age. Many additional covariates were evaluated for inclusion, but only "current use of alcohol" met criteria for inclusion in the final model. Pollutants evaluated were PM_{10}, SO_2, NO_2, and O_3. No interaction terms with the pollutants proved to be significant, including outdoor exposure times. The RR estimates for male lung cancer cases were: (a) positive and statistically significant for all PM_{10} indicators; (b) positive and mostly significant for O_3 indicators, except for mean O_3, number of O_3 exceedances > 60 ppb, and in former smokers; (c) positive and significant for mean SO_2, except when restricted to proximate monitors; and (d) positive but not significant for mean NO_2. When analyses are restricted to the use of air quality data within 32 km of the residences of subjects, the RR for PM_{10} over the IQR of 24 $\mu g/m^3$ in the full data set is 5.21 (or RR = 1.99 per 10 $\mu g/m^3$ PM_{10}). The female RRs were

all much smaller than for males, their being significant for mean SO_2 but not for any indicator of PM_{10} or O_3.

The AHSMOG investigators also attempted to compare effects of fine versus coarse particles (McDonnell et al, 2000). For AHSMOG participants living near an airport (n = 3,769), daily $PM_{2.5}$ levels were estimated from airport visibility using previously-described methods (Abbey et al, 1995b). Given the smaller numbers of subjects in these subset analyses, it is not necessarily surprising that no pollutants were found to be statistically significant, even based on analysis for the male subset near airports (n = 1266). It is important to caveat that (a) the $PM_{2.5}$ exposures were estimated from visibility measurements (increasing exposure measurement error) and yielded a very uneven and clustered distribution of estimated exposures and; (b) the $PM_{10-2.5}$ values were calculated from the differencing of PM_{10} and $PM_{2.5}$, likely adding yet even more measurement error for the coarse particle ($PM_{10-2.5}$) variable.

8.2.3.2.4 The EPRI-Washington University Veterans' Cohort Mortality Study

Lipfert et al. (2000b) reported preliminary results from large-scale mortality analyses for a prospective cohort of up to ~70,000 men assembled by the U.S. Veterans Administration (VA) in the mid-1970s at 32 VA clinics. The VA study group was not originally formed to study air pollution, but was later linked to air pollution data collected separately. The study that led to the development of this clinical cohort (Veterans Administration Cooperative Study Group on Antihypertensive Agents, 1970; 1967) was a "landmark" VA cooperative study demonstrating that anti-hypertensive treatment markedly decreased morbidity and mortality (Perry et al., 1982). The clinical cohort itself involved actual clinical rather than research settings. Lipfert et al. (2000b) noted: "This cohort differs from a general male population in being limited to hypertensive patients and it differs from the cohorts that are randomized into large-scale multicenter trials since it contains a broad spectrum of subjects including many with various co-morbidities."

The VA study cohort was male, middle-aged (51 ± 12 years) and included a larger proportion of African-Americans (35%) than the U.S. population as a whole and a large percentage of current or former smokers (81%). The cohort was selected at the time of

recruitment as being mildly to moderately hypertensive, with screening diastolic blood pressure (DBP) in the range 90 to 114 mm Hg (mean 96, about 7 mm more than the U.S. population average) and average systolic blood pressure (SBP) of 148 mm Hg. The subjects had all been healthy enough to be in the U.S. armed forces at one time. As stated by Lipfert et al. (2000b), "Twelve percent had a pulmonary abnormality on physical examination, 9% were diabetic; 19% had a history of heart disease; 7% had a history of stroke, and 56% had a positive cardiorenal family history." Contextual socioeconomic variables were also assembled at the ZIP-code and county levels. The ZIP-code level variables were average education, income, and racial mix. County-level variables included altitude, average annual heating-degree days, percentage Hispanic, and socioeconomic indices. Census-tract variables included poverty rate and racial mix.

Detailed exposure information was obtained by averaging air quality data by year for each county of residence at the time of entry to the study. County-wide air pollution variables included TSP, PM_{10}, $PM_{2.5}$, PM_{15}, $PM_{15\text{-}2.5}$, SO_4, O_3, CO, and NO_2. The VA $PM_{2.5}$ pollutant data were derived from the same data set as used in the ACS study; that $PM_{2.5}$ data set (103 counties with monitors) was much smaller than the VA TSP data set (1,379 counties). In the 1,379 counties with TSP data, there were 67,537 subjects. For PM_{10}, during the period 1989 to 1996, there were 59,053 subjects; for $PM_{2.5}$ during 1979 to 1981, there were 26,067 subjects; for $PM_{2.5}$ during 1982 to 1984, there were 29,177; for PM_{15} during 1979 to 1981, there were 26,067; for PM_{15} during 1982 to 1984, there were 29,177; for $PM_{15\text{-}2.5}$ during 1979 to 1981, there were 26,067; and for $PM_{15\text{-}2.5}$ during 1982 to 1984, there were 29,177. Lipfert et al. (2000b) stated "The IP data used here were derived from 103 monitors," and "Matching at the county level substantially reduces the errors in estimated exposures incurred by averaging across an entire metropolitan area." Lipfert et al. (2000b) also indicated: "In this study, the mortality risks were based on the mean concentration of pollutants less estimated background weighted by the number of subjects in each county. . . . Background is estimated as the mean concentration less 3 standard deviations. In the few cases for which this value was negative (indicating a skewed distribution) the background was taken as zero."

Besides considering average exposures over the entire period, three sequential mortality follow-up periods (1976 to 1981, 1982 to 1988, 1989 to 1996) were also evaluated in separate statistical analyses that related mortality in each of those periods to air pollution in different preceding, concurrent, or subsequent periods (i.e., up to 1975, 1975 to 1981, 1982 to 1988, and 1989 to 1986, for TSP in the first three periods, PM_{10} for the last, and NO_2, 95th percentile O_3, and 95th percentile CO for all four periods). Mortality in the above-noted periods was also evaluated in relation to SO_4 in each of the same four periods noted for NO_2, O_3, and CO, and to $PM_{2.5}$, PM_{15}, and $PM_{15\text{-}2.5}$ in 1979 to 1981 and 1982 to 1984. Thus, Lipfert et al. (2000b) stated: "With the baseline and final model, deaths during each of the three most recent exposure periods were considered separately, yielding up to 12 combinations of exposure and mortality periods for each pollutant. Associations between concurrent air quality and mortality periods were considered to relate to acute responses, associations with prior exposures were considered to be emblematic of initiation of chronic diseases and preexposure mortality associations could only be indirect (temporality violated by design), that is, noncausal, and the results of intercorrelation or spurious associations."

Results from the VA study are shown in Table 8-11 for various PM indices. Three caveats were expressed by Lipfert et al. (2000b): "First, the different pollutants, both among species and among time period within species, may represent different locations because of missing data. Second, the relative high fraction of mortality within this cohort may have depleted it of susceptible individuals in the late periods of follow-up. Finally, all of the personal characteristics of each subject were determined only at the entry to the study. It is quite likely that many of those characteristics will have changed during the 21 years of follow-up." Lipfert et al. (2000b) concluded that this may be reason to regard the results for the 1976 to 1981 period as the most credible. Within a column of this table, the cohort remains unchanged, but the pollutant differs; however, since missing data vary by pollutant, there are also small changes in the population considered. Within a row of the table the pollutant remains constant, but the cohort is "successively depleted in the passage of time."

In Table 8-11 the column at the far right under the heading "single period" presents regression results from separate model runs for which mortality for the entire follow-up period

TABLE 8-11. PARTICULATE MATTER EFFECTS ON MORTALITY BY EXPOSURE AND MORTALITY PERIOD WITH ECOLOGICAL VARIABLES FOR THE VETERANS COHORT STUDY EXPRESSED AS EXCESS MORTALITY

	Exposure Period	Deaths 1976-1981	Deaths 1982-1988	Deaths 1989-1996	Single Period [A]
TSP	up to 1975	−0.351 [D]	***−0.81*** [D]	***−1.49*** [D]	−0.18
TSP	1975-81	0.078 [C]	−0.680 [D]	***−2.49*** [D]	0.41
TSP	1982-88	***2.060*** [T]	1.08 [C]	−0.20 [D]	***0.94***
PM_{10}	1989-96	***7.060*** [T]	***4.33*** [T]	3.43 [C]	**3.92**
$PM_{2.5}$	1979-81	−5.28 [C]	***−10.07*** [D]	***−15.35*** [D]	0.27
$PM_{2.5}$	1982-84	0.236 [T]	***−6.11*** [C]	***−10.78*** [D]	−0.06
PM_{15}-$PM_{2.5}$	1979-81	−4.27 [C]	−1.99 [D]	***−9.20*** [D]	0.68
PM_{15}-$PM_{2.5}$	1982-84	***−11.00*** [T]	***−7.91*** [C]	***−12.64*** [D]	***−3.64***
PM_{15}	1979-81	−3.03 [C]	***−3.79*** [D]	***−7.65*** [D]	0.3
PM_{15}	1982-84	***−4.46*** [T]	***−5.99*** [C]	***−9.73*** [D]	−1.54

A - Mortality for the entire followup period (1976-1996) regressed against each exposure period
C - Concurrent
D - Delayed
T - Temporality violated by design

All excess mortality in units of percent per 10 ug/m^3. Bold italic print indicates significant at $p < 0.05$.

Source: Lipfert et al. (2000b).

was regressed against each exposure period for the purpose of comparison with the segmented mortality analysis and with previous cohort studies (Dockery et al., 1993; Pope et al., 1995; and Abbey et al., 1999). The single-period analysis represents an aggregated approach to exposure when the follow-up periods are short, say a few years; thus, the exposure aggregation error may be small but the study will have reduced power because of the smaller number of deaths. For longer follow-up periods, say 10 years or more, it becomes important to consider the timing of death relative to exposure in order to preclude attributing associated mortality to subsequent exposure. In the present study, the "indirect" cells of the matrix tend to occur early in the follow-up period while the "delayed" cells tend to occur later.

Lipfert et al (2000b) stated that "The use of specific exposure periods improve the precision of the exposure estimates. Response to $PM_{2.5}$ and PM_{15} differ greatly between the single period and the segmented periods; that is thus a prime example of the value of the segmented analysis in revealing such details. The single mortality period response without ecological variables are qualitatively similar to what has been reported before (SO_4 > $PM_{2.5}$ > PM_{15}) but the segmented analysis shows that responses to all of the IP variables are negative, some significantly so."

Lipfert et al (2000b) also stated that specific attention must be given to significant negative associations between pollution and mortality, which they indicated may be indicative of confounding or an incomplete model specification. They also noted "It is possible that the indirect responses may simply reflect random variation and collinearity among time periods." For example, the correlation between $PM_{2.5}$ concentrations the 1979 to 1981 and 1982 to 1984 exposure periods was 0.69. The study found some responses that were consistent with previous studies but only in the absence of ecological covariates in the model or when responses were aggregated across the entire period of follow-up. The results from this study indicate that peak ozone was the only pollutant with constant positive concurrent response. Lipfert et al. (2000b) state that these overall findings were the result of a more detailed consideration of exposure timing.

It should be noted that the preliminary screening models used proportional hazards regression models (Miller et al., 1994) to identify age, SBP, DBP, BMI (nonlinear), age and race interaction terms, and present or former smoking as baseline predictors, with one or two pollution variables added. In the final model using 233 terms (of which 162 were interactions of categorized SBP, DBP, and BMI variables with age), the most significant non-pollution variables were SBP, DBP, BMI, and their interactions with age, smoking status, average education, race, poverty, and height. Also, Lipfert et al. (2000b) noted that the mortality risk associated with current cigarette smoking (1.43) that they found was lower than reported in other studies. The most consistently positive effects were found for O_3 and NO_2 exposures in the immediately preceding years. This study used peak O_3 rather than mean O_3, as was done in some other cohort studies. This may account for the higher O_3 and NO_2 effects here. While the

PM analyses considering segmented (shorter) time periods gave differing results (including significant negative mortality coefficients for some PM metrics), when methods consistent with past studies were used (i.e., many-year average PM concentrations), similar results were reported: the authors found that "(t)he single-mortality-period responses without ecological variables are qualitatively similar to what has been reported before ($SO_4 \geq PM_{2.5} > PM_{15}$)." With ecological variables included, a significant PM effect was that for TSP for 1982 to 1988 exposure for the single period. Overall, the authors concluded that "the implied mortality risks of long-term exposure to air pollution were found to be sensitive to the details of the regression model, the time period of exposure, the locations included, and the inclusion of ecological as well as personal variables."

In a follow-up study of the Veterans' Cohort Study, Lipfert et al. (2003) investigated the importance of blood pressure (BP) as a covariate in studies of long-term associations between air quality and mortality. The aims of the article were to summarize quantitative relationships between BP and mortality, to discuss the available information on associations between air quality and BP, and to present results of a proportional hazard regression sensitivity analysis for the Veterans' Cohort. The relationship between BP and air quality was considered by reviewing the literature, by deleting variables from the Veterans' Study proportional hazards regression models, and by stratifying the analyses of that cohort by diastolic blood pressure (DBP) level. The literature review found BP to be an important predictor of survival and found small transient associations between air quality and BP that may be either positive or negative. The regression model sensitivity runs indicate that the reported VA model associations with air pollution are robust to the deletion of the BP variables for the entire cohort. For stratified regressions, the confidence intervals for the air pollution-mortality associations overlapped for the two DBP groups. The authors, Lipfert et al. (2003), concluded that there is scant evidence that air pollution affects blood pressure in either healthy or impaired subjects. They went on to note that the inclusion of BP variables is not strictly essential to derive valid estimates of air pollution responses, concluding overall that the associations between air quality and mortality are not mediated through blood pressure.

8.2.3.2.5 Relationship of Six Cities, ACS, AHSMOG, and VA Study Findings

This section compares findings from the earlier Six Cities study (Dockery et al., 1993), the ACS Study (Pope et al., 1995), the HEI reanalyses of the latter two studies, the extension of the ACS Study (Pope et al., 2002), the more recent AHSMOG mortality analyses (Abbey et al., 1999; McDonnell et al., 2000) and the VA study (Lipfert et al., 2000b). In comparing prospective cohort studies, some key issues for consideration are: (1) cohort size and characteristics; (2) study design; and (3) air quality data used in exposure characterization. Table 8-12 compares the estimated RR for total, cardiopulmonary, and cancer mortality among the studies.

The number of subjects in these studies varies greatly: 8,111 subjects in the Six-Cities Study; 295,223 subjects in the 50 fine particle ($PM_{2.5}$) cities and 552,138 subjects in the 151 sulfate cities of the ACS Study; 6,338 in the AHSMOG Study; and 26,000 in the VA Study for $PM_{2.5}$. This may partially account for differences among their results.

The Six City and AHSMOG studies were designed specifically as prospective studies to evaluate long-term effects of air pollution and included concurrent air pollution measurements. The ACS study was also a prospective study, using air pollution data obtained at about the approximate time of enrollment but not subsequently (Pope et al., 1995), and it evaluated air pollution effects among a cohort originally recruited to study factors affecting cancer rates. The extended ACS study incorporated much more air pollution data, including TSP data back to the 1960s and more recent fine particle data. The VA study was originally designed to evaluate the efficacy of hypertension treatments in male military veterans with hypertension.

The Six-Cities cohort was pre-selected, by the investigators, to be a representative population, at least for the region of the country that was (is) heavily impacted by both coal combustion and motor vehicle effluents. By contrast, the ACS study cohort was drawn from a large pool of volunteers who happened to live in communities where several years of fine particle and/or sulfate ambient air concentration data were available. The AHSMOG cohort is drawn from nonsmoking, non-Hispanic white Seventh Day Adventist residents of California. The VA cohort also presents a narrow population (only male veterans having a very high percentage of prior smoking, all of whom were diagnosed as hypertensive). Of these four cohort

TABLE 8-12. COMPARISON OF EXCESS RELATIVE RISKS OF LONG-TERM MORTALITY IN THE HARVARD SIX CITIES, ACS, AHSMOG, AND VA STUDIES

		Total Mortality		Cardiopulmonary Mortality		Lung Cancer Mortality	
Study	**PM [1]**	**Ex. RR [2]**	**95% CI**	**Ex. RR**	**95% CI**	**Ex. RR**	**95% CI**
Six City [3]	$PM_{2.5}$	13%	(4.2, 23%)	18%	(6.0, 32%)	18%	(−11, 57%)
Six City New [4]	$PM_{2.5}$	14%	(5.4, 23%)	19%	(6.5, 33%)	21%	(−8.4, 60%)
ACS [5]	$PM_{2.5}$	6.6%	(3.5, 9.8%)	12%	(6.7, 17%)	1.2%	(−8.7, 12%)
ACS New [6]	$PM_{2.5}$	7.0%	(3.9, 10%)	12%	(7.4, 17%)	0.8%	(−8.7, 11%)
ACS New	$PM_{15\text{-}2.5}$	0.4%	(−1.4, 2.2%)	0.4%	(−2.2, 3.1%)	−1.2%	(−7.3, 5.1%)
ACS New	$PM_{10/15}$ Dicot	4.1%	(0.9, 7.4%)	7.3%	(3.0, 12%)	0.8%	(−8.1, 11%)
ACS New	$PM_{10/15}$SSI	1.6%	(−0.8, 4.1%)	5.7%	(2.5, 9.0%)	−1.6%	(−9.1, 6.4%)
ACS Extend. [7]	$PM_{2.5}$ 1979-1983	4.1%	(0.8, 7.5%)	5.9%	(1.5, 10%)	8.2%	(1.1, 16%)
ACS Extend.	$PM_{2.5}$ 1999-2000	5.9%	(2.0, 9.9%)	7.9%	(2.3, 14%)	12.7%	(4.1, 22%)
ACS Extend.	$PM_{2.5}$ Avg.	6.2%	(1.6, 11%)	9.3%	(3.3, 16%)	13.5%	(4.4, 23%)
AHSMOG [8]	$PM_{10/15}$	2.1%	(−4.5, 9.2%)	0.6%	(−7.8, 10%)	81%	(14, 186%)
AHSMOG [9]	$PM_{2.5}$	8.5%	(−2.3, 21%)	23%	(−3.0, 55%)	39%	(−21, 150%)
AHSMOG [9]	PM_{10}-$PM_{2.5}$	5.2%	(−8.3, 21%)	20%	(−13, 64%)	26%	(−38, 155%)
VA [10]	$PM_{2.5}$	0.3% [11]	NS [13]				
	$PM_{2.5}$	−10% [12]	SS [14]				
VA [10]	$PM_{15\text{-}2.5}$	0.7% [11]	NS [13]				
	$PM_{15\text{-}2.5}$	−2.0% [12]	NS [13]				
VA [10]	PM_{15}	0.7% [11]	NS [13]				
	PM_{15}	−7.6 [12]	SS [14]				

[1] Increments are10 μg/m^3 for $PM_{2.5}$ and $PM_{10/15\text{-}2.5}$ and 20 μg/m^3 for $PM_{10/15}$.
[2] Ex. RR (excess relative risk, percent) = 100 * (RR - 1) where the RR has been converted from the highest-to-lowest range to the standard increment (10 or 20) by the equation RR = exp(log(RR for range) × (standard increment) /range).
[3] From Dockery et al. (1993); Krewski et al. (2000), Part II, Table 21a, original model.
[4] From Krewski et al. (2000), Part I, Table 21c.
[5] From Krewski et al. (2000), Part I, Table 25a.
[6] From Krewski et al. (2000), Part I, Table 25c.
[7] From Pope et al. (2002).
[8] From Abbey et al. (1999), pooled estimate for males and females.
[9] From McDonnell et al. (2000), two-pollutant (fine and coarse) models; males only.
[10] From Lipfert et al. (2000b), Males only, exposure period 1979-1981 from Table 7. Standard errors not provided.
[11] Single period mortality (1976-1996).
[12] Mortality from 1982-88.
[13] Reported by author to be nonsignificant.
[14] Reported to be statistically significant.

studies, the ACS and Six Cities studies are thusly more broadly representative of U.S. populations.

The estimated mean risk of cigarette smoking in the VA cohort (RR = 1.43) was smaller than that of the Six City cohort (RR = 1.59) and the ACS cohort (RR = 2.07 for current smokers). Some possible differences include the higher proportion of former or current smokers in the VA cohort (81%) versus 51% in the ACS study and 42 to 53% in the Six City study. A possibly more important factor may be the difference in education levels, as only 12% of the ACS participants had less than a high school education vs 28% of the Six City cohort. Education level was not reported for the VA Cohort; however, education differences may be associated with smoking behavior (more smokers among the less-educated). The ACS, Six Cities and AHSMOG investigators used Cox Proportional Hazards models to estimate relationships between mortality and long-term PM exposure; in the VA study, linear regression models were used. All incorporated potentially confounding variables, such as body mass index or smoking history; however, as described previously, the VA study included a large number of covariates and interaction terms in the models. The VA study also differed from the other three studies in emphasizing analyses using subsets of air quality and mortality data.

As described in more detail in section 8.4.6.4, the Harvard Six Cities study used dichotomous samplers to measure fine and coarse fraction particles for approximately seven years in each city. AHSMOG investigators relied on available PM monitoring data, initially using TSP, then PM_{10} data, and more recently including $PM_{2.5}$ data estimated from airport visibility measurements. Both the VA and ACS studies used $PM_{2.5}$ data from the same data set, the IP Network which consisted of 157 sites. For the VA study, the cohort was between 26,000 and 29,000 for the two exposure periods derived from 103 monitors and for the ACS study, the cohort was 359,000 in 61 MSAs for one exposure period 1979 to 1983. Both studies may have potentially used up to 61 sites in common, but the VA study breaks the average level into two periods, whereas the ACS study averages the level across the entire time period. For the cities in common, the same data were used to relate an exposure estimate to the county in the VA study and to the Metropolitan Statistical Areas (MSAs) in the ACS study. Thus differences in the base

for deriving exposure estimates for the subjects may have contributed to possible differences between the representativeness of exposures used in the county or the MSA.

Section 3.2.5 and Appendix 3A discuss spatial variability in $PM_{2.5}$ at multiple sites within MSAs across the United States for 27 MSAs. MSA sites may include those in one to several counties. Consistency of $PM_{2.5}$ values between multiple sites within individual MSAs used to derive annual averages for $PM_{2.5}$ can vary by MSAs. The annual averages for many counties differ by 1 to 2 $\mu g/m^2$ across MSAs. In some counties with several monitors, differences between individual monitors can range from 1 to 2 $\mu g/m^2$ to 4 to 6 $\mu g/m^2$, at times, for annual averages.

It is noteworthy that estimated PM effects observed in the VA study appeared to be more negative in the later years of the study rather than in the earlier years. As noted earlier, this may also be due to cohort depletion. The participants in the VA Cohort clearly formed an "at-risk" population, and the results by Vasan et al. (2001) make more plausible the hypothesis stated by Lipfert et al. (2000b, p. 62) that ". . . . the relatively high fraction of mortality within this cohort may have depleted it of susceptible individuals in the later periods of follow-up."

The Six Cities study found significant associations of $PM_{2.5}$ with total and cardiopulmonary (but not lung cancer) mortality, but not with coarse particle indicators. In the Krewski et al. (2000) reanalysis of the ACS study data, significant associations were found for both $PM_{2.5}$ and PM_{15} (excess relative risks of 6.6% for a 10 $\mu g/m^3$ increase in $PM_{2.5}$ and 4% for a 20 $\mu g/m^3$ increase in annual $PM_{10/15}$). The results most recently reported for the AHSMOG study (Abbey et al., 1999; McDonnell et al., 2000) used PM_{10} as its PM mass index and found some significant associations with total mortality and deaths with contributing respiratory causes, even after controlling for potentially confounding factors (including other pollutants). In further evaluation of results found for PM_{10} among males, McDonnell et al. (2000) reported larger associations with $PM_{2.5}$ than $PM_{10-2.5}$ for males in the AHSMOG cohort, though none of the 11 $PM_{2.5}$ associations reached statistical significance. For the VA study, few statistically significant associations were found with PM indicators; in fact, some statistically significant negative associations were reported for some subset analyses. Where significant positive associations were reported, they were generally for the subset of mortality data from the early years of the

study. The authors note that these were sometimes analyses using mortality data that preceded the air quality measurements; it is important to note, however, that the design of these studies uses available air quality data to characterize long-term pollution concentrations, not as a measure of latency or lag period in effects.

There is no clear consistency in relationships among PM effect sizes, gender, and smoking status across these studies. The AHSMOG study cohort is a primarily nonsmoker group while the VA study cohort had a large proportion of smokers and former smokers in an all-male population. The ACS results show similar and significant associations with total mortality for both "never smokers" and "ever smokers", although the ACS cohort may include a substantial number of long-term former smokers with much lower risk than current smokers. The Six Cities Study cohort shows the strongest evidence of a higher PM effect in current smokers than in nonsmokers, with female former smokers having a higher risk than male former smokers. This study suggests that smoking status may be viewed as an effect modifier for ambient PM, just as smoking may be a health effect modifier for ambient O_3 (Cassino et al., 1999).

When the ACS study results are compared with the AHSMOG study results for SO_4^{2-} ($PM_{10-2.5}$ and PM_{10} were not considered in the ACS study, but were evaluated in ACS reanalyses [Krewski et al., 2000; Pope et al, 2002]), the total mortality effect sizes per 15 $\mu g/m^3$ SO_4^{2-} for the males in the AHSMOG population fell between the Six-Cities and the ACS effect-size estimates for males (RR = 1.28 for AHSMOG male participants; RR = 1.61 for Six-Cities Study male nonsmokers; and RR = 1.10 for never smoker males in the ACS study), and the AHSMOG study 95% confidence intervals encompass both of those other studies' sulfate RR's.

In considering the results of these studies together, statistically significant associations are reported between fine particles and mortality in the ACS and Six Cities analyses, inconsistent but generally positive associations with PM were reported in the AHSMOG analyses, and distinctly inconsistent results were reported in the VA study. Based on several factors, the larger study population in the ACS study, the larger air quality data set in the Six Cities study, the more generally representative study populations used in the Six Cities and ACS studies, and the fact that these studies have undergone extensive reanalyses – the greatest weight should be placed on the results of the ACS and Six Cities cohort studies in assessing relationships between

long-term PM exposure and mortality. The results of these studies, including the reanalyses results for the Six Cities and ACS studies and the results of the ACS study extension, provide substantial evidence for positive associations between long-term ambient PM (especially fine PM) exposure and mortality.

8.2.3.2.6 The S-Plus GAM Convergence Problem and Cohort Studies

The long-term pollution-mortality study results discussed above in this section were unaffected by the GAM default convergence issue reported by Dominici et al. (2002) and discussed earlier in this chapter, because they did not use such a model specification. Instead, the cohort studies of long-term PM exposures used Cox Proportional Hazards models. For example, in the recent Pope et al. study (2002), the baseline models were random effects Cox Proportional Hazards models without the inclusion of nonparametric smooths. However, Pope et al. (2002) did include a nonparametric spatial smooth in the model as part of a more extended sensitivity analysis to evaluate more aggressive control of spatial differences in mortality. They found that the estimated pollution-mortality effects were not sensitive to this additional spatial control, so final reported results did not include the smooth; and this study's results, like those from other cohort studies discussed above, were unaffected by the S-Plus convergence issue.

8.2.3.3 Studies by Particulate Matter Size-Fraction and Composition

8.2.3.3.1 Six Cities, ACS, AHSMOG and VA Study Results

Ambient PM consists of mixtures that may vary in composition over time and from place to place. This should logically affect the relative toxicity of PM indexed by mass at different times or locations. Some semi-individual chronic exposure studies have investigated relative roles of various PM components in contributing to observed air pollution associations with mortality. However, only a limited number of the chronic exposure studies have included direct measurements of chemical-specific constituents of the PM mixes indexed by mass measurements used in their analyses.

As shown in Table 8-13, the Harvard Six-Cities Study (Dockery et al., 1993) results indicated that the $PM_{2.5}$ and SO_4^{2-} RR associations (as indicated by their respective 95% CIs and

TABLE 8-13. COMPARISON OF ESTIMATED RELATIVE RISKS FOR ALL-CAUSE MORTALITY IN SIX U.S. CITIES ASSOCIATED WITH THE REPORTED INTERCITY RANGE OF CONCENTRATIONS OF VARIOUS PARTICULATE MATTER METRICS

PM Species	Concentration Range ($\mu g/m^3$)	Relative Risk Estimate	RR 95% CI	Relative Risk t-Statistic
SO_4^{2-}	8.5	1.29	(1.06-1.56)	3.67
$PM_{2.5}$ - SO_4^{2-}	8.4	1.24	(1.16-1.32)	8.79
$PM_{2.5}$	18.6	1.27	(1.06-1.51)	3.73
$PM_{15-2.5}$	9.7	1.19	(0.91-1.55)	1.81
TSP-PM_{15}	27.5	1.12	(0.88-1.43)	1.31

Source: Dockery et al. (1993); U.S. Environmental Protection Agency (1996a).

t-statistics) were more consistent than those for the coarser mass components. Further, the effects of sulfate and non-sulfate $PM_{2.5}$ are quite similar. Acid aerosol (H^+) exposure was also considered by Dockery et al. (1993), but only less than one year of measurements collected near the end of the follow-up period were available in most cities; consequently, the Six-Cities results were much less conclusive for the acidic component of PM than for the other PM metrics measured over many years during the study.

Table 8-14 presents comparative $PM_{2.5}$ and SO_4^{2-} results from the ACS study, indicating that both had substantial, statistically significant effects on all-cause and cardiopulmonary mortality. On the other hand, the RR for lung cancer was notably larger (and substantially more significant) for SO_4^{2-} than $PM_{2.5}$ (not significant).

The most recent AHSMOG analyses also considered SO_4^{2-} as a PM index for all health outcomes studied except lung cancer, but SO_4^{2-} was not as strongly associated as PM_{10} with mortality (as shown in Table 8-8) and was not statistically significant for any mortality category.

Also, extensive results from the VA study were reported in Lipfert et al. (2000b) for various components: TSP, PM_{10}, $PM_{2.5}$, $PM_{15-2.5}$, PM_{15}, SO_4^{2-}. There were no significant positive effects for any exposure period concurrent or preceding any of the segmented mortality periods for any PM component, unlike for O_3. On the other hand, the SO_4^{2-} levels during the 1979 to

TABLE 8-14. COMPARISON OF REPORTED SO_4^{2-} AND $PM_{2.5}$ RELATIVE RISKS FOR VARIOUS MORTALITY CAUSES IN THE AMERICAN CANCER SOCIETY (ACS) STUDY

Mortality Cause	SO_4^{2-} (Range = 19.9 µg/m^3)			$PM_{2.5}$ (Range = 24.5 µg/m^3)		
	Relative Risk	RR 95% CI	RR t-Statistic	Relative Risk	RR 95% CI	RR t-Statistic
All Cause	1.15	(1.09-1.22)	4.85	1.17	(1.09-1.26)	4.24
Cardiopulmonary	1.26	(1.15-1.37)	5.18	1.31	(1.17-1.46)	4.79
Lung Cancer	1.35	(1.11-1.66)	2.92	1.03	(0.80-1.33)	0.38

Source: Pope et al. (1995).

1981 and 1982 to 1984 exposure periods were significantly associated with deaths aggregated across all the segmented follow-up mortality periods (1976 to 1996). The first exposure period was associated with 4.9% increase and the latter with a 6.7% increase in the aggregated ("single period" in Lipfert et al 2000b terminology) total, nonaccidental mortality risk per 10 µg/m^3 SO_4^{2-} increment.

Harvard Six Cities, ACS, and AHSMOG study results are compared in Table 8-15 (total mortality) and Table 8-16 (cause-specific mortality). Results for the VA study are not shown in Tables 8-15 and 8-16 as the VA cohort is all male and largely consists of current or former smokers (81%) and is thusly not comparable to the total or male nonsmoker populations of the other studies. Also, results for females are not presented, as the overall effects were driven largely by males (female associations generally being statistically nonsignificant).

Estimates for Six Cities parameters were calculated in two ways: (1) mortality RR for the most versus least polluted city in Table 3 of Dockery et al. (1993), adjusted to standard increments; and (2) ecological regression fits in Table 12-18 of U.S. Environmental Protection Agency (1996a). The Six Cities study of eastern and mid-western U.S. cities suggests a strong and highly significant relationship for fine particles and sulfates, a slightly weaker but still highly significant relationship to PM_{10}, and a marginal relationship to $PM_{10-2.5}$. The ACS study looked at a broader spatial representation of cities, and found a stronger statistically significant

TABLE 8-15. COMPARISON OF TOTAL MORTALITY RELATIVE RISK ESTIMATES AND t-STATISTICS FOR PARTICULATE MATTER COMPONENTS IN THREE PROSPECTIVE COHORT STUDIES

PM Index	Study	Subgroup	Relative Risk	t Statistic
PM_{10} (50 μg/m^3)	Six Cities	All	1.50 [a]; 1.53 [b]	2.94 [a]; 3.27 [b]
		Male Nonsmoker	1.28 [a]	0.81 [a]
	AHSMOG	Male Nonsmoker	1.24	1.61
$PM_{2.5}$ (25 μg/m^3)	Six Cities	All	1.36 [a]; 1.38 [b]	2.94 [a]; 3.73 [b]
		Male Nonsmoker	1.21 [a]	0.81 [a]
	ACS (50 cities)	All	1.17	4.35
		Male Nonsmoker	1.25	1.96
SO_4^{2-} (15 μg/m^3)	Six Cities	All	1.50 [a]; 1.57 [b]	2.94 [a]; 3.67 [b]
		Male Nonsmoker	1.35	0.81 [a]
	ACS (151 cities)	All	1.11	5.11
		Male Nonsmoker	1.1	1.59
	AHSMOG	Male Nonsmoker	1.28	0.96
Days/year with PM_{10} > 100 μg/m^3 (30 days)	AHSMOG	Male Nonsmoker	1.08	2.18
$PM_{10-2.5}$ (25 μg/m^3)	Six Cities	All	1.81 [a]; 1.56 [b]	2.94 [a,c] 1.81 [b]
		Male Nonsmoker	1.43 [a]	0.81 [a]

[a] Method 1 compares Portage versus Steubenville (Table 3, Dockery et al., 1993).
[b] Method 2 is based on ecologic regression models (Table 12-18, U.S. Environmental Protection Agency, 1996a).
[c] Method 1 not recommended for $PM_{10-2.5}$ analysis, due to high concentration in Topeka.

relationship to $PM_{2.5}$ than to sulfate (no other pollutants were examined). The AHSMOG study at California sites (where sulfate levels are typically low) found significant effects in males for PM_{10} 100 μg/m^3 exceedances and a marginal effect of mean PM_{10}, but no PM effects for females or with sulfates. On balance, the overall results shown in Tables 8-15 and 8-16 suggest statistically significant relationships between long-term exposures to PM_{10}, $PM_{2.5}$, and/or sulfates and excess total and cause-specific cardiopulmonary mortality.

TABLE 8-16. COMPARISON OF CARDIOPULMONARY MORTALITY RELATIVE RISK ESTIMATES AND t-STATISTICS FOR PARTICULATE MATTER COMPONENTS IN THREE PROSPECTIVE COHORT STUDIES

PM Index	Study	Subgroup	Relative Risk	t Statistic
PM_{10} (50 µg/m^3)	Six Cities	All	1.744 [a]	2.94 [a]
	AHSMOG	Male Nonsmoker	1.219	1.12
		Male Non-CRC [c]	1.537	2.369
$PM_{2.5}$ (25 µg/m^3)	Six Cities	All	1.527 [a]	2.94 [a]
	ACS (50 cities)	All	1.317	4.699
		Male	1.245	3.061
		Male Nonsmoker	1.245	1.466
SO_4^{2-} (15 µg/m^3)	Six Cities	All	1.743 [a]	2.94 [a]
	ACS (151 cities)	All	1.19	5.47
		Male	1.147	3.412
		Male Nonsmoker	1.205	2.233
	AHSMOG	Male Nonsmoker	1.279	0.072
		Male Non.-CRC [c]	1.219	0.357
Days/year with $PM_{10} > 100$ (30 days)	AHSMOG	Male Nonsmoker	1.082	1.31
		Male Non.-CRC [c]	1.188	2.37
$PM_{10-2.5}$ (25 µg/m^3)	Six Cities	All	2.251 [a]	2.94 [a,b]

[a] Method 1 compares Portage versus Steubenville (Table 3, Dockery et al., 1993).
[b] Method 1 not recommended for $PM_{10-2.5}$ analysis due to high concentration in Topeka.
[c] Male non. - CRC = AHSMOG subjects who died of any contributing nonmalignant respiratory cause.

The prospective cohort long-term PM exposure studies conducted to date collectively appear to confirm earlier cross-sectional study indications that the fine mass component of PM_{10} (and usually especially its sulfate constituent) are more strongly correlated with mortality than is the coarse $PM_{10-2.5}$ component. However, the greater precision of $PM_{2.5}$ population exposure measurement (both analytical and spatial) relative to $PM_{10-2.5}$ makes conclusions regarding their

relative contributions to observed PM_{10}-related associations less certain than if the effect of their relative errors of measurement could be addressed.

8.2.3.3.2 Lipfert and Morris (2002): An Ecological Study

Although the use of prospective cohort studies in assessing the long-term exposure effects of particles and gases is preferred, additional useful information may be derived from ecological studies. In particular, repeated cross-sectional studies may provide another tool for examining changes in air-pollution-attributable mortality over time. Lipfert and Morris (2002) carried out cross-sectional regressions for five time periods using data on mortality, air pollution including various measures of PM, O_3, NO_2, SO_2, CO, climate, and sociodemographic factors using county-level data. Data were available for TSP and gaseous co-pollutants as far back as 1960 and for $PM_{2.5}$, PM_{15}, and SO_4^{2-} from the inhalable particulate network (IPN). The authors investigated longitudinal and spatial relations between air pollution and age-specific mortality using 3- to 5-year subsets of data from 1960 to the end of 1997, with the addition of $PM_{2.5}$ data from 1999.

One of the key features of this study is the presentation of attributable risk estimates for different age groups across varying time periods. It is important to note that cross-sectional studies such as this one do not directly investigate temporality or latency of effects. One or more years of pollution measurements are used as estimates of long-term pollution concentrations for the communities. Lipfert and Morris (2002) note that $PM_{2.5}$ data from the two available time periods (1979 to 1984 and 1999) were well correlated ($r = 0.71$)[2] and, in fact, used the 1999 data for "back-extrapolation" of data for some of the counties where data were not available in 1979 to 1984[3]. The different time periods may provide data that more or less adequately represent long-term PM concentrations, and it is more important that the measurements reflect long-term trends than that the PM concentrations predate the mortality data by any specific time period.

---

[2] Pope et al. (2002) also reported a strong correlation ($r = 0.78$) between $PM_{2.5}$ concentrations averaged over 1979 to 1983 and 1999 to 2000 in the extended analysis for the ACS cohort.

[3] It appears that the extrapolated data were used in the main analyses. EPA observes that it was difficult to interpret the methodological discussions in the paper and obtained further information via personal communication with the author.

While well-motivated, the use of multiple mortality and pollution time periods clearly reduces the power of any individual analysis.

The counties included in any given analysis varied by time period based on available data. Lipfert and Morris (2002) stated that "the number of counties with valid air quality data vary substantially...by pollutant and over time" and that they attempted to differentiate "among many air quality variables that differ according to species, timing, and in some cases measurement technology." They stated, "Environmental monitoring coverage increased substantially during this period [1970 to 1974] (1,258 counties had TSP data) and air quality began to improve in major cities in response to emission controls and use of clean fuels." There have also been changes in the measurement of PM (e.g., TSP, $PM_{10,}$ and $PM_{2.5}$) over time as well as changes in the location of monitors as they were sited for different purposes.

An interesting conclusion drawn by Lipfert and Morris (2002) is that pollution-mortality relationships vary across age groups, with stronger effects among younger age groups. It is important, however, to note that the results of this study are presented as attributable risks; with attributable risk defined as the mortality risk based on the mean concentration of the pollutant and the mean mortality rate. A problem with attributable risk arises when one compares the risks of different age groups. In Table 8-17, it can be seen that among the young a higher percentage of mortality is reduced by reducing air pollution, as reflected in the higher attributable risks. However, with the more standard presentation of risk per 10 $\mu g/m^3$ change in $PM_{2.5}$, the risk increases for older age groups.

Lipfert and Morris (2002) also reported that they generally found that risk estimates were highest for pollution estimates in the earlier time periods and decreased in analyses using more recent pollution and mortality data. This can be seen in Table 8-17, where statistically significant associations are reported for all but the youngest age group using 1989 to 1991 mortality data, but with 1995 to 1997 data the associations were smaller and only significant for one age group. The same pattern can be seen for TSP, $PM_{10,}$ and $PM_{2.5}$ as summarized in Figure 7 in the authors' report (Lipfert and Morris, 2002). The authors concluded that mortality responses to air pollution have been decreasing over time for PM and several other pollutants.

TABLE 8-17. PERCENT ATTRIBUTABLE RISK OF MORTALITY (from Lipfert and Morris, 2000) AND RISK ESTIMATES CALCULATED PER 10 μg/m^3 $PM_{2.5}$. SELECTED TIME PERIODS FOR MORTALITY DATA OF 1989-91 AND 1995-97 WITH $PM_{2.5}$ DATA FROM THE IP NETWORK DATA (1979-84) FOR COUNTIES IN THE U.S. WITH IP NETWORK MONITORS.

	1989-91 Mortality Data				1995-97 Mortality Data			
	Lipfert and Morris Results		EPA Estimates (per 100,000)		Lipfert and Morris Results		EPA Estimates (per 100,000)	
Age	Attributable Risk[A]	SE	Mortality Rate	Risk Estimate[B]	Attributable Risk[A]	SE	Mortality Rate	Risk Estimate[B]
15-44	5.2	4.9	70	4	4.2	3.6	74	3
45-64	7.9*	2.4	778	62	5.4*	2.7	701	38
65-74	3.7*	1.2	2643	98	1.1	1.4	2577	27
75-84	2.0*	1	5943	119	1.5	1.9	5885	88
≥ 85	2.1*	0.8	15145	316	1.6	1.4	15795	246

*P < 0.05

[A] adapted from Lipfert and Morris (2002) Tables 7 and 8; converted to %attributable risk per 10 μg/m^3.

[B] risk estimate = (coefficient)(10 μg/m^3 $PM_{2.5}$) per 100,000 over a 3-year period; where coefficient = [(AR) (mean mortality rate)]/(mean $PM_{2.5}$ concentration). Mortality rates per 100,000 over a 3-year period from Table 1 and mean $PM_{2.5}$ concentration (19.19 μg/m^3) from Table 2 of Lipfert and Morris (2002).

In any cross-sectional study, exposure misclassification and confounding are important issues to consider in interpreting the results. For all studies discussed in this section, exposure is characterized by pollution concentration averaged for a given geographic region. In cohort studies, some information is generally available on participants' residence histories but in cross-sectional studies the exposure level is assigned based on the subjects' location according to the death record. Between the years 1995 to 2000, approximately 20% of people aged 5 to 64 years moved to a different state. Older adults were slightly less mobile as a group, with 18.8% of those 65 and older moving to a different state; the rate was 21.2% for adults aged 65 to 74 and declined with greater age, though there was some evidence of return migration at advanced ages of 85 years and older (U.S. Census Bureau, 2003). To address potential confounding, the authors used county-level data on a variety of risk factors, using stepwise regression methods to

select the best-fitting model, then apparently used the residuals from these models to evaluate relationships with air pollution concentrations. While an impressive list of variables were included in these analyses, it must be noted that there can be considerable variation in socioeconomic or personal risk factors across areas within a given county as well as from county to county.

The inhalable particle network data used in Lipfert and Morris (2002) is basically the same air quality data set used in analyses for the ACS and VA study cohorts. A major distinction, of course, is that individual health data were used in the cohort studies, but only county-level data for the cross-sectional study. Lipfert and Morris (2002) noted reasonable agreement with Pope et al. (1995) and Dockery et al. (1993), but observed that the VA study analyses (Lipfert et al., 2000b) "found apparent beneficial effects of $PM_{2.5}$...whereas the present study does not." While subject to the limitations of cross-sectional analyses, the Lipfert and Morris study reports associations between fine particles and mortality that are generally similar to those from the large cohort studies, although it is difficult to compare the quantitative results across studies. Interpreting the results of the many subset analyses conducted is difficult, but the results of analyses across time periods would appear to indicate reduced mortality risk with pollution from more recent time periods.

8.2.3.3.3 Mortality and Chronic Exposure to Traffic-Related Ambient PM

Hoek et al. (2002): Traffic and Mortality in the Netherlands

Hoek et al. (2002) assessed the relationship between traffic-related air pollution and mortality among participants of the Netherlands Cohort Study on Diet and Cancer (NLCS), an ongoing study. They investigated a random sample of 5000 middle-aged people (aged 55 to 69 years) from the full cohort of the NLCS study during 1986 to 1994. Long-term exposures to traffic-related air pollutants were estimated using participants' 1986 home address. In a novel attempt to take into account within-city variation of air pollution concentrations by quantifying small-scale spatial variations in air pollution concentrations, the home addresses were geocoded with a geographic information system (GIS). Long-term average exposure to outdoor air pollution was calculated as a function of an estimation method that consisted of interpolation of

regional background stations, the estimation of urban background increases for BS and NO_2, and the characterization of local contributions, with indicator variables also indicating whether a subject lived within 100 m of a freeway or 50 m of a major city road.

Associations between exposure to air pollution and (cause-specific) mortality were assessed with Cox's proportional hazards models, with adjustment for potential confounders. Cardiopulmonary mortality was reported to be associated with living near a major road (relative risk 1.95, CI: 1.09, 3.52). The relative risk for living near a major road was 1.41 (0.94 , 2.12) for total deaths. The authors considered the potential role of residual confounding factors, finding that the unadjusted effects estimates were consistently similar to the effects after adjustment for confounders, and concluding that residual confounding was very unlikely to account for the association between living near a major road and mortality. The authors concluded that long-term exposure to traffic-related air pollution may shorten life expectancy. Hoek et al. (2002) also noted that living near a major road might also include factors other than air pollution as a factor for mortality.

The use of estimated concentrations for pollutant levels (as contrasted to quantitatively measured mass levels such as PM_{10} or $PM_{2.5}$) indicates that the Hoek et al. (2002) study was a hypothesis-generating study, the main value of which is more at providing insights into potential areas for well-designed hypothesis-testing studies that include more quantitative measurements of PM_{10} and/or $PM_{2.5}$. Without adequate actual measurements, estimates of exposure are uncertain. Neither BS nor NO_2 measures were likely to have provided adequate quantitative data for the estimation of PM_{10} or $PM_{2.5}$. For example, Hoek et al. (2001) observed that the contrast in PM_{10} concentrations across in the Netherlands is relatively small and that BS concentrations are not a good proxy for PM_{10} or $PM_{2.5}$.

This long-term study is unique in that it attempted to examine within-metropolitan-area small-scale variations in exposures. However, given that exposure estimates were characterized by interpolation (based on the measured regional and urban background concentration, as well as using an indicator variable for living near major roads, during only one year at the beginning of the study period), much caution is warranted in viewing the study's key results as noted above. Nevertheless, the overall approach used appears to be a promising one, to the extent that future

analogous studies employ more refined interpolation of exposure estimates based on more extensive measured data obtained over longer periods.

8.2.3.4 PM-Mortality Intervention Studies

Although many studies have reported short-term associations between PM indices and mortality, a largely unaddressed question remains as to the extent to which reductions in ambient air PM actually lead to reductions in deaths attributable to PM. This question is not only important in terms of "accountability" from the regulatory point of view, but it is also a scientific question that challenges the predictive validity of statistical models and their underlying assumptions used thus far to estimate excess mortality due to ambient PM.

The opportunities to address this question are rare. However, at the time of the 1996 PM AQCD, one situation presented a good opportunity for a PM intervention study—that being the Utah Valley situation evaluated by Pope. In the Pope (1989) analysis of PM_{10} and children's hospital admissions in Utah Valley, the study period contained the 13-month steel mill closure mentioned earlier (during which time PM_{10} concentrations averaged 35 $\mu g/m^3$ versus 50 $\mu g/m^3$ when the mill was opened). Analyses of children's respiratory admissions in Utah Valley before and after the steel mill closure provided evidence of decreased morbidity resulting from the lower PM_{10} concentrations during the mill closure.

Two more recent mortality intervention studies have examined: (1) the impact of a ban on coal sale in Dublin, Ireland (Clancy et al., 2002); and (2) the impact of a regulation to use fuel oil with low sulfur content in Hong Kong (Hedley et al., 2002). These regulations were enforced across very short time frames and, as such, they provided opportunities to observe any change in mortality rate before and after the intervention.

Clancy et al. (2002) examined the impact of the ban on coal sales that took place in September 1990 in the city of Dublin, Ireland. They assessed the ban's impact on mortality by conducting Poisson regression of the standardized mortality rate during 72 months before and after the ban on coal sales (13 years total study period), adjusting for temperature on the same day and previous days, mean relative humidity and previous days, day-of-week, respiratory epidemics, and directly standardized deaths rates in the rest of Ireland. The impact of the ban

was estimated by an indicator variable of the post-ban period. They also reported means for black smoke (BS), SO_2, temperature and relative humidity before and after the ban by season, as well as age-standardized deaths rates before and after the ban by seasons. A substantial reduction (35.6 μg/m^3 reduction, or 70% for all seasons) in BS, especially for winter season (63.8 μg/m^3 reduction) was observed. The reduction for SO_2 was less (34% reduction). The post-ban means of age-standardized mortality rates were significantly lower for total (nonaccidental), cardiovascular, and respiratory categories for all seasons combined and especially for the winter season. In contrast, the mean of the other mortality categories slightly increased for spring and fall (but decreased for summer). The Poisson regression results with adjustments for time-varying covariates showed statistically significant ($p < 0.05$) reductions in age-standardized mortality rate for total (−5.7% [−7.2, −4.1]), cardiovascular (−10.3% [−12.6, −8.0]), and respiratory (−15.5% [−19.1, - 11.6]) mortality, but not mortality for other causes (1.7% [−0.7, 4.2]). The results without adjustments for other time-varying covariates showed larger reductions.

Clancy et al. compared their mortality reduction estimates to the projected reduction based on APHEA 1 study (Katsouyanni et al., 1997) results. They noted that the BS mortality regression coefficient from APHEA 1 results would have translated to only a 2.1% reduction in total deaths had they been applied to the Dublin data where a BS concentration reduction of 35.6 μg/m^3 was observed, compared to a 5.7% decrease that Clancy and colleagues estimated for the intervention period in their analysis. They also noted that the actual reduction (~3.2% when the PM_{10} average was 15 μg/m^3 lower than the period when the mill was operating) in average deaths during the steel mill closure in Utah Valley, as noted by Pope et al. (1992), would have translated to 8.0% had it been applied to the BS reduction in the Dublin data (assuming that BS approximately = PM_{10}) — about the same as their unadjusted estimate (8.0%). It should be noted, however, that the reduction estimate in Clancy et al.'s study is the "average" reduction comparing the two 6-year periods before and after the ban of coal sales. In contrast, most time-series studies, including APHEA, estimate excess mortality risk in response to a short-term change, usually for mortality on a single day or a few days. As discussed in Section 8.4.5, there is some suggestive evidence that risk estimates based on a single- or a few-day exposures may

underestimate the possible multiday effects. The apparent lack of the evidence for "harvesting" (see Section 8.4.9.1) further suggests that the excess risk (or reduction) estimates based on the prevailing time-series study design may not predict longer-term effects. Therefore, comparisons of estimates of reduction in mortality due to interventions and predicted reductions based on results of time-series studies are not straightforward; and it may not be surprising that Clancy et al.'s estimate of mortality reduction was larger than predicted based on PM coefficients derived from most time-series studies. Clancy et al.'s study nevertheless provides suggestive evidence that a substantial reduction in PM leads to a significant reduction in mortality.

Hedley et al. (2002) assessed the impact on mortality rate of the restriction on use of low sulfur (not more than 0.5%) fuel oil implemented in July 1990 in Hong Kong. Changes in trends in deaths were estimated using Poisson regression of monthly mortality rate between 1985 and 1995, adjusting for trends, seasonal cycles (by sine/cosine terms), temperature, and relative humidity, with stratification by the two five-year pre- and post-intervention periods. They also estimated a measure of warm to cool season change in death rates relative to the mean by fitting monthly deaths as a function of sine and cosine terms for each of the five years after the intervention and by cause (total, respiratory, cardiovascular, neoplasms, and others) and by age groups (all ages, age 15 to 64, age 65 years and older). Interestingly, although SO_2 did decrease substantially (~50%), PM_{10} levels did not change at all after the intervention. Even sulfate levels, while reported to be lower by ~20% for the first 2 years after the intervention, were unchanged five years after the intervention, apparently due to regional influences. Ozone showed an increasing trend during the study period. The seasonal mortality analysis results show that the apparent reduction in seasonal death rate occurred only during the first winter, and this was followed by a rebound (i.e., higher than expected) in the following winter. This pattern was seen for total, respiratory, and cardiovascular categories. Based on the Poisson regression of the monthly mortality data analysis, the average annual trend in death rate significantly declined after the intervention for all cause (2.1%), respiratory (3.9%), and cardiovascular causes (2.0%). Hedley et al. also estimated expected average gain in life expectancy per year due to the lower SO_2 level to be 20 days for females and 41 days for males.

Interpreting Hedley et al.'s results is somewhat complicated by an upward trend noted by them in mortality across the intervention point, due to increased population size and aging. The results suggest that such an upward trend is less steep after the introduction of low sulfur fuel. While their Poisson regression model of monthly deaths does adjust for trend and seasonal cycles, the regression model does not specifically address the influence of influenza epidemics. Since the magnitude of influenza epidemics can change from year to year, the included sine/cosine terms will not necessarily fit the year-to-year variation. This issue also applies to the analysis of warm to cool season change in death rates. The most prominent feature of the time-series plot (or the fitted annual cycle of monthly deaths) presented in Hedley et al.'s paper is the lack of a winter peak for respiratory and all cause mortality during the year immediately following the intervention. Much could be made out of this lack of a winter peak, but no discussion of potential impact of (or a lack of) influenza epidemics is provided. These issues make the interpretation of the estimated decline in upward trend of mortality rate or the apparent lack of winter peak difficult. In any case, since the intervention did not result in the reduction of PM (PM_{10} in this case), this study does not provide direct information on the impact of PM intervention.

The Clancy et al. and Hedley et al. studies share a similar situation in which regulations caused a sudden reduction in PM and/or SO_2. Both studies estimated reductions in mortality rate before and after an intervention (6-year periods in Clancy et al. study, and 5-year periods in Hedley et al. study). Both studies attempted to adjust for unmeasured secular changes in social or other variables that can affect the trend in mortality rate by direct standardization or in the regression models. The challenge of these analyses is that, unlike regular time-series mortality analyses in which only the associations in short-term fluctuations are estimated by filtering out the longer-wave fluctuations, the parameter that is being estimated is in the longer-wave length where effective sample size of "events" can be small. For example, the number of influenza epidemics in these data is "small", and yet their magnitude can vary substantially from year to year, making their influence on the average statistics of long-wave events possibly large. Furthermore, because the regular short-term daily time-series studies specifically filter out these long-wave events, it may not be appropriate to directly compare projected risk reductions based

on PM risk coefficients derived from the daily time-series studies with estimated mortality reductions based on these intervention studies. Clearly, there is much uncertainty between mortality risk estimates derived from daily time-series studies versus those derived from cohort studies (that may be capturing the very long-term effects). The intervention studies appear to capture the risk (reduction) in a time scale that is in between these two types of studies.

In summary, the Clancy et al. (2002) intervention study suggests evidence of mortality reduction in response to reduced levels of PM, whereas Hedley et al.'s intervention study presents an unusual case, where SO_2 levels declined substantially (but PM levels did not) and the SO_2 decrease was paralleled by mortality decrements. As such, these specific intervention studies are valuable in drawing qualitative conclusions that imply likely causal relationships underlying the observed mortality decrements occurring in concert with declines in ambient PM and/or SO_2 levels.

8.2.3.5 Salient Points Derived from Analyses of Chronic Particulate Matter Exposure Mortality Effects

A review of the studies summarized in the previous PM AQCD (U.S. Environmental Protection Agency, 1996a) indicates that past epidemiologic studies of chronic PM exposures collectively indicated that increases in mortality are associated with long-term exposure to airborne particles of ambient origins. The PM effect size estimates for total mortality from these studies also indicate that a substantial portion of these deaths reflected cumulative PM effects above and beyond those exerted by acute exposure events.

The HEI-sponsored reanalyses of the ACS and Harvard Six-Cities studies (Krewski et al., 2000) "replicated the original results, and tested those results against alternative risk models and analytic approaches without substantively altering the original findings of an association between indicators of particulate matter air pollution and mortality." Several questions, including the questions (1 to 4) posed at the outset of this Section (8.2.3) were investigated by the Krewski et al. (2000) sensitivity analyses for the Six City and ACS studies data sets. Key results emerging from the HEI reanalyses and other new chronic PM mortality studies are as follows:

(1) A much larger number of confounding variables and effects modifiers were considered in the Reanalysis Study than in the original Six City and ACS studies. The only significant air pollutant other than $PM_{2.5}$ and SO_4 in the ACS study was SO_2, which greatly decreased the $PM_{2.5}$ and sulfate effects when included as a co-pollutant (Krewski et al., 2000, Part II, Tables 34-38). A similar reduction in particle effects occurred in any multipollutant model with SO_2. The most important new effects modifier was education. The AHSMOG study also suggested that other metrics for air pollution, and other personal covariates such as time spent outdoors and consumption of anti-oxidant vitamins, might be useful. Both individual-level covariates and ecological-level covariates shown in (Krewski et al., 2000, Part II, Table 33) were evaluated, including whether or not the observations are independent or spatially correlated.

(2) Specific attribution of excess long-term mortality to any specific particle component or gaseous pollutant was refined in the reanalysis of the ACS study. Both $PM_{2.5}$ and sulfate were significantly associated with excess total mortality and cardiopulmonary mortality and to about the same extent whether the air pollution data were mean or median long-term concentrations or whether based on original investigator or Reanalysis Team data. The association of mortality with PM_{15} was much smaller, though still significant; and the associations with the coarse fraction ($PM_{15-2.5}$) or TSP were even smaller and not significant. The lung cancer effect was significant only for sulfate with the original investigator data or for new investigators with regional sulfate artifact adjustment for the 1980 to 1981 data (Krewski et al., 2000, Part II, Table 31). Associations of mortality with long-term mean concentrations of criteria gaseous co-pollutants were generally nonsignificant except for SO_2 (Krewski et al., 2000, Part II, Tables 32, 34-38), which was highly significant, and for cardiopulmonary disease with warm-season ozone. However, the regional association of SO_2 with SO_4 and SO_2 with $PM_{2.5}$ was very high; and the effects of the separate pollutants could not be distinguished. Krewski et al. (2000, p. 234) concluded that, "Collectively, our reanalyses suggest that mortality may be associated with more than one component of the complex mix of ambient air pollutants in urban areas of the United States." In the most recent extension of the ACS study, Pope et al. (2002) confirmed the strong association with SO_2 but found little evidence of effects for long-term exposures to other gaseous pollutants.

(3) The extensive temporal data on air pollution concentrations over time in the Six City Study allowed the Reanalysis Team to evaluate time scales for mortality for long-term exposure to a much greater extent than was reported in Dockery et al. (1993). The first approach was to estimate the log-hazard ratio as a function of follow up time using a flexible spline-function model (Krewski et al., 2000, Part II, Figures 2 and 3). The results for both SO_4^{2-} and $PM_{2.5}$ suggest very similar relationships, with larger risk after initial exposure decreasing to 0 after about 4 or 5 years, and a large increase in risk at about 10 years follow-up time.

The analyses of the ACS Study proceeded somewhat differently, with less temporal data but many more cities. Flexible spline regression models for $PM_{2.5}$ and sulfate as function of estimated cumulative exposure (not defined) were very nonlinear and showed quite different relationships (Krewski et al., 2000, Part II, Figures 10 and 11). The $PM_{2.5}$ relationship shows the mortality log-hazard ratio increasing up to ~15 $\mu g/m^3$ and relatively flat above ~22 $\mu g/m^3$, then increasing again. The sulfate relationship is almost piecewise linear, with a low near- zero slope below ~11 $\mu g/m^3$ and a steep increase above that concentration.

A third approach evaluated several time-dependent $PM_{2.5}$ exposure indicators in the Six City Study: (a) constant (at the mean) over the entire follow-up period; (b) annual mean within each of the 13 years of the study; (c) city-specific mean concentration for the earliest years of the study (i.e., very long-term effect); (d) exposure estimate in 2 years preceding death; (e) exposure estimate in 3 to 5 years preceding death; and (f) exposure estimate > 5 years preceding death. The time-dependent estimates (a-e) for mortality risk are generally similar and statistically significant (Krewski et al., 2000, Part II, Table 53), with RR of 1.14 to 1.19 per 24.5 $\mu g/m^3$ being much lower than the risk of 1.31 estimated for exposure at the constant mean for the period. Thus, it is highly likely the duration and time patterns of long-term exposure affect the risk of mortality; and further study of this question (along with that of mortality displacement from short-term exposures) would improve estimates of life-years lost from PM exposure.

(4) The Reanalysis Study also advanced our understanding of the shape of the relationship between mortality and PM. Again using flexible spline modeling, Krewski et al. (2000, Part II,

Figure 6) found a visually near-linear relationship between all-cause and cardiopulmonary mortality residuals and mean sulfate concentrations, near-linear between cardiopulmonary mortality and mean $PM_{2.5}$, but a somewhat nonlinear relationship between all-cause mortality residuals and mean $PM_{2.5}$ concentrations that flattens above ~20 $\mu g/m^3$. The confidence bands around the fitted curves are very wide, however, neither requiring a linear relationship nor precluding a nonlinear relationship if suggested by reanalyses. An investigation of the mortality relationship for other indicators may be useful in identifying a threshold, if one exists, for chronic PM exposures.

(5) With regard to the role of various PM constituents in the PM-mortality association, past cross-sectional studies have generally found the fine particle component, as indicated either by $PM_{2.5}$ or sulfates, to be the PM constituent most consistently associated with mortality. While relative measurement errors of various PM indicators must be further evaluated as a possible source of bias in these estimate comparisons, the Six-Cities and AHSMOG prospective cohort studies both indicate that the fine mass components of PM are more strongly associated with mortality effects of chronic PM exposure than are coarse fraction indicators.

(6) The spatial regression methods suggested that part of the relation between sulfate and mortality was probably due to some unobserved variable or group of confounding variables. In particular, they found that the sulfate-associated effect drops from a relative risk of 1.25 with the Independent Cities Model to 1.19 with the Regional Adjustment Model, but all models continued to show an association between elevated risks of mortality and exposure to airborne sulfate.

(7) The newly available (2002) ACS study extension more than doubles the original follow-up period (now to 16 versus 7 years originally); and it both (a) confirms the original ACS study findings of significant associations between long-term $PM_{2.5}$ exposures and increased cardiopulmonary mortality risks and (b) provides the strongest evidence to date for increased lung cancer risk associations with ambient fine particles measured as $PM_{2.5}$.

8.3 MORBIDITY EFFECTS OF PARTICULATE MATTER EXPOSURE

The effects of ambient PM on morbidity endpoints are assessed below in subsections focused on: (a) effects of acute ambient PM exposure on cardiovascular morbidity; (b) effects of short-term PM exposure on the incidence of respiratory and other medical visits and hospital admissions; and (c) short- and long-term PM exposure effects on lung function and respiratory symptoms in asthmatics and nonasthmatics.

8.3.1 Cardiovascular Morbidity Effects Associated with Acute Ambient Particulate Matter Exposure

8.3.1.1 Introduction

Very little information specifically addressing cardiovascular morbidity effects of acute PM exposure existed at the time of the 1996 PM AQCD. Since then, a significantly expanded body of literature has emerged, both on the ecologic relationship between ambient particles and cardiovascular hospital admissions and associations of PM exposures with changes in various physiological and/or biochemical measures. The latter studies are particularly important in that they are suggestive of possible mechanisms underlying PM cardiovascular effects. However, it should be noted that the mechanistic interpretation of the cardiovascular physiology results observed to date (some of which are conflicting) remain unclear, as discussed in more detail in Chapter 7.

This section begins with a brief summary of key findings from the 1996 PM AQCD on acute cardiovascular effects of PM. Next, key new studies are reviewed in the two categories noted above, i.e., ecologic time-series studies and individual-level studies of physiological measures of cardiac function and/or biochemical measures in blood as they relate to ambient pollution. This is followed by discussion of several issues of importance for interpreting the available data, including identification of potentially susceptible subpopulations, roles of environmental co-factors such as weather and other air pollutants, temporal lags in the relationship between exposure and outcome, and the relative importance of various size-classified PM components (e.g., $PM_{2.5}$, PM_{10}, $PM_{10-2.5}$).

8.3.1.2 Summary of Key Findings on Cardiovascular Morbidity from the 1996 Particulate Matter Air Quality Criteria Document

Just two studies were available for review in the 1996 PM AQCD that provided results for acute cardiovascular (CVD) morbidity outcomes (Schwartz and Morris, 1995; Burnett et al., 1995). Both studies were of ecologic time-series design and used standard statistical methods. Analyzing four years of data on the ≥ 65 year old Medicare population in Detroit, MI, Schwartz and Morris (1995) reported significant associations between PM_{10} and ischemic heart disease admissions, controlling for environmental covariates. Based on analysis of admissions data from 168 hospitals throughout Ontario, Canada, Burnett et al. (1995) reported significant associations between fine particle sulfate concentrations (as well as other air pollutants) and daily cardiovascular admissions. The relative risk due to sulfate particles was slightly larger for respiratory than for cardiovascular hospital admissions. The 1996 PM AQCD concluded on the basis of these studies that: "There is a suggestion of a relationship to heart disease, but the results are based on only two studies, and the estimated effects are smaller than those for other endpoints" (U.S. Environmental Protection Agency, 1996a, p. 12-100). The PM AQCD also stated that acute effects on CVD admissions had been demonstrated for elderly populations (i.e., ≥ 65 years), but that insufficient data existed to assess relative effects on younger populations.

When viewed alongside the more extensive literature on acute CVD mortality that was available at the time, the evidence from ecologic time-series studies reviewed in the 1996 PM AQCD was consistent with acute health risks of PM being larger for cardiovascular and respiratory causes than for other causes. Given the tendency for end-stage disease states to include both respiratory and cardiovascular impairment, and the associated diagnostic overlap that often exists, it was not possible on the basis of these studies alone to determine which of the two organ systems, if either, was more critically affected.

8.3.1.3 New Particulate Matter-Cardiovascular Morbidity Studies

8.3.1.3.1 Acute Hospital Admission Studies

Salient methodological features and results of numerous newly available studies that examine associations between daily measures of ambient PM and daily hospital admissions for

cardiovascular disease are summarized in Table 8B-1 (see Appendix 8B). As discussed earlier in Sections 8.1.4 and 8.2.2, many studies published since 1995 used GAM with default convergence criteria. Several of those studies have been reanalyzed by original investigators using GAM with more stringent convergence criteria and GLM with parametric smooths, such as natural splines (NS) or penalized splines (PN). Again, since the extent of possible bias in PM effect-size estimates caused by the default criteria setting in the GAM models is difficult to estimate for individual studies, the discussion here focuses mainly on the studies that either did not use GAM Poisson models or those GAM studies which have been reanalyzed using more stringent convergence criteria and/or alternative approaches. Newly available U.S. and Canadian studies on relationships between short-term PM exposure and hospital admissions or emergency visits that meet these criteria are summarized in Table 8-18, along with a few non-North American studies. Reanalyses studies are indicated in Table 8-18 by indentation of the reference citation to the pertinent short communication in the HEI Special Report (HEI, 2003b). The table is organized by first summarizing single-pollutant (PM only) analyses and then multipollutant (PM plus one or more co-pollutant) analyses for U.S. and non-U.S. studies.

Of much interest are NMMAPS multicity analyses (Samet et al., 2000a,b; Zanobetti et al., 2000a), as reanalyzed (Zanobetti and Schwartz, 2003a), which provide evidence for significant PM_{10} effects on cardiovascular-related hospital admissions and visits, using a variety of statistical models. These results are supported by another multicity study (Schwartz, 1999) which, however, has not been reanalyzed with alternative statistical models. Numerous other studies, carried out by individual investigators in a variety of locales, present a more varied picture, especially when gaseous co-pollutants have been analyzed in multipollutant models. Most CVD hospital admissions studies reported to date have used PM_{10} as the main particle measure due to the wide availability of ambient PM_{10} monitoring data.

Samet et al. (2000a,b) analyzed daily emergency-only CVD hospital admissions in persons 65 and older in relation to PM_{10} in 14 cities from the NMMAPS multicity study. The cities included Birmingham, AL; Boulder, CO; Canton, OH; Chicago, IL; Colorado Springs, CO; Detroit, MI; Minneapolis/St. Paul, MN; Nashville, TN; New Haven, CT; Pittsburgh, PA; Provo/Orem, UT; Seattle, WA; Spokane, WA; and Youngstown, OH. The range of years

TABLE 8-18. SUMMARY OF STUDIES OF PM_{10}, $PM_{10-2.5}$, OR $PM_{2.5}$ EFFECTS ON TOTAL CVD HOSPITAL ADMISSIONS AND EMERGENCY VISITS

Reference Citation, Location, etc.	Outcome Measure	Mean PM Levels (IQR) in µg/m³	Co-Pollutants Analyzed with PM	Lag Structure	Method	Effect Measures Standardized to 50 µg/m³ PM_{10} or 25 µg/m³ $PM_{2.5}$*, $PM_{10-2.5}$**
U.S. Results Without Co-Pollutants						
Samet et al. (2000a,b) 14 Cities	Total CVD admissions ≥ 65 yrs	PM_{10} Means: 24.4-45.3	none	0 day	Default GAM	5.5% (4.7, 6.2)
Zanobetti and Schwartz, (2003a) 14 Cities		PM_{10} Means: 24.4-45.3		0-1 day	Default GAM Strict GAM GLM NS GLM PS	5.9% (5.1-6.7) 4.95% (3.95-5.95) 4.8% (3.55-6.0) 5.0% (4.0-5.95)
Lippmann et al., 2000 Detroit (Wayne County), MI	Ischemic heart disease ≥ 65 yrs	PM_{10}: 31(19) $PM_{2.5}$: 18 (11) $PM_{10-2.5}$: 13 (7)	none	2 day	Default GAM Default GAM Default GAM	8.9% (0.5-18.0) 4.3% (−1.4-10.4)* 10.5% (2.75-18.9)**
Ito 2003 Detroit (Wayne County), MI		PM_{10}: 31(19)			Strict GAM GLM NS	8.0% (−0.3-17.1) 6.2% (−2.0-15.0)
		$PM_{2.5}$: 18 (11)			Strict GAM GLM NS	3.65% (−2.05-9.7)* 3.0% (−2.7-9.0)*
		$PM_{10-2.5}$: 1 3 (7)			Strict GAM GLM NS	10.2% (2.4-18.6)** 8.1% (0.4-16.4)**
Lippmann et al., 2000 Detroit (Wayne County), MI	Dysrhythmias ≥ 65 yrs	PM_{10}: 31(19) $PM_{2.5}$: 18 (11) $PM_{10-2.5}$: 13 (7)	none	1 day 1 day* 0 day**	Default GAM Default GAM Default GAM	2.9% (−10.8-18.8) 3.2% (−6.5-14.0)* 0.2% (−12.2-14.4)**
Ito 2003 Detroit (Wayne County), MI		PM_{10}: 31(19)			Strict GAM GLM NS	2.8% (−10.9-18.7) 2.0% (−11.7-17.7)
		$PM_{2.5}$: 18 (11)			Strict GAM GLM NS	3.2% (−6.6-14.0)* 2.6% (−7.1-13.3)*
		$PM_{10-2.5}$: 13 (7)			Strict GAM GLM NS	0.1% (−12.4-14.4)** 0.0% (−12.5-14.3)**
Lippmann et al., 2000 Detroit (Wayne County), MI	Heart Failure ≥ 65 yrs	PM_{10}: 31(19) $PM_{2.5}$: 18 (11) $PM_{10-2.5}$: 13 (7)	none	0 day 1 day* 0 day**	Default GAM Default GAM Default GAM	9.7% (0.15-20.2) 9.1% (2.4-16.2)* 5.2% (−3.25-14.4)**
Ito 2003 Detroit (Wayne County), MI		PM_{10}: 31(19)			Strict GAM GLM NS	9.2% (−0.3-19.6) 8.4% (−1.0-18.7)
		$PM_{2.5}$: 18 (11)			Strict GAM GLM NS	8.0% (1.4-15.0)* 6.8% (0.3-13.8)*
		$PM_{10-2.5}$: 13 (7)			Strict GAM GLM NS	4.4% (−4.0-13.5)** 4.9% (−3.55-14.1)**
Morris and Naumova (1998) Chicago, IL	Congestive heart failure ≥ 65 yrs	PM_{10}: 41 (23)	none	0 day	GAM not used	3.9% (1.0-6.9)

TABLE 8-18 (cont'd). SUMMARY OF STUDIES OF PM_{10}, $PM_{10-2.5}$, OR $PM_{2.5}$ EFFECTS ON TOTAL CVD HOSPITAL ADMISSIONS AND EMERGENCY VISITS

Reference Citation, Location, etc.	Outcome Measure	Mean PM Levels (IQR) in µg/m³	Co-Pollutants Analyzed with PM	Lag Structure	Method	Effect Measures Standardized to 50 µg/m³ PM_{10} or 25 µg/m³ $PM_{2.5}$*, $PM_{10-2.5}$**
U.S. Results Without Co-Pollutants (cont'd)						
Linn et al. (2000) Los Angeles, CA	Total CVD admissions ≥ 30 yrs	PM_{10}: 45 (18)	none	0 day	GAM not used	3.25% (2.04, 4.47)
Moolgavkar (2000b) Cook County, IL	Total CVD admissions ≥ 65 yrs	PM_{10}: 35‡ (22)	none	0 day	Default GAM	4.2% (3.0, 5.5)
Moolgavkar (2003) Cook County, IL					Strict GAM_{100df} GLM NS_{100df}	4.05% (2.9-5.2) 4.25% (3.0-5.5)
Moolgavkar (2000b) Los Angeles County, CA	Total CVD admissions ≥ 65 yrs	PM_{10}: 44‡ (26) $PM_{2.5}$: 22‡ (16)	none	0 day	Default GAM Default GAM	3.2% (1.2, 5.3) 4.3% (2.5, 6.1)*
Moolgavkar (2003) Los Angeles County, CA		PM_{10}: 44‡ (26)			Strict GAM_{30df} Strict GAM_{100df} GLM NS_{100df}	3.35% (1.2-5.5) 2.7% (0.6-4.8) 2.75% (0.1-5.4)
		$PM_{2.5}$: 22‡ (16)			Strict GAM_{30df} Strict GAM_{100df} GLM $nspline_{100df}$	3.95% (2.2-5.7)* 2.9% (1.2-4.6)* 3.15% (1.1-5.2)*
Tolbert et al., (2000a) Atlanta, GA 1993-1998	Total CVD emerg. dept. visits, ≥ 16 yrs	Period 1 PM_{10}: 30.1, 12.4	none	0-2 day avg.	GAM not used	−8.2% (p=0.002)
Tolbert et al., (2000a) Atlanta, GA 1998-1999	Total CVD emerg. dept. visits, ≥ 16 yrs	Period 2 PM_{10}: 29.1, 12.0 $PM_{2.5}$: 19.4, 9.4 $PM_{10-2.5}$: 9.4, 4.5	none	0-2 day avg.	GAM not used	5.1% (−7.9, 19.9) 6.1% (−3.1, 16.2)* 17.6% (−4.6, 45.0)**
U.S. Results With Co-Pollutants						
Lippmann et al., 2000 Detroit (Wayne County), MI	Ischemic heart disease ≥ 65 yrs	PM_{10}: 31(19) $PM_{2.5}$: 18 (11) $PM_{10-2.5}$: 13 (7)	CO	2 day	Default GAM Default GAM Default GAM	8.5% (-0.45-18.3) 3.7% (-2.4-10.3)* 10.1% (2.25-18.6)**
Lippmann et al., 2000 Detroit (Wayne County), MI	Dysrhythmias ≥ 65 yrs	PM_{10}: 31(19) $PM_{2.5}$: 18 (11) $PM_{10-2.5}$: 13 (7)	CO	1 day 1 day 0 day	Default GAM Default GAM Default GAM	−1.3% (−15.5-15.4) 0.55% (−9.7-12.0)* −1.0% (−13.4-13.05)**

TABLE 8-18 (cont'd). SUMMARY OF STUDIES OF PM_{10}, $PM_{10-2.5}$, OR $PM_{2.5}$ EFFECTS ON TOTAL CVD HOSPITAL ADMISSIONS AND EMERGENCY VISITS

Reference Citation, Location, etc.	Outcome Measure	Mean PM Levels (IQR) in µg/m³	Co-Pollutants Analyzed with PM	Lag Structure	Method	Effect Measures Standardized to 50 µg/m³ PM_{10} or 25 µg/m³ $PM_{2.5}$*, $PM_{10-2.5}$**
U.S. Results With Co-Pollutants (cont'd)						
Lippmann et al., 2000 Detroit (Wayne County), MI	Heart Failure ≥ 65 yrs	PM_{10}: 31(19) $PM_{2.5}$: 18 (11) $PM_{10-2.5}$: 13 (7)	CO	0 day 1 day 0 day	Default GAM Default GAM Default GAM	7.5% (−2.6-18.7) 8.9% (2.2-16.1)* 3.9% (−4.7-13.2)**
Morris and Naumova (1998) Chicago, IL	Congestive heart failure ≥ 65 yrs	PM_{10}: 41, 23	CO, NO_2, SO_2, O_3	0 day	GAM not used	2% (−1-6)
Moolgavkar (2000b) Cook County, IL	Total CVD admissions ≥ 65 yrs	PM_{10}: 35, 22	NO_2	0 day	Default GAM	1.8% (0.4, 3.2)
Moolgavkar (2003) Cook County, IL		PM_{10}: 35, 22	CO		Strict GAM_{100df} GLM NS_{100df}	2.95% (1.7-4.2) 3.1% (1.8-4.4)
Moolgavkar (2000b) Los Angeles County, CA	Total CVD admissions ≥ 65 yrs	PM_{10}: 44‡ (26) $PM_{2.5}$: 22‡ (16)	CO	0 day	Default GAM Default GAM	−1.8% (−4.4, 0.9) 0.8% (−1.3, 2.9)*
Moolgavkar (2003) Los Angeles County, CA		PM_{10}			Strict GAM_{100df} GLM NS_{100df}	−1.3% (−3.8-1.2) −1.1% (-4.2-2.0)
		$PM_{2.5}$			Strict GAM_{100df} GLM NS_{100df}	1.0% (−1.1-3.3)* 1.45% (−1.1-4.0)*
Non-U.S. Results Without Co-Pollutants						
Burnett et al., (1997a) Toronto, Canada	Total CVD admissions all ages	PM_{10}: 28, 22 $PM_{2.5}$: 17, 15 $PM_{10-2.5}$: 12, 7	none	1-4 day avg.	GAM not used	12.1% (1.4, 23.8) 7.2% (−0.6, 15.6)* 20.5% (8.2, 34.1)**
Stieb et al. (2000) Saint John, Canada	Total CVD emerg. dept. visits, all ages	PM_{10}: 14.0, 9.0 $PM_{2.5}$: 8.5, 5.9	none	1-3 day avg.	GAM not used	29.3% (p=0.003) 14.4% (p = 0.055)*
Atkinson et al. (1999a) Greater London, England	Total emerg. CVD admissions ≥ 65 yrs	PM_{10}: 28.5, 90-10 %tile range: 30.7	none	0 day	GAM not used	2.5% (−0.2, 5.3)
Prescott et al. (1998) Edinburgh, Scotland	Total CVD admissions ≥ 65 yrs	PM_{10}: 20.7, 8.4	none	1-3 day avg.	GAM not used	12.4% (4.6, 20.9)
Wong et al. (1999a) Hong Kong	Total emerg. CVD admissions ≥ 65 yrs	PM_{10}: Median 45.0, IQR 34.8	none	0-2 day avg.	GAM not used	4.1% (1.3, 6.9)

TABLE 8-18 (cont'd). SUMMARY OF STUDIES OF PM_{10}, $PM_{10-2.5}$, OR $PM_{2.5}$ EFFECTS ON TOTAL CVD HOSPITAL ADMISSIONS AND EMERGENCY VISITS

Reference Citation, Location, etc.	Outcome Measure	Mean PM Levels (IQR) in $\mu g/m^3$	Co-Pollutants Analyzed with PM	Lag Structure	Method	Effect Measures Standardized to 50 $\mu g/m^3$ PM_{10} or 25 $\mu g/m^3$ $PM_{2.5}$*, $PM_{10-2.5}$**
Non-U.S. Results With Co-Pollutants						
Burnett et al., (1997a) Toronto, Canada	Total CVD admissions all ages	PM_{10}: 28, IQR 22	O_3, NO_2, SO_2, CO	1-4 day avg.	GAM not used	−1.4% (−12.5, 11.2)
		$PM_{2.5}$: 17, 15				−1.6% (−10.5, 8.2)*
		$PM_{10-2.5}$: 12, 7				12.1% (−1.9, 28.2)**
Stieb et al. (2000) Saint John, Canada	Total CVD emerg. dept. visits, all ages	PM_{10}: 14.0, 9.0	CO, H_2S, NO_2, O_3, SO_2, total reduced sulfur	1-3 day avg.	GAM not used	PM_{10} not significant; no quantitative results presented
Atkinson et al. (1999a) Greater London, England	Total emerg. CVD admissions ≥ 65 yrs	PM_{10}: 28.5, 90-10 %tile range: 30.7	NO_2, O_3, SO_2, CO	0 day	GAM not used	PM_{10} not significant; no quantitative results presented
Prescott et al. (1998) Edinburgh, Scotland	Total CVD admissions ≥ 65 yrs	PM_{10}: 20.7, 8.4	SO_2, NO_2, O_3, CO	1-3 day avg.	GAM not used	PM_{10} effect robust; no quantitative results presented
Wong et al. (1999a) Hong Kong	Total emerg. CVD admissions ≥ 65 yrs	PM_{10}: Median 45.0, IQR 34.8	NO_2, O_3, SO_2	0-2 day avg.	GAM not used	PM_{10} effect robust; no quantitative results presented

* $PM_{2.5}$ entries, **$PM_{10-2.5}$. All others relate to PM_{10}; ‡Median.

studied encompassed 1985 to 1994, but this varied by city. Covariates included SO_2, NO_2, O_3, and CO not analyzed directly as regression covariates; rather, individual cities were analyzed first by Poisson regression methods on PM_{10} for lags from 0 to 5 days. An overall PM_{10} risk estimate was then computed by taking the inverse-variance weighted mean of the city-specific risk estimates. The city-specific risk estimates for PM_{10} were also examined for correlations with omitted covariates, including other pollutants. No relationship was observed between city-specific risk estimates and measures of socioeconomic status, including percent living in poverty, percent non-white, and percent college educated. The overall weighted mean risk estimate for PM_{10} was greatest for lag 0 and for the mean of lags 0-1. For example, the mean risk estimate for the mean of lags 0-1 was a 5.9% (CI: 5.1 - 6.7) increase in CVD admissions per

50 μg/m^3 PM_{10}. The mean risk was larger in a subgroup of data where PM_{10} was less than 50 μg/m^3, suggesting the lack of a threshold. A weakness of this study was its failure to report multipollutant results. The authors argued that confounding by co-pollutants was not present because the city-specific risk estimates did not correlate with city-specific regressions of PM_{10} on co-pollutant levels. However, the validity of this method for identifying meaningful confounding by co-pollutants at the daily time-series level has not been demonstrated. Thus, it is not possible to conclude from these results alone that the observed PM_{10} associations were independent of co-pollutants.

Samet et al. (2000a,b) reported results based on use of GAM LOESS smoothing to control for time and weather covariates. Data from the 14 city NMMAPs analysis of CVD hospital admissions were reanalyzed by Zanobetti and Schwartz (2003a) using three alternative control methods. A small decrease in overall effects was observed as compared with the original study results. Whereas the original 14 city pooled analysis yielded a 5.9% (CI: 5.1-6.7%) increase in CVD admissions per 50 μg/m^3 increase in mean lags 0 and 1 day PM_{10}, the reanalysis found 4.95% (3.95 to 5.95, 4.8% (3.55 to 6.0), and 5.0 (4.0 to 5.95) when reanalyzed by GAM with stringent convergence criteria, GLM with natural spline, and GLM with penalized spline, respectively. Based on these results, no change is warranted with regard to overall conclusions for the original published study.

Zanobetti et al. (2000a) reanalyzed a subset of 10 cities from among the 14 evaluated by Samet et al. (2000a,b). The same basic pattern of results obtained by Samet et al. (2000a,b) were found, with strongest PM_{10} associations on lag 0 day, smaller effects on lag 1 and 2, and none at longer lags. The cross-city weighted mean estimate at 0 day lag was excess risk = 5.6% (CI: 4.7, 6.4) per 50 μg/m^3 PM_{10} increment. For the 0-1 day lag average, excess CVD risk = 6.2% (CI: 5.4, 7.0) per 50 μg/m^3 PM_{10} increment. Effect-size estimates increased when data were restricted to days with $PM_{10} < 50$ μg/m^3. As before, no evidence of gaseous (CO, O_3, SO_2) co-pollutant modification of PM effects was seen in the second stage analyses. Again, however, co-pollutants were not tested as independent explanatory variables in the regression analysis. Like the larger NMMAPS morbidity analyses reported by Samet et al. (2000a,b), this sub-study utilized the GAM function in SPlus. These 10 cities were among the 14 cities that Zanobetti and

Schwartz (2003a) reanalyzed using alternative statistical methods, and the reanalyses results noted above would thus also apply in general here.

Janssen et al. (2002), in further analyses of the data set examined above by Samet et al. (2000a,b), evaluated whether differences in prevalence of air conditioning (AC) use and/or the contribution of different sources to total PM_{10} emissions could partially explain the observed variability in exposure-effect relations in the 14 cities. Cities were characterized and analyzed as either winter- or nonwinter-peaking for the AC analyses. Data on the prevalence of AC from the 1993 American Housing Survey of the United States Census Bureau (1995) were used to calculate the percentage of homes with central AC for each metropolitan area. Data on PM_{10} emissions by source category were obtained by county from the U.S. EPA emissions and air quality data web site (U.S. Environmental Protection Agency, 2000a). In an analysis of all 14 cities, central AC was not strongly associated with PM_{10} coefficients. However, separate analysis for nonwinter-peaking and winter-peaking PM_{10} cities yielded coefficients for CVD-related hospital admissions that decreased significantly with increased percentage of central AC for both groups of cities. There were also significant positive relationships between CVD effects and PM_{10} percent emissions from highways or from diesel vehicles, suggesting that mobile source particles may have more potent cardiovascular effects than other particle types. For both analyses, similar though weaker, patterns were found for hospitalization for COPD and pneumonia. The authors note that the stronger relationship for hospital admission rates for CVD over COPD and pneumonia may relate to the 10 times higher CVD hospital admissions rate (which would result in a more precise estimate). However, no co-pollutant analyses were reported. The ecologic nature and limited sample size also indicate the need for further study. Because Janssen et al.'s analysis utilized the GAM function in SPlus, Zanobetti et al. (2003a) reanalyzed the main findings from this study using alternative methods for controlling time and weather covariates. While the main conclusions of the study were not significantly altered, some changes in results are worth noting. The effect of air conditioning remained significant for the nonwinter PM_{10}-peaking cities. The impact of highway vehicles and diesels on PM_{10} effect sizes remained significant, as did oil combustion. However, the effect of air conditioning use on PM_{10} effect estimates was less pronounced and no longer statistically significant at $p < 0.05$ for the

winter PM_{10}-peaking cities using natural splines or penalized splines, in comparison to the original Janssen et al. GAM analysis.

Schwartz (1999) extended the analytical approach he had used in Tucson (described below) to eight other U.S. metropolitan areas, limiting analyses to a single county in each location to enhance the representativeness of the air pollution data. The locations analyzed were Chicago, IL; Colorado Springs, CO; New Haven, CT; Minneapolis, MN; St. Paul, MN; Seattle, WA; Spokane, WA; and Tacoma, WA. Again, the analyses focused on total cardiovascular (CVD) hospital admissions among persons ≥ 65 years old. In univariate regressions, remarkably consistent PM_{10} associations with CVD admissions were found across the eight locations, with a 50 $\mu g/m^3$ increase in PM_{10} being associated with 3.6 to 8.6% increases in admissions. The univariate eight-county pooled PM_{10} effect was 5.0% (CI: 3.7 to 6.4), similar to the 6.1 % effect per 50 $\mu g/m^3$ observed in the previous Tucson analysis. In a bivariate model that included CO, the pooled PM_{10} effect size diminished somewhat to 3.8% (CI: 2.0 to 5.5) and the CO association with CVD admissions was generally robust to inclusion of PM_{10} in the model. The Schwartz 1999 paper used GAM LOESS smoothing with default convergence criteria to control for time and weather covariates. Although no direct reanalyses of this study using alternative statistical methods have been reported, six of the eight cities included in Schwartz (1999) were included in the NMMAPS reanalyses (Zanobetti et al., 2003; Zanobetti and Schwartz, 2003a).

Turning to some examples of independent single-city analyses, PM_{10} associations with CVD hospitalizations were also examined in a study by Schwartz (1997a), which analyzed three years of daily data for Tucson, AZ linking total CVD hospital admissions for persons ≥ 65 years old with PM_{10}, CO, O_3, and NO_2. Only one site monitored daily PM_{10}, whereas multiple sites did so for gaseous pollutants (O_3, NO_2, CO). Both PM_{10} and CO were independently (i.e., robustly) associated with CVD-related admissions; but O_3 and NO_2 were not. The percent effect of a 50 $\mu g/m^3$ increase in PM_{10} changed only slightly from 6.07% (CI: 1.12, 11.27) to 5.22% (CI: 0.17, 10.54) when CO was included in the model along with PM_{10}. The Schwartz 1997 paper utilized GAM smoothing to control for time and weather covariates. To date, no revised results have been reported using alternative statistical methods.

Morris and Naumova (1998) reported results for PM_{10}, as well as for O_3, NO_2, and SO_2, in an analysis of four years of congestive heart failure data among people ≥ 65 years old in Chicago, IL. As many as eight monitoring sites were available for calculating daily gaseous pollutant concentrations; but only one site in Chicago monitored daily PM_{10}. Only same-day results were presented, based on an initial exploratory analysis showing strongest effects for same-day pollution exposure (i.e., lag 0). Associations between hospitalizations and PM_{10} were observed in univariate regressions (3.9% [1.0, 6.9] per 50 μg/m^3 PM_{10} increase), but these diminished somewhat in a multipollutant model (2.0%, [−1.4, 5.4]). Strong, robust associations were seen between CO and congestive heart failure admissions. These results seem to suggest a more robust association with CO than with PM_{10}. However, the observed differences might also be due in part to differential exposure misclassification for PM_{10} (monitored at one site) as compared with CO (eight sites). This study did not use GAM functions to control for time and weather covariates.

In a study designed to compare the effects of multiple PM indices, Lippmann et al. (2000) analyzed associations between PM_{10}, $PM_{2.5}$, or $PM_{10-2.5}$ and various categories of CVD hospital admissions (only emergency and urgent admissions) among the elderly (65+ years old) in Detroit on 344 days in the period 1992 to 1994. Whereas no consistent differences were observed in the relative risks for the alternative PM indices, many of the associations involving PM were significant: (a) ischemic heart disease (IHD) in relation to PM indices (i.e., 8.9% [0.5, 18.0] per 50 μg PM_{10}); 10.5% (2.8, 18.9) per 25 μg/m^3 $PM_{10-2.5}$; and 4.3% (−1.4, 10.4) per 25 μg/m^3 $PM_{2.5}$ (all at lag 2 day); and (b) heart failure (i.e., 9.7% [0.2, 20.2] per 50 μg/m^3 PM_{10}); 5.2% (−3.3, 14.4) per 25 μg/m^3 $PM_{10-2.5}$; and 9.1% (2.4, 16.2) per 25 μg/m^3 $PM_{2.5}$ (the first two at lag 0 day and the latter at lag 1 day). No associations with dysrythmias were seen however. The PM effects generally were robust when co-pollutants were added to the model. Results for two-pollutant models involving CO are given in Table 8-16 above. As discussed earlier with regard to the Lippmann et al. (2000) mortality findings, it is difficult to discern whether the observed associations with coarse fraction particles ($PM_{10-2.5}$) are independently due to such particles or may possibly be attributed to the moderately correlated fine particle ($PM_{2.5}$) fraction in Detroit. In addition, power was limited by the small sample size. Because GAM was used in the

analyses reported in Lippmann et al. (2000), Ito (2003) has reported reanalyses results for the Detroit study using GAM with more stringent convergence criteria and GLM with natural splines. PM effect sizes diminished somewhat (up to 30%) and sometimes lost significance. However, these changes tended to affect all PM metrics in a similar fashion. Thus, there was no change in basic conclusions for the original Lippmann et al. (2000) study, i.e., that there was no evidence for stronger effects for one size fraction versus others. Ito (2003) also noted that study results were more sensitive to alternative weather models and degree of smoothing (degrees of freedom used for the smoothing function) than to whether or not GAM, with strict convergence criteria, was used.

Tolbert et al. (2000a) reported preliminary results for multiple PM indices in relation to daily hospital emergency department (ED) visits for dysrhythmias (DYS) and all CVD categories for persons aged 16 years or older, based on analyses of data from 18 of 33 participating hospitals in Atlanta, GA. During Period 1 of the study (1993 to 1998), PM_{10} from the EPA AIRS database was reported to be negatively associated with CVD visits. In a subsequent one-year period (Aug. 1998 to Aug. 1999), when data became available from the Atlanta PM supersite, positive but nonsignificant associations were seen between CVD and PM_{10} (RR of 5.1% per 50 $\mu g/m^3$ PM_{10}) and $PM_{2.5}$ (RR of 6.1% per 25 $\mu g/m^3$ $PM_{2.5}$); and significant positive associations were seen with certain fine particle components, i.e., elemental carbon ($p \leq 0.005$) and organic carbon ($p \leq 0.02$), and CO ($p \leq 0.005$). No multipollutant results were reported. Study power was limited due to the short data record in Period 2.

In an analysis of 1992 to 1995 Los Angeles data, Linn et al. (2000) also found that PM_{10}, CO, and NO_2 were all significantly associated with increased CVD admissions in single-pollutant models among persons aged 30 years and older. Associations generally appeared to be stronger for CO than for PM_{10}. No PM_{10} results were presented with co-pollutants in the model.

Lastly, Moolgavkar (2000b) analyzed PM_{10}, CO, NO_2, O_3, SO_2 and limited $PM_{2.5}$ data in relation to daily total cardiovascular (CVD) and total cerebrovascular (CRV) admissions for persons aged $\geq$ 65 from three urban counties (Cook, IL; Los Angeles, CA; Maricopa, AZ) during 1987-1995. Of particular note was the availability of $PM_{2.5}$ data in LA, though only for every sixth day. Consistent with most studies, in univariate regressions, PM_{10} (and $PM_{2.5}$ in LA) were

associated at some lags with CVD admissions in Cook and LA counties, but not in Maricopa county. However, in two-pollutant models in Cook and LA counties, the PM risk estimates diminished substantially and/or were rendered nonsignificant, whereas co-pollutant (CO or NO_2) risk estimates were less affected. These results suggest that gaseous pollutants, with the exception of O_3, may have been more strongly associated with CVD hospitalizations than were PM indices. These findings were based on an analysis that used GAM functions for time and weather controls. Moolgavkar (2003) reported results of a reanalysis using improved GAM convergence criteria and GLM with natural splines (nspline) and a range of degrees of freedom (30 versus 100) for the smooth function of time. Results were not very sensitive to the use of default versus improved GAM or splines (Table 8-18) but did appear to be more sensitive to degrees of freedom. The nspline results were given only with 100 degrees of freedom. This is an unusually large number, especially for $PM_{2.5}$, where data were available only every sixth day over a nine-year period.

The above analyses of daily PM_{10} and CO in U.S. cities, overall, indicate that elevated concentrations of both PM_{10} and CO may enhance risk of CVD-related morbidity leading to increased ED visits or hospitalizations. The Lippmann results appear to implicate both $PM_{2.5}$ and $PM_{10-2.5}$ in increased hospital admissions for some categories of CVD among the elderly.

8.3.1.3.2 Studies in Non-U.S. Cities

Four separate analyses of hospitalization data in Canada have been reported by Burnett and coworkers since 1995 (Burnett et al., 1995, 1997a,b, 1999). A variety of locations, outcomes, PM exposure metrics, and analytical approaches were used. The first study (Burnett et al., 1995), reviewed briefly in the 1996 PM AQCD, analyzed six years of data from 168 hospitals in Ontario, CN. Respiratory and CVD hospital admissions were analyzed in relation to sulfate and O_3 concentrations. Sulfate lagged one day was associated with CVD admissions, with an effect of 2.8% (CI: 1.8, 3.8) increase per 13 $\mu g/m^3$ SO_4^{2-} without O_3 in the model and 3.3% (CI: 1.7, 4.8) with O_3 included. When CVD admissions were split out into sub-categories, larger associations were seen between sulfates and coronary artery disease and heart failure than for cardiac dysrhythmias. Sulfate associations with total admissions were larger for the

elderly ≥ 65 years old (3.5% per 13 μg/m^3) than for those < 65 years old (2.5% per 13 μg/m^3). There was little evidence for seasonal differences in sulfate associations.

Burnett et al. (1997b) analyzed daily congestive heart failure hospitalizations in relation to CO and other air pollutants (O_3, NO_2, SO_2, CoH) in ten large Canadian cities as a replication of an earlier U.S. study by Morris et al. (1995). The Burnett Canadian study expanded upon the previous work both by its size (11 years of data for each of 10 large cities) and by including a measure of PM air pollution (coefficient of haze, CoH); whereas no PM data were included in the earlier Morris et al. study. The Burnett study was restricted to the population ≥ 65 years old. The authors noted that all pollutants except O_3 were correlated, making it difficult to separate out their effects statistically. CoH, CO, and NO_2 measured on the same day as admission (i.e., lag 0) were all strongly associated with congestive heart failure admissions in univariate models. In multipollutant models, CO remained a strong predictor, but CoH did not (no gravimetric PM data used).

The roles played by size-selected gravimetric and chemically-speciated particle metrics as predictors of CVD hospitalizations were explored in analyses of data from metropolitan Toronto for the summers of 1992 to 1994 (Burnett et al., 1997a). The analyses used dichotomous sampler ($PM_{2.5}$, PM_{10}, and $PM_{10-2.5}$), H^+,and SO_4^{2-} data collected at a central site as well as O_3, NO_2, SO_2, CO, and CoH data collected at multiple sites in Toronto. Hospital admissions categories included total cardiovascular (i.e., the sum of ischemic heart disease, cardiac dysrhythmias, and heart failure) and total respiratory-related admissions. Model specification with respect to pollution lags was based on evaluation of all lags and averaging times out to 4 days prior to admission in exploratory analyses and "best" metrics being chosen on the basis of maximal t-statistics. The relative risks of CVD admissions were positive and generally statistically significant for all pollutants analyzed in univariate regressions, but especially so for O_3, NO_2, CoH, and $PM_{10-2.5}$ (i.e., regression t-statistics > 3). Associations for gaseous pollutants were generally robust to inclusion of PM covariates, whereas the PM indices (aside from CoH) were not robust to inclusion of multiple gaseous pollutants. In particular, $PM_{2.5}$ was not a robust predictor of CVD admissions in multipollutant models: whereas an 25 μg/m^3 increase in $PM_{2.5}$ was associated with a 7.2% increase (t = 1.8) in CVD admissions in a

univariate model, the effect was reduced to −1.6% (t = 0.3) in a model that included O_3, NO_2, and SO_2. CoH, like CO and NO_2, is generally thought of as a measure of primary motor-vehicle emissions during the non-heating season. The authors concluded that "particle mass and chemistry could not be identified as an independent risk factor for exacerbation of cardiorespiratory diseases in this study beyond that attributable to climate and gaseous air pollution."

Burnett et al. (1999) later reported results of a more extensive attempt to explore cause-specific hospitalizations for persons of all ages in relation to a large suite of gaseous and PM air pollutant measures, using 15 years of Toronto data. Cardiovascular admissions were split out into separate categories for analysis: dysrhythmias, heart failure, and ischemic heart disease. Burnett et al. (1999) selected only those admissions to acute care treatment hospitals that were considered an emergency or urgent. The analyses also examined several respiratory causes, as well as cerebrovascular and diseases of the peripheral circulation; the latter categories were included because they should show PM associations if one mechanism of PM action is related to increased plasma viscosity, as suggested by Peters et al. (1997a). The PM metrics analyzed were $PM_{2.5}$, PM_{10}, and $PM_{10-2.5}$ estimated from daily TSP and TSP sulfate data, based on a regression analysis for dichotomous sampling data that were available every sixth day during an eight-year subset of the full study period. Although some statistically significant associations with one or another PM metric were found in univariate models, no significant PM associations were seen with any of the three CVD hospitalization outcomes in multipollutant models. For example, whereas a 25 $\mu g/m^3$ increase in estimated $PM_{2.5}$ was associated with a 8.05% increase (t = 6.08) in ischemic heart disease admissions in a univariate analysis, the $PM_{2.5}$ association was reduced to 2.25% (n.s.) when NO_2 and SO_2 were included in the model. The gaseous pollutants dominated most regressions. There also were no associations between PM and cerebral or peripheral vascular disease admissions. However, the use of estimated rather than measured PM components limits interpretation of the reported PM results: that is, use of estimated PM exposure metrics should, in general, tend to increase exposure measurement error and thereby tend to decrease effects estimates.

The Burnett et al. studies provide some of the most extensive results for PM in conjunction with multiple gaseous pollutants, but the inconsistent use of alternative PM metrics in the various analyses confuses the picture. A general finding appears to be lack of robustness of associations between cardiovascular outcomes and PM in multipollutant analyses. This was seen for CoH in the analysis of 10 Canadian cities (Burnett et al., 1997b), for $PM_{2.5}$ and PM_{10} in the analysis of summer data in Toronto (Burnett et al., 1997a), and for linear combinations of TSP and sulfates (i.e., estimated $PM_{2.5}$, PM_{10}, and $PM_{10-2.5}$) in the analysis of 15 years of data in Toronto (Burnett et al., 1999). One exception was the association reported between CVD admissions to 168 Ontario hospitals and sulfate concentrations (Burnett et al., 1995), where the sulfate association was robust to the inclusion of O_3. Also, although gravimetric PM variables were not robust predictors in the Toronto summer analysis, CoH was (Burnett et al., 1997a), perhaps reflecting the influence of primary motor vehicle emissions. This contrasts, however, with lack of robustness for CoH in the 10-city analysis (Burnett et al., 1997b).

Stieb et al. (2000) studied all-age acute cardiac emergency room visits in relation to a rich set of pollution covariates in Saint John, Canada for the period 1992 to 1996. Daily data were available on $PM_{2.5}$, PM_{10}, fine fraction hydrogen and sulfate ions, CoH, CO, H_2S, NO_2, O_3, SO_2, and total reduced sulfur. In a multipollutant model, neither PM_{10} nor $PM_{2.5}$ were significantly related to total cardiac ED visits, although O_3 and SO_2 were.

The APHEA II (Le Tertre et al., 2002) project examined the association between PM_{10} and hospital admissions for cardiac causes in eight European cities. They found a significant PM_{10} effect (0.5%; CI: 0.2, 0.8) on admission for cardiac causes (all ages), as well as for both cardiac causes (0.7%; CI: 0.4, 1.0) and ischemic heart disease (0.8%; CI: 0.3, 1.2) for people > 65 years old, the effect per unit of PM_{10} pollution being half that reported for the U.S. NMMAPS reanalyses (Zanobetti and Schwartz, 2003a). PM_{10} did not seem to be confounded by O_3 or SO_2. The PM_{10} effect was reduced when CO was incorporated in the regression model and eliminated when controlling for NO_2. In contrast to PM_{10}, BS was robustly associated with CVD hospital admissions when co-pollutants were introduced into the model. This led the authors to suggest that diesel PM may be especially important. GAM functions were used in the original analysis.

In a reanalysis (Le Tertre et al., 2003) using GAM with stringent convergence criteria and GLM with either natural or penalized splines, no marked changes from original results were observed.

Several additional non-U.S. studies, mainly in the United Kingdom (UK), have also been published since the 1996 PM AQCD. Most of these studies evaluated co-pollutant effects along with those of PM. Interpretation is hindered somewhat, however, by the failure to report quantitative results for PM_{10} in the presence of co-pollutants. In univariate models, Atkinson et al. (1999a) reported PM associations for persons aged < 65 years and for those ≥ 65 years. Significant associations were reported for both ambient PM_{10} and black smoke (BS), as well as all other co-pollutants, with daily admissions for total cardiovascular disease and ischemic heart disease for 1992 to 1994 in London, UK, using standard time-series regression methods. In two-pollutant models, the associations with PM_{10}, NO_2, SO_2, and CO were moderated by the presence of BS in the model, but the BS association was robust to co-pollutants. Interpretation is hampered somewhat by the lack of quantitative results for two-pollutant models.

In another U.K. study, associations with PM_{10}, and to a lesser extent BS, SO_2, and CO, were reported for analyses of daily emergency hospital admissions for cardiovascular diseases from 1992 to 1995 for Edinburgh, UK (Prescott et al., 1998). No associations were observed for NO_2 and O_3. Significant PM_{10} associations for CVD admissions were present only in persons < 65 years old. The authors reported that the PM_{10} associations were unaffected by inclusion of other pollutants; however, results were not shown. On the other hand, no associations between PM_{10} and daily ischemic heart disease admissions were observed by Wordley and colleagues (1997) in an analysis of two years of daily data from Birmingham, UK. However, PM_{10} was associated with respiratory admissions and cardiovascular mortality during the same study period. This inconsistency of results across causes and outcomes is difficult to interpret, but may relate in part to the relatively short time-series analyzed. The authors stated that gaseous pollutants did not have significant associations with health outcomes independent of PM, but no results were presented for models involving gaseous pollutants.

A study in Hong Kong by Wong et al. (1999a) found associations between CVD hospital admissions and PM_{10}, SO_2, NO_2, and O_3 in univariate models, but did not examine multipollutant models. In models including PM_{10} and dichotomous variables for gaseous pollutants (high

versus low concentration), the PM_{10} effects remained relatively stable. Ye et al. (2001) analyzed a 16-year record of daily emergency hospital visits for July and August in Tokyo among persons ≥ 65 years. In addition to PM_{10}, the study included NO_2, O_3, SO_2, and CO. Models were built using an objective significance criterion for variable inclusion. NO_2 was the only pollutant found to be significantly associated with angina, cardiac insufficiency, and myocardial infarction hospital visits.

8.3.1.3.3 Summary of Salient Findings for Acute PM Exposure Effects on CVD Hospital Admissions

The ecologic time-series studies reviewed here add to a growing body of evidence on acute CVD morbidity effects of PM and co-pollutants. Two U.S. multicity studies offer the strongest current evidence for effects of PM_{10} on acute CVD hospital admissions, but uncertainties regarding the possible role of co-pollutants in the larger of the two studies hinders interpretation with respect to independent PM_{10} effects. Among single-city studies carried out in the U.S. and elsewhere by a variety of investigators (see Table 8-18), less consistent evidence for PM effects is seen. Of particular importance are possible roles of gaseous co-pollutants (e.g., CO) as potential confounders of the PM effect. Among 13 independent studies that included gravimetrically-measured PM_{10} and co-pollutants, three reported PM effects that appeared to be independent of co-pollutants (Schwartz, 1997; Lippmann et al., 2000; Prescott et al., 1998); eight reported no significant PM_{10} effects after inclusion of co-pollutants (Morris and Naumova, 1998; Moolgavkar, 2000b; Tolbert et al., 2000a; Burnett et al., 1997a; Steib et al., 2000; Atkinson et al., 1999a; Wordley et al. (1997); Morgan et al., 1998; Ye et al., 2001); and two studies were unclear regarding independent PM effects (Linn et al., 2000; Wong et al., 1999a). In a quantitative review of published results from 12 studies on airborne particles and CVD hospital admissions, Morris (2001) noted that adjustment for co-pollutants consistently reduced the PM_{10} effect, with reductions ranging from 10 to 320% across studies. Thus, although several studies do appear to provide evidence for PM effects on CVD hospital admissions independent of co-pollutant effects, a number of other studies examining co-pollutants did not find results indicative of independent PM_{10} effects on CVD hospital admissions.

With respect to particle size, only a handful of studies have examined the relative effects of different particle indicators (Lippmann et al., 2000; Burnett et al., 1997a; Steib et al., 2000; Moolgavkar, 2000b). Perhaps due to statistical power issues, no clear picture has emerged as to particle-size fraction(s) most associated with acute CVD effects.

As discussed above, several studies originally based on statistical analyses involving the SPlus GAM function have reported new results using alternative statistical methods. The reanalyses yielded some slightly reduced effect estimates and/or increased confidence intervals or little or no change resulted in other cases. Thus, based on these new results, the overall conclusions from the cardiovascular hospitalization studies remain the same.

Because hospitalization likely reflects some of the same pathophysiologic mechanisms that may be responsible for acute mortality following PM exposure, it is of interest to assess the coherence between the morbidity results reviewed here and the mortality results reviewed in Section 8.2.2 (Borja-Aburto et al., 1997, 1998; Braga et al., 2001a; Goldberg et al., 2000; Gouveia and Fletcher, 2000; Hoek et al., 2001; Kwon et al., 2001; Michelozzi et al., 1998; Morgan et al., 1998; Pönkä et al., 1998; Schwartz et al., 1996a; Simpson et al., 1997; Wordley et al., 1997; Zeghnoun et al., 2001; Zmirou et al., 1998). The mortality studies reported significant associations between acute CVD mortality and measures of ambient PM, though the PM metrics used and the relative risk estimates obtained varied across studies. The PM measurement methods included gravimetrically analyzed filter samples (TSP, PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$), beta gauge (particle attenuation of beta radiation), nephelometry (light scattering), and black smoke (filter reflectance). When tested, PM associations with acute CVD mortality appeared to be generally more robust to inclusion of gaseous covariates than was the case for acute hospitalization studies (Borja-Aburto et al., 1997, 1998; Morgan et al., 1998; Wordley et al., 1997; Zmirou et al., 1998). Three studies (Braga et al., 2001a; Goldberg et al., 2000; Hoek et al., 2001), as noted in Section 8.2.2, provide data indicating that some specific CVD causes of mortality (such as heart failure) were more strongly associated with air pollution than total CVD mortality; but it was noted that ischemic heart disease (which contributes about half of all CVD deaths) was the strongest contributor to the association between air pollution and cardiovascular

mortality. The above-noted results for acute CVD mortality are qualitatively consistent with those reviewed earlier in this section for hospital admissions.

Figure 8-10 illustrates PM_{10} excess risk estimates for single-pollutant models derived from selected U.S. studies of PM_{10} exposure and total CVD hospital admissions, standardized to a 50 $\mu g/m^3$ exposure to PM_{10} as shown in Table 8-16. Results are shown both for studies yielding pooled outcomes for multiple U.S. cities and for studies of single U.S. cities. The Zanobetti and Schwartz (2003a) and Samet et al. (2000a) pooled cross-city results for 14 U.S. cities provide the most precise estimate for relationships of U.S. ambient PM_{10} exposure to increased risk for CVD hospitalization. That estimate, and those derived from most other studies seen in Figure 8-10, generally appear to confirm likely excess risk of CVD-related hospital admissions for U.S. cities in the range of 3 to 9% per 50 $\mu g/m^3$ PM_{10}, especially among the elderly ($\geq$ 65 year). Other individual-city results (see Table 8-16) from Detroit are also indicative of excess risk being in the range of approximately 3.0 and 8.1% per 25 $\mu g/m^3$ of $PM_{2.5}$ or $PM_{10-2.5}$, respectively, for ischemic heart disease and 6.8% and 4.9% excess risk per 25 $\mu g/m^3$ of $PM_{2.5}$ and $PM_{10-2.5}$, respectively, for heart failure. However, the extent to which PM affects CVD-hospitalization risks independently of, or together with other co-pollutants (such as CO), remains to be further resolved.

8.3.1.3.4 Individual-Level Studies of Cardiovascular Effect Markers

Several new studies have evaluated longitudinal associations between ambient PM and cardiovascular effect markers (i.e., physiologic measures of cardiovascular function or biochemical changes in the blood that may be associated with increased cardiac risks).
In contrast to the ecologic time-series studies discussed above, these studies measure outcomes and most covariates at the individual level, making it possible to draw conclusions regarding individual risks, as well as to explore mechanistic hypotheses. Heterogeneity of responses across individuals, and across subgroups defined on the basis of age, sex, preexisting health status, etc., also can be assessed, in principle. While exposure assessment remains largely ecologic (i.e., the entire population is usually assigned the same exposure value on a given day), exposure is generally well characterized in the small, spatially-clustered study populations. The

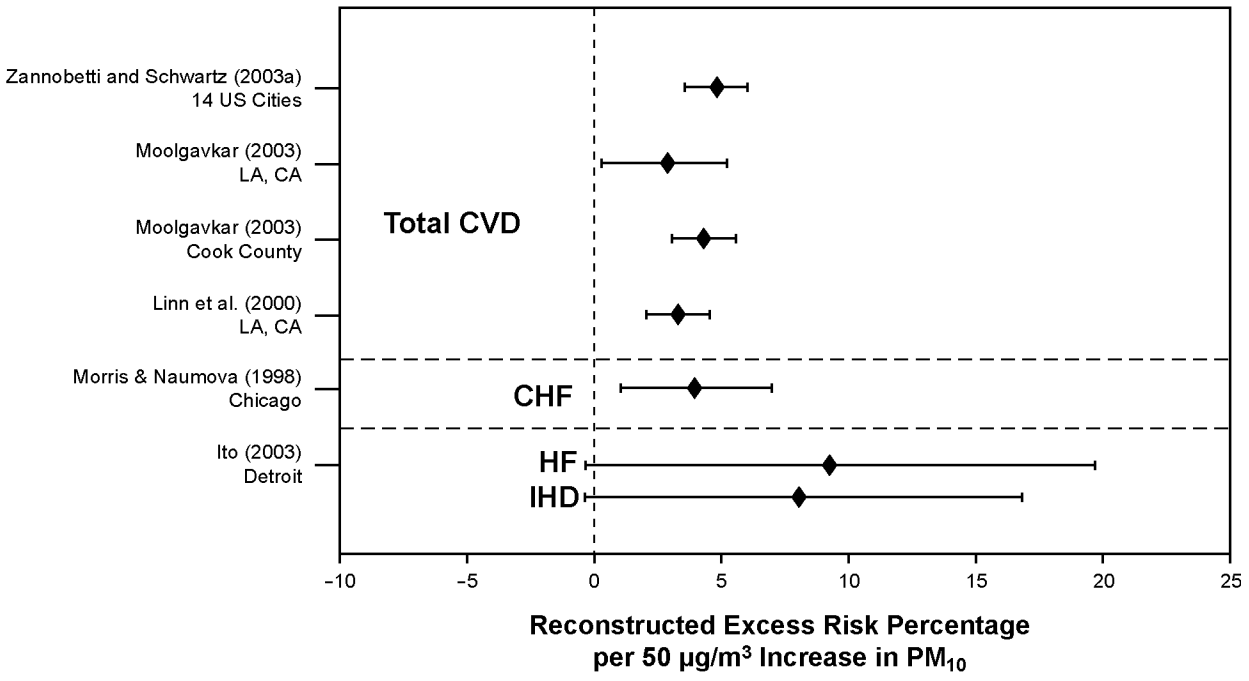

Figure 8-10. Acute cardiovascular hospitalizations and PM exposure excess risk estimates derived from U.S. PM_{10} studies based on single-pollutant models from GAM strict convergence criteria reanalyses (2003 studies) or alternative (non-GAM) original analyses. Both multipollutant models and $PM_{2.5}$ and $PM_{10-2.5}$ results are shown in Table 8-16. CVD = cardiovascular disease. CHF = congestive heart failure. HF = heart failure. IHD = ischemic heart disease.

recent studies fall into two broad classes: (1) those addressing heart rate, cardiac rhythm, blood pressure, or other cardiac function indicators; and (2) those addressing blood characteristics. While significant uncertainty still exists regarding the interpretation of results from these new studies, the varied responses that have been reported to be associated with ambient PM and co-pollutants are of much interest in regard to mechanistic hypotheses concerning pathophysiologic processes potentially underlying CVD-related mortality/morbidity effects discussed in preceding sections.

Cardiac physiology and adverse cardiac events

Alterations in heart rate and/or rhythm are thought to reflect pathophysiologic changes that may represent possible mechanisms by which ambient PM exposures may exert acute effects on

human health. Decreased heart rate variability, in particular, has been identified as a predictor of increased cardiovascular morbidity and mortality. Several independent studies have reported temporal associations between PM exposures and various measures of heart beat rhythm in panels of elderly subjects (Liao et al., 1999; Pope et al., 1999a,b,c; Dockery et al., 1999; Peters et al., 1999a, 2000a; Gold et al. 2000; Creason et al., 2001). Changes in blood pressure may also reflect increases in CVD risks (Linn et al., 1999; Ibald-Mulli et al., 2001). Finally, one important new study (Peters et al., 2001a) has linked acute (2- and 24-h) ambient $PM_{2.5}$ and PM_{10} concentrations with increased risk of myocardial infarction in subsequent hours and days.

Liao et al. (1999) studied 26 elderly subjects (age 65 to 89 years; 73% female) over three consecutive weeks at a retirement center in metropolitan Baltimore, 18 of whom were classified as "compromised" based on previous cardiovascular conditions (e.g., hypertension). Daily 6-min resting electrocardiogram (ECG) data were collected, and time intervals between sequential R-R intervals recorded. A Fourier transform was applied to the R-R interval data to separate its variance into two major components: low frequency (LF, 0.04-0.15 Hz) and high frequency (HF, 0.15-0.40 Hz). The standard deviation of all normal-to-normal (N–N; also designated R-R) heartbeat intervals (SDNN) was computed as a time-domain outcome variable. $PM_{2.5}$ was monitored indoors by TEOM and outdoors by dichotomous sampler. Outdoor $PM_{2.5}$ levels ranged from 8.0 to 32.2 $\mu g/m^3$ (mean = 16.1 $\mu g/m^3$). Regression analyses controlled for inter-subject differences in average variability, allowing each subject to serve as his/her own control. Consistent associations were seen between increases in $PM_{2.5}$ levels (both indoors and outdoors) and decreases in all three outcome variables (LF, HF, SDNN), with associations being stronger for the 18 "compromised" subjects. The short time interval (6 min per day) of measurement for these parameters hampers interpretation of the possible medical significance of the reported positive results; longer or several measurements per day would have allowed for clearer indications of likely underlying perturbation of CV function.

Creason et al. (2001) reported results of a subsequent study using similar methods among 56 elderly residents of a retirement center in Baltimore County, MD. The 11 men and 45 women ranged in age from 72 to 97 years and were all Caucasian. Associations between ambient $PM_{2.5}$ and decreased HRV were not statistically significant at $p < 0.05$. When two episodic $PM_{2.5}$ days

with rainfall were excluded from the 24-day data set, trends associating decreased HRV and $PM_{2.5}$ were present, but did not meet significance at $p < 0.05$. There was no evidence of effects among subsets of subjects with compromised health status as observed previously in the study by Liao et al. (1999). No results were presented for pollutants other than $PM_{2.5}$.

Pope and colleagues (1999c), using ambulatory ECG monitoring, studied HRV and PM_{10} in a panel of six elderly subjects (69 to 89 years, 5/6 male) and one 23-year old male subject, all compromised by some form of heart disease. SDNN, SDANN, and r-MSSD were used as measures of HRV based on 48-hr holter readings. Daily gravimetric PM_{10} data from three sites in the study area ranged from ~10 $\mu g/m^3$ to 130 $\mu g/m^3$ during the study, with high levels occurring only during the first half of the 1.5 month study period. No co-pollutants (e.g., O_3, CO, NO_2, etc.) were studied. Regression analyses with subject-specific intercepts were performed, with and without control for daily barometric pressure and mean heart rate. Same-day and previous-day ambient PM_{10} were negatively associated with SDNN and SDANN; and the results were unaffected by inclusion of covariates. Heart rate, as well as r-MSSD, were both positively, but less strongly, associated with PM_{10}. The specific heart rate variability findings (i.e., PM associations with decreased SDANN and SDNN and increased r-MSSD) make it difficult to interpret the results or their cardiac health significance. The decreased SDANN and SDNN suggests decreased sympathetic activity, whereas the r-MSSD increase suggests increase parasympathetic (vagal) input to the heart (which is likely protective in terms of risk of ischemic related arrhythmia, but might increase the risk of atrial arrhythmia). These specific HRV findings do not allow clear conclusions as to how PM may be affecting cardiac functioning.

The Pope et al. (1999c) study discussed above was nested within a larger cohort of 90 subjects who participated in a study of heart rate and oxygen saturation in the Utah Valley (Dockery et al., 1999; Pope et al., 1999b). The investigators hypothesized that decreases in oxygen saturation might occur as a result of PM exposure and that this could be a risk factor for adverse cardiac outcomes. The study was carried out in winter months (mid-November through mid-March), when frequent inversions lead to fine particle episodes. PM_{10} levels at the three nearest sites averaged from 35 to 43 $\mu g/m^3$ during the study, and daily 24-h levels ranged from 5 to 147 $\mu g/m^3$. Two populations were studied: 52 retired Brigham Young University

faculty/staff and their spouses, and 38 retirement home residents. Oxygen saturation (SpO_2) and heart rate (HR) were measured once or twice daily by an optical sensor applied to a finger. In regression analyses controlling for inter-individual differences in mean levels, SpO_2 was not associated with PM_{10}, but was highly associated with barometric pressure. In contrast, HR association with PM_{10} significantly increased but significantly decreased with barometric pressure in joint regressions. Including CO in the regressions did not change these basic findings. This was the first study of this type to examine the interrelationships among physiologic measures (i.e., SpO_2 and HR), barometric pressure, and PM_{10}. The profound physiological effects of barometric pressure noted here highlight the importance of carefully controlling for barometric pressure effects in studies of cardiac physiology.

Gold and colleagues (2000) obtained somewhat different results in a study of heart rate variability among 21 active elderly subjects, aged 53 to 87 years, in a Boston residential community. Resting, standing, exercising, and recovering ECG measurements were performed weekly using a standardized protocol on each subject, which involved 25 min/week of continuous Holter ECG monitoring. Two time-domain measures were extracted: SDNN and r-MSSD (see above for definitions). Heart rate also was analyzed as an outcome. Continuous PM_{10} and $PM_{2.5}$ monitoring was conducted by TEOM at a site 6 km from the study site and PM data were corrected for the loss of semivolatile mass. Data on CO, O_3, NO_2, SO_2, temperature and relative humidity were available from nearby sites. Outcomes were regressed on $PM_{2.5}$ levels in the 0 to 24 h period prior to ECG testing, with and without control for HR and temperature. As for the other studies discussed above, declines in SDNN were associated with $PM_{2.5}$ levels, in this case averaged over 4 h. These associations reached statistical significance at the $p < 0.05$ level only when all testing periods (i.e., resting, standing, exercise) were combined. In contrast to the above studies, both HR and r-MSSD here were negatively associated with $PM_{2.5}$ levels (i.e., lower HR and r-MSSD) when $PM_{2.5}$ was elevated. These associations were statistically significant overall, as well as for several of the individual testing periods, and were unaffected by covariate control. Gold et al. (2003) subsequently reported reanalyses involving temperature with either a GAM function with stringent convergence criteria or a GLM with natural splines, with no substantial changes in results being reported. The

negative associations between $PM_{2.5}$ and decreases in both HR and r-MSSD are puzzling, given that decreased HR is indicative of increased parasympathetic tone whereas decreased r-MSSD is reflective of decreased parasympathetic modulation of heart function. This discrepancy raises the possibility that one or another or both of the observed outcomes may be due to chance.

Evidence for altered HRV in response to $PM_{2.5}$ exposures comes from two other recent studies. Magari et al. (2001) found significant decreases in SDNN of 1.4% (CI: 2.1, 0.6) per 100 ug/m^3 3-h mean $PM_{2.5}$ in young healthy Boston area boilermakers studied during non-work periods. Another study of 40 boilermakers (including the 20 studied above) analyzed data collected during both work and non-work periods (Magari et al., 2002). That study found a significant 2.7% decrease in SDNN and a 1.0% increase in HR for every 100 μg/m^3 increase in 4-h moving average of estimated $PM_{2.5}$. The larger effect size for the non-work PM exposure study may reflect differing health effects of ambient versus occupational PM composition. These studies are suggestive of PM-related HRV effects in young healthy adults, but use of estimated $PM_{2.5}$ based on light scattering precludes firm quantitative interpretation of exposure levels.

Peters et al. (1999a) reported HR results from a retrospective analysis of data collected as part of the MONICA (monitoring of trends and determinants in cardiovascular disease) study in Augsburg, Germany. Analyses focused on 2,681 men and women aged 25 to 64 years who had valid ECG measurements taken in winter 1984-1985 and again in winter 1987-1988. Ambient pollution variables included TSP, SO_2, and CO. The earlier winter included a 10-day episode with unusually high levels of SO_2 and TSP, but not of CO. Pollution effects were analyzed in two ways: dichotomously comparing the episode and non-episode periods, and continuously using regression analysis. However, it is unclear from the report as to what extent the analyses reflect between-subject versus within-subject effects. A statistically significant increase in mean heart rate was seen during the episode period versus other periods, controlling for cardiovascular risk factors and meteorology. Larger effects were seen in women. In single-pollutant regression analyses, all three pollutants were associated with increased HR.

More recently, Ibald-Mulli et al. (2001) reported similar findings from a study of blood pressure among 2,607 men and women aged 25 to 64 years in the MONICA study. Systolic

blood pressure increased on average during an episode of elevated TSP and SO_2, but the effect disappeared after controlling for meteorological parameters (e.g., temperature and barometric pressure). However, when TSP and SO_2 were analyzed as continuous variables, both were associated with elevated systolic blood pressure, controlling for meteorological variables. In two-pollutant models, TSP was more robust than SO_2, and the TSP association was greater in subgroups of subjects with elevated blood viscosity and heart rates.

Linn et al. (1999) reported associations between both diastolic and systolic blood pressure and PM_{10} in a panel study of 30 Los Angeles residents with severe COPD. The relationship was not observed when inside-home PM levels were used in the analyses. Also, no relationship was found between PM levels and heart rate or arrhythmias, based on 48 h of Holter data.

In a retrospective study, Peters and colleagues (2000a) examined incidence of cardiac arrhythmias among 100 patients (mean age 62.2 years; 79% male) with implanted cardiovertex defibrillators followed over a three year period. Shocks from cardiovertex defibrillators are frequently used for life-threatening arrhythmias but not always (only ~65-70% are for life-threatening arrhythmias). $PM_{2.5}$ and PM_{10} were measured in South Boston by the TEOM method, along with black carbon, O_3, CO, temperature and relative humidity; SO_2 and NO_2 data were obtained from another site. The 5th percentile, mean, and 95th percentiles of PM_{10} levels were 7.8, 19.3, and 37.0 $\mu g/m^3$, respectively. The corresponding $PM_{2.5}$ values were 4.6, 12.7, and 26.6 $\mu g/m^3$. Logistic regression was used to analyze events in relation to pollution variables, controlling for between-person differences, seasons, day-of-week, and meteorology in two subgroups: 33 subjects with at least one arrhythmia event and 6 subjects with 10 or more such events. In the larger subgroup, only NO_2 on the previous day, and the mean NO_2 over five days, were significantly associated with arrhythmia incidence. In patients with 10 or more events, the NO_2 associations were stronger. Also, some of the $PM_{2.5}$ and CO lags became significant in this subgroup. Important caveats regarding this study include the fact that the vast majority of cardiovertex defibrillator discharges occurred among a small subset (i.e., 6) of the patients. Also, potentially important variables, e.g., cardiovascular drug usage and anti-arrhythmia drug changes during follow-up, were not reported.

An exploratory study of a panel of COPD patients (Brauer et al., 2001) examined several PM indicators in relation to CVD and respiratory health effects. The very low levels of ambient particles (PM_{10} mean = 19 $\mu g/m^3$) and low variability in these levels plus the small sample size of 16 limit the conclusions that can be drawn. Still, for cardiovascular endpoints, single-pollutant models indicated that both systolic and diastolic BP decreased with increasing PM exposure, but this was not statistically significant. Also, 24-h Holter monitoring data recorded on 7 separate days for each individual did not show any heart rate variability changes associated with PM levels. The size of the ambient PM_{10} effect estimate for ΔFEV_1 was larger than the effect estimate for ambient $PM_{2.5}$ and personal $PM_{2.5}$ but not statistically significant. This initial effort indicated that ambient PM_{10} consistently had the largest effect estimates, whereas while models using personal exposure measurements did not show larger or more consistently positive effect estimates relative to those models using ambient exposure metrics.

A potentially important study by Peters et al. (2001a) reported associations between onset of myocardial infarction (MI) and ambient PM (either PM_{10} or $PM_{2.5}$) as studied in a cohort of 772 MI patients in Boston, MA. Precise information on the timing of the MI, obtained from patient interviews, was linked with concurrent air quality data measured at a single Boston site. A case crossover design enabled each subject to serve as his/her own control. One strength of this study was its analysis of multiple PM indices and co-pollutants, including real-time $PM_{2.5}$, PM_{10}, the $PM_{10-2.5}$ difference, black carbon, O_3, CO, NO_2, and SO_2. Only $PM_{2.5}$ and PM_{10} were significantly associated with MI risk in models adjusting for season, meteorological parameters, and day of week. Both the mean $PM_{2.5}$ concentration in the previous two hours and in the 24 h lagged one day were independently associated with MI, with odds ratios of 1.48 (CI: 1.09, 2.02) for 25 $\mu g/m^3$ and 1.62 (CI: 1.13, 2.34) for 20 $\mu g/m^3$, respectively. PM_{10} associations were similar. The nonsignificant findings for other pollution metrics should be interpreted in the context of potentially differing exposure misclassification errors associated with the single monitoring site.

Checkoway et al. (2000) has reported a Seattle mortality study of PM_{10} levels and cases of patients experiencing out-of-hospital sudden cardiac death (SCD). They used a case-crossover study design in 362 subjects suffering an SCD episode. They evaluated PM levels over the

5 days preceding SCD and compared those levels to levels recorded in the same month and during the same days of the week (Mean PM_{10} level = 31.9 $\mu g/m^3$). They evaluated lags of 0 to 5 days looking for a correlation, but found no correlation between SCD episodes and PM levels even after controlling for multiple confounding variables. They reported an estimated relative risk at a one day lag of 0.87 (CI: 0.74, 1.01). The HEI (2000) review commentary noted that the authors reported, from their power calculations, that the sample size (362) was not large enough to either find or rule out a relative risk less than 1.5 and that lack of association with PM in this study does not imply that other cardiac or cardiovascular disease outcomes are not associated with PM. These negative findings suggest that PM may not be a risk factor for acute myocardial infarction in previously healthy individuals, or that the pattern and/or mix of PM exposures in Seattle, where woodsmoke may be an important component, may convey lesser risk than observed elsewhere.

The above studies present a range of findings regarding possible effects of $PM_{2.5}$ on cardiac rhythm and other cardiac endpoints. However, the studies offer conflicting results, especially with regard to HRV findings. Several studies reported PM levels to be associated with decreases in one or more HR variability measured in elderly subjects with preexisting cardiopulmonary disease, although increased r-MSSD (a measure of high-frequency HR variability) was found to be associated with PM elevations in at least one study (Pope et al., 1999a). Several other found no changes related to PM levels (Creason, et al., 2001) or blood pressure (Brauer et al., 2001). Some recent studies have also reported effects in healthy elderly and young adult populations. All those studies which examined HR found associations with PM most being positive associations; but one (Gold et al., 2000; Gold et al., 2003) reported a negative relationship. Overall, variations in methods used and discrepancies in results obtained across the studies argue for caution in drawing any conclusions yet regarding ambient PM effects on heart rate variability or other ECG measures of cardiovascular parameters.

Viscosity and other blood characteristics

Peters et al. (1997a) state that plasma viscosity, a risk factor for ischemic heart disease, is affected by fibrinogen and other large asymmetrical plasma proteins, e.g., immunoglobulin M

and α_2-macroglobulin. They noted that, in a cohort study (Woodhouse et al., 1994) of elderly men and women, fibrinogen levels were strongly related to inflammatory markers, such as neutrophil count and acute-phase proteins (C-reactive protein and α_1-antichymotrypsin) and self-reported infections. They further noted that another prospective study (Thompson et al., 1995; Haverkate et al., 1997) showed baseline fibrinogen and C-reactive protein concentrations to be highly correlated in angina patients and to be independently associated with increased risk of myocardial infraction.

Support for a mechanistic hypothesis, relating to enhanced blood viscosity, was suggested by an analysis of plasma viscosity data collected in a population of 3,256 German adults in the MONICA study (Peters et al., 1997a). Each subject provided one blood sample during October 1984 to June 1985. An episode of unusually high air pollution levels occurred during a 13-day period while these measurements were being made. Among the 324 persons who provided blood during the episode, there was a statistically significant elevation in plasma viscosity as compared with 2,932 persons studied at other times. The odds ratio for plasma viscosity exceeding the 95th percentile was 3.6 (CI: 1.6, 8.1) among men and 2.3 (CI: 1.0, 5.3) among women. Analysis of the distribution of blood viscosity data suggested that these findings were driven by changes in the upper tail of the distribution rather than by a general shift in mean viscosity, consistent with the likelihood of a susceptible subpopulation.

A prospective cohort study of a subset of male participants from the above-described Augsburg, Germany MONICA study was reported by Peters et al. (2001b). Based on a survey conducted in 1984/85, a sample of 631 randomly selected men (aged 45 to 64 years and free of cardiovascular disease at entry) were evaluated in a 3-year follow-up that examined relationships of air pollution to serum C-reactive protein concentrations. C-reactive protein is a sensitive marker of inflammation, tissue damage, and infections, with acute and chronic infections being related to coronary events. Inflammation is also related to systemic hypercoagulability and onset of acute ischemic syndromes. During the 1985 air pollution episode affecting Augsburg and other areas of Germany, the odds of abnormal increases in serum C-reactive protein (i.e., $\geq$ 90th percentile of pre-episode levels = 5.7 mg/L) tripled; and associated increases in TSP levels of 26 $\mu g/m^3$ (5-day averages) were associated with an odds ratio of 1.37 (CI: 1.08, 1.73)

for C-reactive protein levels exceeding the 90th percentile levels in two pollutant models that included SO_2 levels. The estimated odds ratio for a 30 $\mu g/m^3$ increase in the 5-day mean for SO_2 was 1.12 (CI: 0.92, 1.47).

Other studies have examined blood indices in relation to PM pollution in United Kingdom cities. Seaton and colleagues (1999) collected sequential blood samples (up to 12) over an 18-month period in 112 subjects (all over age 60) in Belfast and Edinburgh, UK. Blood samples were analyzed for hemoglobin, packed cell volumes, fibrinogen, blood counts, factor VII, interleukin-6, and C-reactive protein. In a subset of 60 subjects, plasma albumin also was measured. PM_{10} data monitored by TEOM were collected from ambient sites in each city. Personal exposure estimates for three days preceding each blood draw were derived from ambient PM data adjusted by time-activity patterns and I/O penetration factors. No co-pollutants were analyzed. Data were analyzed by analysis of covariance, controlling for city, seasons, temperature, and between-subject differences. In this relatively small panel study, significant changes in several blood indices were associated with either ambient or estimated personal PM_{10} levels; but all the associations were negative, except for C reactive protein in relation to ambient PM_{10}.

Prescott et al. (2000) also investigated factors that might increase susceptibility to PM-related cardiovascular events for a large cohort of 1,592 subjects aged 55 to 74 in Edinburgh, UK. Baseline measurements of blood fibrinogen and blood and plasma viscosity were examined as modifiers of PM effects (indexed by BS) on the incidence of fatal and nonfatal myocardial infarction or stroke. All three blood indices were strong predictors of increased cardiac event risk; but there was no clear evidence of either a main effect of BS, nor interactions between BS and blood indices.

In another European study, Pekkanen and colleagues (2000) analyzed plasma fibrinogen data from a cross-sectional survey of 4,982 male and 2,223 female office workers in relation to same-day and previous three-day PM_{10}, BS, NO_2, CO, SO_2, and O_3 concentrations. In the full analysis, NO_2 and CO were significantly associated with increased fibrinogen levels. When the analysis was restricted to the summer season, PM_{10} and BS, as well as NO_2 and CO showed significant univariate associations.

Schwartz (2001) later reported even larger analyses of possible PM effects on factors affecting blood coagulability among a subset of the NHANES III cohort. The NHANES III cohort was comprised of a stratified random sample of the U.S. population, with oversampling of minorities (Black and Mexican-Americans represented 30% of the cohort) and of the elderly (20% of the cohort was ≥ 60 years old versus their being 16% of the U.S. population). The NHANES III study included evaluations of numerous health and nutritional endpoints conducted in two phases during 1989 to 1994, each phase sampling ~20,000 subjects in 44 communities and including persons representative of the U.S. population. Analyzing data for first phase subjects living in 30 urban areas having every-six-day PM_{10} monitoring (no. of PM_{10} observations = 1,373) by mixed models (PROC MIXED, SAS), Schwartz (2001) found not only significant positive associations between PM_{10} exposures and plasma fibrinogen levels in a subset of the NHANES III cohort, but also PM_{10} associations with platelet and white cell counts. The PM_{10} associations were robust when O_3, NO_2, or SO_2 were included with PM_{10} in two-pollutant models. In univariate models, SO_2 was only significant for white cell counts and NO_2 with platelet counts and fibrinogen but not O_3 with any of the three blood coaguability markers. Given that CO data were not matched to specific subjects, no CO analyses were done.

Overall, the above findings add some limited support for hypotheses about possible mechanisms by which PM exposure may be linked to adverse cardiac outcomes. They appear to most clearly implicate ambient PM as likely contributing to increases in C-reactive protein (a biological marker of inflammatory responses), blood fibrinogen levels, and blood viscosity, all of which are thought to be predictive of increased risk for serious cardiac events.

8.3.1.4 Issues in the Interpretation of Acute Cardiovascular Effects Studies

Susceptible subpopulations. Because they lack extensive data on individual subject characteristics, hospital admissions studies provide only limited information on susceptibility factors based on stratified analyses. The relative effect sizes for PM-cardiovascular associations (and respiratory) admissions reported in ecologic time-series studies are generally somewhat higher than those for total admissions. This provides some limited support for hypothesizing that acute PM effects operate via cardiopulmonary pathways or that persons with preexisting

cardiopulmonary disease have greater susceptibility to PM, or both. Although there are some data from ecologic time-series studies showing larger PM effects on cardiovascular admissions in adults aged ≥ 65 years versus younger populations, the differences are neither striking nor consistent. One recent study reported larger CVD hospitalization among persons with current respiratory infections. The other individual-level studies of cardiophysiologic function assessed above are suggestive, but do not yet fully confirm that elderly persons with preexisting cardiovascular or respiratory disease are susceptible to subtle changes in heart rate variability in association with PM exposures. More data are needed before that conclusion can be drawn with confidence. Because younger and healthier populations have not yet been much studied, it is not yet possible to assess the extent to which ambient PM exposures may affect their cardiovascular health status or whether they are at lower risk for PM-related CVD effects than are the elderly.

Role of other environmental factors. The time-series studies published since 1996 have generally attempted to control for weather influences. In contrast, with one possible exception (Pope et al., 1999a), the roles of meteorological factors have not been analyzed extensively as yet in the individual-level studies of cardiac function. Thus, the possibility of weather-related influences in such studies cannot yet be discounted. Also, various co-pollutants have been analyzed extensively in many recent time-series studies of PM and hospital admissions. In some studies, certain PM indices clearly have an independent association after controlling for gaseous co-pollutants. In others, the PM effects are reduced once co-pollutants are added to the model; but this may be in part due to colinearity between PM indices and co-pollutants and/or gaseous pollutants (e.g., CO) having independent effects on cardiovascular function.

Temporal patterns of responses following PM exposure. The evidence from recent time-series studies of CVD admissions suggests rather strongly that PM effects tend to be maximal at lag 0, with some carryover to lag 1, with little evidence for important effects beyond lag 1.

Relationship of CVD effects to PM size and chemical composition attributes. Insufficient data exist from the time-series CVD admissions studies or the emerging individual-level studies

to provide clear guidance as to which ambient PM components, defined on the basis of size or composition, determine ambient PM CVD effect potency. The epidemiologic studies have been constrained by limited availability of multiple PM metrics. Where multiple metrics exist, they often are highly correlated or are of differential quality due to differences in numbers of monitoring sites and monitoring frequency.

PM effects on blood characteristics related to CVD events. Interesting, though limited, new evidence has also been derived which is highly suggestive of associations between ambient PM indices and increased blood viscosity, increased serum C-reactive protein, and increased blood fibrinogen (all biological markers related to increased risks of serious cardiac events). However, much more research will be needed to order to both confirm such associations and to better understand which specific ambient PM species may contribute to them.

8.3.2 Effects of Short-Term Particulate Matter Exposure on the Incidence of Respiratory-Related Hospital Admissions and Medical Visits

8.3.2.1 Introduction

This section evaluates information on epidemiologic associations of ambient PM exposure with both respiratory hospital admissions and medical visits. Although hospital admissions represent one severe morbidity measure evaluated in regard to ambient PM exposures, hospital emergency department (ED) visits are another notable related outcome. Doctors' visits also represent yet another related health measure that, although less studied, is still very relevant to assessing air pollution public health impacts. This category of pollution-affected persons can represent a large population, one generally not evaluated due to the usual lack of centralized data records for doctors' visits in the United States.

The section intercompares various studies examining size-related PM mass exposure measures (e.g., for PM_{10}, $PM_{2.5}$, etc.) or various PM chemical components vis-à-vis their associations with such health endpoints, and discusses their respective extents of coherence with PM associations across related health effects measures. In the following discussion, the main focus for quantitative intercomparisons is on U.S. and Canadian studies considering PM metrics that measure mass or a specific mass constituent, i.e., PM_{10}, $PM_{10-2.5}$, $PM_{2.5}$, or sulfates (SO_4^{2-}).

Study results for other related PM metrics (e.g., BS) are also considered, but mostly only qualitatively, primarily with respect to their relative coherence with studies using mass or composition metrics measured in North America. In order to consider potentially confounding effects of other coexisting pollutants, study results for various PM metrics are presented both for (1) when the PM metric is the only pollutant in the model and (2) the case where a second pollutant (e.g., O_3) is also included. Results from models with more than two pollutants included simultaneously, however, are not used here for quantitative estimates of effect size or statistical strength, because of increased likelihood of bias and variance inflation due to multicolinearity of various pollutants (e.g., see Harris, 1975).

8.3.2.2 Summary of Key Respiratory Hospital Admissions Findings from the 1996 Particulate Matter Air Quality Criteria Document

In the 1996 PM AQCD, both COPD and pneumonia hospitalization studies were found to show moderate, but statistically significant, relative risks in the range of 1.06 to 1.25 (or 6 to 25% excess risk increment) per 50 $\mu g/m^3$ PM_{10} increase or its equivalent. Whereas many hospitalizations for respiratory illnesses occur in those > 65 years of age, there were also increased hospitalizations for those < 65 years of age. Several hospitalization studies restricted their analysis by age group, but did not explicitly examine younger age groups. One exception noted was Pope (1991), who reported increased hospitalization for Utah Valley children (0 to 5 years) for monthly numbers of admissions in relation to PM_{10} monthly averages, as opposed to daily admissions in relation to daily PM levels used in other studies. Studies examining acute associations between indicators of components of fine particles (e.g., BS; sulfates, SO_4^{2-}; and acidic aerosols, H^+) and hospital admissions were reported, too, as showing significant relationships. While sulfates were especially predictive of respiratory health effects, it was not clear whether the sulfate-related effects were attributable to their acidity, to the broader effects of associated combustion-related fine particles, or to other factors.

8.3.2.3 New Respiratory-Related Hospital Admissions Studies

New studies appearing since the 1996 PM AQCD have examined various admissions categories, including: total respiratory admissions for all ages and by age; asthma for all ages

and by age; chronic obstructive pulmonary disease (COPD) admissions (usually for patients > 64 years), and pneumonia admissions (for patients > 64 years). Table 8B-2, Appendix 8B summarizes salient details regarding the study area, study period, study population, PM indices considered and their concentrations, methods employed, study results, and "bottom-line" PM index percent excess risks per standard PM increment (e.g., 50 $\mu g/m^3$ for PM_{10}) for the newer studies.

The percent excess risk (ER) estimates presented in Table 8B-2 are based upon the relative risks (RRs) provided by the authors, but converted into percent increments per standardized increments used by the U.S. EPA to facilitate direct intercomparisons of results across studies (as discussed in Section 8.1). The ER's shown in the table are for the most positively significant pollutant coefficient; and the maximum lag model is used to provide estimates of potential pollutant-health effects associations.

Based on information from Dominici et al. (2002) indicating that the default convergence criteria used in the S-Plus function GAM may not guarantee convergence to the best unbiased estimate (as discussed earlier), only those studies that used other statistical algorithms or which have reported reanalyzed S-Plus GAM results are assessed in the text below. However, given the modest effects of such reanalyses on most study results (i.e., while effect estimates are modified somewhat, the study conclusions remain largely unchanged), Table 8B-2 includes all studies and notes those that originally used the S-Plus GAM algorithm as well as those studies that have since been reanalyzed with more appropriate methods.

Of most pertinence here are those newly available studies that evaluate associations between one or another ambient PM metric and respiratory hospital admissions in U.S. or Canadian cities, such as those for PM_{10} mass concentrations summarized in Table 8-19.

Among numerous new epidemiologic studies of PM_{10} morbidity, many evaluated relatively high PM_{10} levels. However, some did evaluate associations with PM_{10} concentrations ranging to rather low levels. Of note is the fact that several investigators have reported associations between acute PM_{10} exposures and total respiratory-related hospital admissions for numerous U.S. cities with annual mean PM_{10} concentrations extending to below 50 $\mu g/m^3$. On this account, the results of the NMMAPS multicity study (Samet et al., 2000a,b) of PM_{10} levels and

TABLE 8-19. SUMMARY OF UNITED STATES PM_{10} RESPIRATORY-RELATED HOSPITAL ADMISSION STUDIES

Reference	Outcome Measures	Mean Levels (ug/m^3)	Co-pollutants Measured	Day Lag	Method	Effect Estimate (95% CL) (% increase per 50 ug/m^3)
Schwartz et al. (1996b)	Respiratory	PM_{10} = 43	SO_3	—	Poisson GLM	5.8 (0.5, 11.4)
Samet et al. (2000a,b)*	COPD	PM_{10} = 33	SO_2, O_3, NO_2, CO	1	Default GAM Default GAM	7.4 (5.1, 9.8) 7.5 (5.3, 9.8)
Reanalysis by Zanobetti and Schwartz (2003b)				0-1 0-1 0-1 0-1	Default GAM Strict GAM NS GLM PS GLM	9.4 (5.9, 12.9) 8.8 (4.8, 13.0) 6.8 (2.8, 10.8) 8.0 (4.3, 11.9)
Lippmann et al. (2000)*	COPD	PM_{10} = 45.4	SO_2, O_3, NO_2, CO, H^+	3	Default GAM Default GAM	No Co Poll: 9.6 (−5.3, 26.8) Co Poll: 1.0 (−15, 20)
Reanalysis by Ito (2003)				3	Default GAM Strict GAM NS GLM	No Co Poll: 9.6 (−5.3, 26.8) No Co Poll: 6.5 (−7.8, 23.0) No Co Poll: 4.6 (−9.4, 20.8)
Moolgavkar (2000c)*	COPD (> 64 yrs) (median)	PM_{10} = 35, Chicago PM_{10} = 44, LA PM_{10} = 41, Phoenix PM_{10} = 44, LA	— — — CO	0	Default GAM: 30df Default GAM: 30df Default GAM: 30df Default GAM: 30df	2.4 (−0.2, 5.11) 6.1 (1.1, 11.3) 6.9 (−4.1, 19.3) 0.6 (−5.1, 6.7) (two poll. model)
Reanalysis by Moolgavkar (2003)	COPD (> 64 yrs)	Chicago		0	Strict GAM: 100df	3.24 (.031, 6.24)
Reanalysis by Moolgavkar (2003)	COPD (all ages)	Los Angeles		0	Strict GAM: 30df Strict GAM: 100df NS GLM: 100df	7.78 (4.32-10.51) 5.52 (2.53-8.59) 5.00 (1.22, 8.91)
Samet et al. (2000a,b)*	Pneumonia	PM_{10} = 33	SO_2, O_3, NO_2, CO	1	Default GAM Default GAM	8.1 (6.5, 9.7) 6.7 (5.3, 8.2)
Reanalysis by Zanobetti and Schwartz (2003a)				0-1 0-1 0-1 0-1	Default GAM Strict GAM NS GLM PS GLM	9.9 (7.4, 12.4) 8.8 (5.9, 11.8) 2.9 (0.2, 5.6) 6.3 (2.5, 10.3)
Lippmann et al. (2000)	Pneumonia	PM_{10} = 45.4	SO_2, O_3, NO_2, CO, H^+	3	Default GAM Default GAM	No Co Poll: 21.4 (8.2, 36.3) Co Poll: 24 (8.2, 43)
Reanalysis by Ito (2003)	Pneumonia			3	Default GAM Strict GAM NS GLM	No Co Poll: 21.5 (8.3, 36) No Co-Poll: 18.1 (5.3, 32.5) No Co-Poll: 18.6 (5.6, 33.1
Jacobs et al. (1997)	Asthma	PM_{10} = 34	O_3, CO	—	Poisson GLM	6.11 (CI not reported)
Nauenberg and Basu (1999)	Asthma	PM_{10} = 45	O_3	0	Poisson GLM	16.2 (2.0, 30)
Tolbert et al. (2000b)	Asthma	PM_{10} = 39	O_3, NO_X	1	GEE	13.2 (1.2, 26.7)
Sheppard et al. (1999)*	Asthma	PM_{10} = 31	CO, O_3, SO_2	1	Default GAM	13.2 (5.5, 22.6)
Reanalysis by Sheppard (2003)					NS GLM Strict GAM	10.9 (2.8, 19.6) 8.1 (0.1, 16.7)

NS = Natural Spline General Linear Model; PS = Penalized Spline General Additive Model

hospital admissions by persons ≥ 65 years old in 14 U.S. cities are of particular interest. As noted in Table 8-19, this study indicates PM_{10} effects similar to other cities, but with narrower confidence bands, due to its greater power derived by combining multiple cities in the same analysis. This allows significant associations to be identified, despite the fact that many of the cities considered have relatively small populations and that each had mean PM_{10} below 50 $\mu g/m^3$. The cities considered and their respective annual mean/daily maximum PM_{10} concentrations (in $\mu g/m^3$) are Birmingham (34.8/124.8); Boulder (24.4/125.0); Canton (28.4/94.8); Chicago (36.4/144.7); Colorado Springs (26.9/147.2); Detroit (36.8/133.6); Minneapolis/St Paul (36.8/133.6); Nashville (31.6/128.0); New Haven (29.3/95.4); Pittsburgh (36.0/139.3); Provo/Orem (38.9/241.0); Seattle (31.0/145.9); Spokane (45.3/605.8); and Youngstown (33.1/104.0).

Table 8-20 also shows the results of reanalyzing a number of models considered in original research with the use of models using more stringent convergence requirements than the original default option. These reanalyses (Zanobetti and Schwartz, 2003a) show that the effect estimates decline somewhat, but that the basic direction of effect and conclusions about the significance of the PM effect on hospital admissions remained unchanged. In their reanalyses, Zanobetti and Schwartz, (2003a) also considered spline models that are thought to better estimate confidence intervals around pollutant effect estimates than the original GAM analyses. With the spline models, confidence intervals usually increased over the original GAM model and the coefficients also decreased somewhat (similar to GAM with more stringent convergence criteria). As for possible co-pollutant confounding, it was reported that "In our previous studies we did not find confounding due to other pollutants. These results are confirmed in this reanalysis by the meta-regression analyses." Overall, the authors concluded that "the general result is that the association of PM_{10} with hospital admissions remains and in most cases is little changed."

Janssen et al. (2002) did further analyses for the Samet et al. (2000a,b) 14-city data set examining associations for variable prevalence in air-conditioning (AC) and/or contributions of different sources to total PM_{10}. For COPD and pneumonia, the associations were less significant, but the pattern of association was similar to that for CVD. The Zanobetti and

TABLE 8-20. PERCENT INCREASE IN HOSPITAL ADMISSIONS PER 10-μg/m^3 INCREASE in PM_{10} IN 14 U.S. CITIES (ORIGINAL AND REANALYZED RESULTS)

Constrained lag models (Fixed Effect Estimates)	% Increase	CVD (95% CI)	% Increase	COPD (95% CI)	% Increase	Pneumonia (95% CI)
Original One day mean (lag 0)	1.07	(0.93, 1.22)	1.44	(1.00, 1.89)	1.57	(1.27, 1.87)
Original Previous day mean	0.68	(0.54, 0.81)	1.46	(1.03, 1.88)	1.31	(1.03, 1.58)
Original Two day mean (for lag 0 and 1)	1.17	(1.01, 1.33)	1.98	(1.49, 2.47)	1.98	(1.65, 2.31)
Reanalyzed Two day mean (for lag 0 and 1)	0.99	(0.79, 1.19)	1.71	(0.95, 2.48)	1.98	(1.65, 2.31)
Original $PM_{10} < 50$ μg/m^3 (two day mean)	1.47	(1.18, 1.76)	2.63	(1.71, 3.55)	2.84	(2.21, 3.48)
Reanalyzed $PM_{10} < 50$ μg/m^3 (two day mean)	1.32	(0.77, 1.87)	2.21	(1.02, 3.41)	1.06	(0.06, 2.07)
Original Quadratic distributed lag	1.18	(0.96, 1.39)	2.49	(1.78, 3.20)	1.68	(1.25, 2.11)
Reanalyzed Quadratic distributed lag	1.09	(0.81, 1.38)	2.53	(1.20, 3.88)	1.47	(0.86, 2.09)
Unconstrained distributed lag						
Fixed effects estimate	1.19	(0.97, 1.41)	2.45	(1.75, 3.17)	1.9	(1.46, 2.34)
Original Random effects estimate	1.07	(0.67, 1.46)	2.88	(0.19, 5.64)	2.07	(0.94, 3.22)
Reanalyzed Random effects estimate	1.12	(0.84, 1.40)	2.53	(1.21, 3.87)	2.07	(0.94, 3.22)

Source: Samet et al. (2000a,b) and Zanobetti and Schwartz (2003a) reanalyses.

Schwartz (2003b) reanalyses also examined these results, and they stated that "We still found a decreased PM_{10} effect with increasing percentage of home with central AC."

Moolgavkar (2003) also reanalyzed his earlier GAM analyses of hospital admissions for chronic obstructive pulmonary disease (Moolgavkar, 2000c) in Los Angeles (Los Angeles County) and Chicago (Cook County). In his original publication, Moolgavkar found ~5.0% excess risk for COPD hospital admissions among the elderly (64+ years) in Los Angeles to be significantly related to both $PM_{2.5}$ and $PM_{10-2.5}$ in one pollutant models; but the magnitudes of the risk estimates dropped by more than half to non-statistically significant levels in two-pollutant

models including CO. However, unlike the meta-regression approach to the multiple pollutant issue used by Zanobetti and Schwartz (2003a), simultaneous regression of moderately to highly correlated pollutants can lead to biased pollutant coefficients and commonly results in diminished effect estimates for some or all of the pollutants considered. In the same study, similar magnitudes of excess risk (i.e., in the range of ~4 to 7%) were found in one-pollutant models to be associated with $PM_{2.5}$ or $PM_{10-2.5}$ for other age groups (0-19 years; 20-64 years) in Los Angeles, as well.

In his reanalyses of these GAM results using the more stringent convergence criteria, Moolgavkar (2003) combined all three Los Angeles age groups into one analysis, providing greater power, but also complicating before/after comparisons as to the actual effect of using the more stringent convergence criteria on the results. In the Cook County analyses, the author changed other model parameters (i.e., the number of degrees of freedom in the model smooths) at the same time as implementing more stringent convergence criteria; so direct before/after comparisons are not possible for Moolgavkar's (2003) Chicago analyses. Moolgavkar noted that "changes in the convergence criteria and the use of GLM instead of GAM can, but does not always, have substantial impact on the results of the analyses and their interpretation." He also concluded: "Given that different analytic strategies can make substantial differences to the estimates of effects of individual pollutants, I do not believe that these numerical estimates are too meaningful. Patterns of association appear to be robust, however. For example, in Los Angeles, with the exception of COPD admissions with which NO_2 appears to show the most robust association, it is clear that CO is the best single index of air pollution associations with health end points, far better than the mass concentration of either PM_{10} or of $PM_{2.5}$. In Cook County the results are not so clear-cut, however, any one of the gases is at least as good an index of air pollution effects on human health as is PM_{10}."

Tolbert et al. (2000b) used generalized estimating equations (GEE), logistic regression, and Baysian models to evaluate associations between emergency department visits for asthma (by those < 17 years old) in Atlanta during the summers of 1993 to 1995 (~6000 visits for asthma out of ~130,000 total visits) and several air pollution variables (PM_{10}, O_3, total oxides of nitrogen). Logistic regression models controlling for temporal and demographic variables gave statistically

significant ($p < 0.05$) lag 1 day relative risk estimates of 1.04 per 15 $\mu g/m^3$ 24-h PM_{10} increment and 1.04 per 20 ppb increase in maximum 8-h O_3 levels. In multipollutant models including both PM_{10} and O_3, the terms for each became nonsignificant due to high collinearity of the two variables ($r^2 = 0.75$). The authors interpreted their findings as suggesting positive associations between pediatric asthma visits and both PM_{10} and O_3. The PM_{10} effects appeared to be stronger for concentrations > 20 $\mu g/m^3$ than below that 24-h value.

Other U.S. studies finding associations of respiratory-related hospital admissions or medical visits with PM_{10} levels extending below 50 $\mu g/m^3$ include: Schwartz (1994a) in Minneapolis/St. Paul, Minnesota; Schwartz et al. (1996b) in Cleveland; Sheppard et al. (1999) in Seattle; Linn et al. (2000) in Los Angeles; and Nauenberg and Basu (1999) in Los Angeles; in Minneapolis/St. Paul, MN, but not in Birmingham, AL. The excess risk estimates most consistently fall in the range of 5 to 25% per 50 $\mu g/m^3$ PM_{10} increment, with those for asthma visits and hospital admissions often being higher than those for COPD and pneumonia admissions.

Similar associations between increased respiratory related hospital admissions/medical visits and low short-term PM_{10} levels were also reported by various investigators for several non-U.S. cities. Wordley et al. (1997), for example, reported positive and significant associations between PM_{10} (mean = 25.6 $\mu g/m^3$, max = 131 $\mu g/m^3$) and respiratory admissions in Birmingham, UK using multivariate linear regression methods; and Atkinson et al. (1999a), using Poisson modeling, reported significant increases in hospital admissions for respiratory disease to be associated with PM_{10} (mean = 28.5 $\mu g/m^3$) in London, UK. Hagen et al. (2000) and Prescott et al. (1998) also found positive but nonsignificant associations of hospital admissions and, PM_{10} levels in Drammen, Norway (mean = 16.8 $\mu g/m^3$) and Edinburgh, Scotland (mean = 20.7 $\mu g/m^3$). Admissions in Drammen considered relatively small populations, limiting statistical power in this study. Petroeschevsky et al. (2001) examined associations between outdoor air pollution and hospital admissions in Brisbane, Australia during 1987 to 1994 using a light scattering index (BSP) for fine PM. The levels of PM are quite low in this city, relative to most U.S. cities, but BSP was positively and significantly associated with total respiratory admissions, but not for asthma.

8.3.2.3.1 Particulate Matter Mass Fractions and Composition Comparisons

While PM_{10} mass has generally been the metric most often used as the particle pollution index in the U.S. and Canada, some new studies have examined the relative roles of various PM_{10} mass fractions (e.g., $PM_{2.5}$ and $PM_{10-2.5}$) and chemical constituents (such as SO_4^{2-}) contributing to PM-respiratory hospital admissions associations. Several new studies (from among those summarized in Tables 8-21 and 8-22, respectively) report significant associations of increased respiratory-cause medical visits and/or hospital admissions with ambient $PM_{2.5}$ and/or $PM_{10-2.5}$ ranging to quite low concentrations. These include the Lippmann et al. (2000) study in Detroit, where all PM metrics (PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, H^+) were positively related to pneumonia and COPD admissions among the elderly (aged 65+ yr) in single pollutant models, with their RR values for pneumonia generally remaining little changed (but with broader confidence intervals) in multipollutant models including one or more gaseous pollutant (e.g., CO, O_3, NO_2, SO_2). However, for COPD admissions, the effect estimates were reduced and became nonsignificant in multipollutant models including gaseous co-pollutants. Excess risks for pneumonia admissions in the one pollutant model using default GAM were 13% (CI: 3.7, 22) and 12% (CI: −0.6, 24) per 25 μg/m^3 of $PM_{2.5}$ and $PM_{10-2.5}$, respectively; those for COPD admissions were 5.5% (CI: −4.7, 17) and 9.3% (CI: −4.2, 25) per 25 μg/m^3 $PM_{2.5}$ and $PM_{10-2.5}$, respectively.

Lippmann et al. (2000) reported weaker associations with sulfate and acidic components of $PM_{2.5}$ than with $PM_{2.5}$ mass overall, but the acidity levels during this study were very low, being below detection on most study days. In contrast, past studies of sulfates and aerosol acidity associations with respiratory hospital admissions have found stronger sulfate associations when the acidity of those aerosols was higher (e.g., Thurston et al, 1994). As noted by Lippman et al. (2000), "a notable difference between the data of Thurston and colleagues from Toronto and our data is the H^+ levels: the H^+ levels in Toronto were 21.4, 12.6, and 52.3 nmol/m^3 for the summers of 1986, 1987, and 1988, respectively, whereas in our study, the H^+ level averaged only 8.8 nmol/m^3."

In order to evaluate the potential influence of the GAM convergence specification on the results of the original Detroit data analysis, Ito (2003) re-examined associations between PM

TABLE 8-21. SUMMARY OF UNITED STATES $PM_{2.5}$ RESPIRATORY-RELATED HOSPITAL ADMISSION STUDIES

Reference	Outcome Measures	Mean Levels µg/m³	Co-Pollutants Measured	Lag	Method	Effect Estimate (95% CL) (% increase per 25 ug/m³)
Lippmann et al. (2000)	COPD	$PM_{2.5}$ = 18	SO_2, O_3, NO_2, CO, H+	3 3	Default GAM Default GAM	No Co Poll: 5.5 (−4.7, 16.8) Co Poll: 2.8 (−9.2, 16)
Reanalysis by Ito (2003)	COPD				Default GAM Strict GAM NS GLM	No Co Poll: 5.5 (−4.7, 16.8) No Co Poll: 3.0(−6.9, 13.9) No Co Poll: 0.3(−9.3, 10.9)
Moolgavkar (2000c)*	COPD (> 64 yrs) (median)	$PM_{2.5}$ = 22, LA $PM_{2.5}$ = 22, LA	— CO	2 2	Default GAM Default GAM	5.1 (0.9, 9.4) 2.0 (-2.9, 7.1) Two poll. model
Reanalysis by Moolgavkar (2003)	COPD (all ages)				Strict GAM: 30df Strict GAM: 100df NS GLM: 100df	4.69 (2.06, 7.38) 2.87 (0.53, 5.27) 2.59 (-0.29, 5.56)
Lippmann et al. (2000)	Pneumonia	$PM_{2.5}$ = 18	SO_2, O_3, NO_2, CO, H^+	1 1	Default GAM Default GAM	No Co-Poll: 12.5 (3.7, 22.1) Co Poll: 12 (1.7, 23)
Reanalysis by Ito (2003)	Pneumonia				Default GAM Strict GAM NS GLM	No Co-Poll: 12.5 (3.7, 22.1) No Co-Poll: 10.5 (1.8, 19.8) No Co-Poll: 10.1 (1.5, 19.5)
Sheppard et al. (1999)*	Asthma	$PM_{2.5}$ = 16.7	CO, O_3, SO_2	1	Default GAM	8.7 (3.3, 14.3)
Reanalysis by Sheppard (2003)			CO		Default GAM Strict GAM NS GLM Strict GAM NS GLM	No Co-Poll: 8.7 (3.3, 14.3) No Co-Poll: 8.7 (3.2,14.4) No Co-Poll: 6.5 (1.1,12.0) With Co-poll: 6.5 (2.1, 10.9) With Co-poll: 6.5 (2.1, 10.9)
Freidman et al. (2001)	Asthma	$PM_{2.5}$ = 36.7-30.8	O_3	3 day cum	Poisson GEE	1.4 (0.80-2.48)

NS = Natural Spline General Linear Model; PS = Penalized Spline General Additive Model.

components and daily mortality/morbidity by using more stringent GAM convergence criteria and by applying GLM analyses that approximated the original GAM models. The reanalysis of GAM Poisson models used more stringent convergence criteria, as suggested by Dominici et al. (2002): the convergence precision (epsilon) was set to 10-14, and the maximum iteration was set to 1000 for both the local scoring and back-fitting algorithms. The GLM model specification approximated the original GAM models. Natural splines were used for smoothing terms. To model time trend, the same degrees of freedom as the smoothing splines in the GAM models

TABLE 8-22. SUMMARY OF UNITED STATES $PM_{10-2.5}$ RESPIRATORY-RELATED HOSPITAL ADMISSION STUDIES

Reference	Outcome Measures	Mean Levels $\mu g/m^3$	Co-Pollutants Measured	Lag	Method	Effect Estimates (95% CL) (% increase per 25 ug/m^3)
Moolgavkar (2000c)*	COPD		—	3	Default GAM	5.1% (−0.4, 10.9)
Lippmann et al. (2000)*	COPD	$PM_{10-2.5}$ = 12	SO_2, O_3, NO_2, CO, H+	3 3	Default GAM Default GAM	No Co-Poll: 9.3 (−4.2, 24.7) Co-Poll: 0.3 (−14, 18)
Reanalysis by Ito (2003)					Default GAM Strict GAM NS GLM	No Co-Poll: 9.3 (−4.2, 24.7) No Co-Poll: 8.7 (−4.8, 24.0) No Co-Poll: 10.8 (−3.1, 26.5)
Lippmann et al. (2000)*	Pneumonia	$PM_{10-2.5}$ = 12	SO_2, O_3, NO_2, CO, H^+	1 1	Default GAM Default GAM	No Co-Poll: 11.9 (−0.6, 24.4) Co-Poll: 13.9 (0.0, 29.6)
Reanalysis by Ito (2003)				1 1 1	Default GAM Strict GAM NS GLM	No Co-Poll: 11.9 (−0.6, 24.4) No Co-Poll: 9.9 (−0.1, 22.0) No Co-Poll: 11.2 (−0.02, 23.6)
Sheppard et al. (1999)*	Asthma	$PM_{10-2.5}$ = 16.2	CO, O_3, SO_2	1	Default GAM	11.1 (2.8, 20.1)
Reanalysis by Sheppard (2003)				1 1	Strict GAM NS GLM	5.5 (−2.7 11.1) 5.5 (0, 14.0)

NS = Natural Spline General Linear Model; PS = Penalized Spline General Additive Model.

were used, with the default placement of knots. For weather models, to approximate LOESS smoothing with a span of 0.5 in the GAM model, natural splines with degrees of freedom were used. Generally, the GAM models with stringent convergence criteria and GLM models resulted in somewhat smaller estimated relative risks than those reported in the original study, e.g., for pneumonia admissions in Table 8-23. It was found that the reductions in the estimated relative risks were not different across the PM indices. Thus, conclusions of the original study about the relative roles of PM components by size and chemical characteristics remained unaffected. Lumley and Heagerty (1999) illustrate the effect of reliable variance estimation on data from hospital admissions for respiratory disease on King County, WA for eight years (1987-94), together with air pollution and weather information, using estimating equations and weighted empirical variance estimators. However, their weather controls were relatively crude (i.e.,

TABLE 8-23. INTERCOMPARISON OF DETROIT PNEUMONIA HOSPITAL ADMISSION RELATIVE RISKS (± 95% CI below) OF PM INDICES (per 5th-to-95th percentile pollutant increment) FOR VARIOUS MODEL SPECIFICATIONS.*

	Original GAM (default)	GAM (stringent)	GLM
$PM_{2.5}$ (1)	1.185 (1.053, 1.332)	1.154 (1.027, 1.298)	1.149 (1.022, 1.292)
$PM_{10-2.5}$ (1)	1.114 (1.006, 1.233)	1.095 (0.990, 1.211)	1.107 (1.00, 1.226)
PM_{10} (1)	1.219 (1.084, 1.372)	1.185 (1.054, 1.332)	1.190 (1.057, 1.338)
H^+ (3)	1.060 (1.005, 1.118)	1.049 (0.994, 1.107)	1.049 (0.994, 1.107)
$SO_4^=$ (1)	1.156 (1.050, 1.273)	1.128 (1.025, 1.242)	1.123 (1.020, 1.235)

*The selected lag is indicated in parenthesis next to the pollutant name.

Source: Ito (2003).

seasonal dummy variables and linear temperature terms). This study is notable for having compared sub-micron PM ($PM_{1.0}$) versus coarse $PM_{10-1.0}$ and for finding significant hospital admission associations only with $PM_{1.0}$. This may suggest that the $PM_{2.5}$ versus PM_{10} separation may not always be sufficient to differentiate submicron fine particle versus coarse-particle toxicities.

Asthma hospital admission studies in various U.S. communities provide additional important new data. Of particular note is a study by Sheppard et al. (1999) which evaluated relationships between measured ambient pollutants (PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, SO_2, O_3, and CO) and nonelderly adult (< 65 years of age) hospital admissions for asthma in Seattle, WA. PM and CO were found to be jointly associated with asthma admissions. The authors noted ". . . .we observed unexpected associations for CO that dominated the PM effects. Nevertheless, although there is substantial literature on the effects of CO on the cardiovascular system, there is no evidence for an effect on the underlying physiology of asthma. CO may be an important environmental indicator of incomplete combustion, particularly from mobile sources."

An estimated 4 to 5% increase in the rate of asthma hospital admissions (lagged 1 day) was reported to be associated with interquartile range changes in PM indices (19 $\mu g/m^3$ for PM_{10}, 11.8 $\mu g/m^3$ for $PM_{2.5}$, and 9.3 $\mu g/m^3$ for $PM_{10-2.5}$), equivalent to excess risk rates as follows: 13% (CI: 0.5-23) per 50 $\mu g/m^3$ for PM_{10}; 9% (CI: 3-14) per 25 $\mu g/m^3$ $PM_{2.5}$; 11% (CI: 3-20) per 25 $\mu g/m^3$ $PM_{10-2.5}$. Also of note for the same region are analyses by the same research team using similar methods (Norris et al., 1999) which showed associations of low levels of $PM_{2.5}$ (mean = 12 $\mu g/m^3$) with markedly increased asthma ED, i.e., excess risk = 44.5% (CI: 21.7-71.4) per 25 $\mu g/m^3$ $PM_{2.5}$.

Sheppard (2003) recently conducted a reanalysis of their nonelderly hospital admissions data for asthma in Seattle, WA, to evaluate the effect of the fitting procedure on their previously published analyses. As shown in Figure 8-11, the effect estimates were slightly smaller when more stringent convergence criteria were used with GAM, and there was an additional small reduction in the estimates when GLM with natural splines were used instead. The average reduction in effect estimate between the default and stringent convergence criteria for $PM_{2.5}$, PM_{10}, and $PM_{10-2.5}$ (coarse) mass averaged 10.7%. The coefficients remained statistically significant for both $PM_{2.5}$ and PM_{10} but not for coarse mass. Confidence intervals were slightly wider for the GLM model fit. Sheppard concluded that,

> "Overall the results did not change meaningfully. There were small reductions in estimates using the alternate fitting procedures. I also found that the effect of single imputation (i.e., not adjusting for replacing missing exposure data with an estimate of its expected value) was to bias the effect estimates slightly upward. In this data set this bias is of the same order as the bias from using too liberal convergence criteria in the generalized additive model."

Moolgavkar (2003) also conducted reanalyses of respiratory-related hospital admissions, but for COPD data for all ages in Los Angeles. Using GAM with strict convergence criteria and 30 degrees of freedom (df), an excess risk estimate of 4.7% (CI: 2.1, 7.4) was obtained per 25 $\mu g/m^3$ $PM_{2.5}$ increment. The notable effect of increasing degrees of freedom on modeling results is well illustrated by the excess risk estimate dropping to 2.9% (CI: 0.5, 5.3) with strict GAM and 100 df or 2.6% (CI: –0.3, 5.6) with NS GLM 100 df.

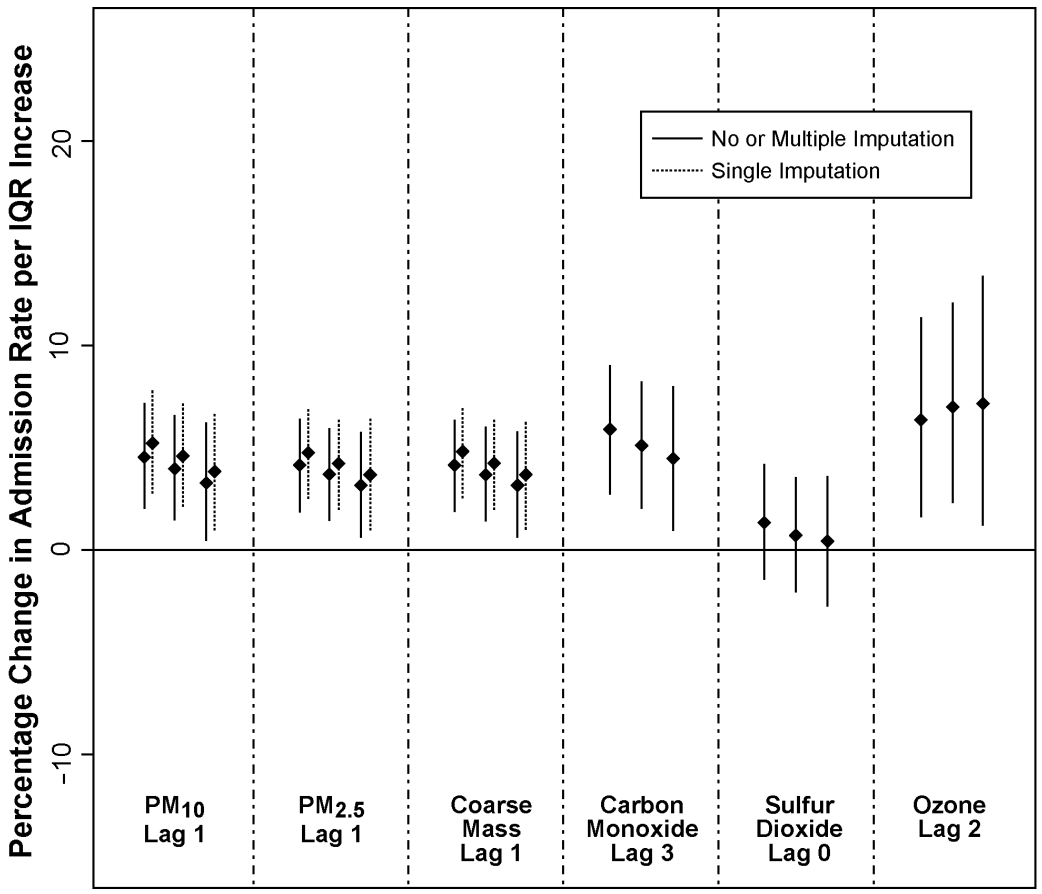

Figure 8-11. Percent change in hospital admission rates and 95% CIs for an IQR increase in pollutants from single-pollutant models for asthma. Poisson regression models are adjusted for time trends (64-*df* spline), day-of-week, and temperature (4-*df* spline). The IQR for each pollutant equals: 19 μg/m^3 for PM_{10}, 11.8 μg/m^3 for $PM_{2.5}$, 9.3 μg/m^3 for coarse PM, 20 ppb for O_3, 4.9 ppb for SO_2, and 924 ppb for CO. Triplets of estimates for each pollutant are for the original GAM analysis using smoothing splines, the revised GAM analysis with stricter convergence criteria, and the GLM analysis with natural splines. For pollutants that required imputation (i.e., estimation of missing value) estimates ignoring (single imputation) or adjusting for (multiple imputation) the imputation are shown.

Source: Sheppard (2003).

Burnett et al. (1997a) evaluated the role that the ambient air pollution mix, comprised of gaseous pollutants and PM indexed by various physical and chemical measures, plays in exacerbating daily admissions to hospitals for cardiac diseases and for respiratory diseases

(tracheobronchitis, chronic obstructive lung disease, asthma, and pneumonia). They employed daily measures of $PM_{2.5}$ and $PM_{10-2.5}$, aerosol chemistry (sulfates and H+), and gaseous pollutants (O_3, NO_2, SO_2, CO) collected in Toronto, Ontario, Canada, during the summers of 1992, 1993, and 1994. Positive associations were observed for all ambient air pollutants for both respiratory and cardiac diseases. Ozone was the most consistently significant pollutant and least sensitive to adjustment for other gaseous and particulate measures. The PM associations with respiratory hospital admissions were significant for: PM_{10} (RR = 1.11 for 50 μg/m^3; CI: 1.05, 1.17); $PM_{2.5}$ (fine) mass (RR = 1.09 for 25 μg/m^3; CI: 1.03, 1.14);$PM_{10-2.5}$ (coarse) mass (RR = 1.13 for 25 μg/m^3; CI: 1.05, 1.20); sulfate levels (RR = 1.11 for 155 nmoles/m^3 = 15 μg/m^3; CI: 1.06, 1.17); and H^+ (RR = 1.40 for 75 nmoles/m^3 = 3.6 μg/m^3, as H_2SO_4; CI: 1.15, 1.70). After inclusion of O_3 in the model, the associations with the respiratory hospital admissions remained significant for: PM_{10} (RR = 1.10, CI: 1.04, 1.16); fine mass (RR = 1.06; CI: 1.01, 1.12); coarse mass (RR = 1.11; CI: 1.04, 1.19); sulfate levels (RR = 1.06; CI: 1.0, 1.12); and H^+ (RR = 1.25; CI: 1.03, 1.53), using the same increments. Of the PM metrics considered here, H^+ yielded the highest RR estimate. Regression models that included all recorded pollutant simultaneously (with high intercorrelations among the pollutants) were also presented.

A recent study by Lin et al. (2002) used both case-crossover and time-series analyses to assess the associations between size-fractionated PM and asthma hospitalization among children 6 to 12 years old living in Toronto between 1981 and 1993. The authors used exposures averaged over periods varying from 1 to 7 days to assess the PM effects on asthma hospitalization. Estimates of the relative risk of asthma hospitalization were adjusted for daily weather conditions (maximum and minimum temperatures, and average relative humidity) for an incremental exposure corresponding to the PM interquartile range. However, direct measurements of PM components were available only every sixth day in this data set, and 5 out of every 6 PM data points in the analysis were based on estimated $PM_{2.5}$, $PM_{2.5-10}$, and PM_{10} data, weakening confidence in these input data. Time-series plots of the $PM_{2.5-10}$ data showed much stronger seasonality in the estimated coarse PM data than in the estimated fine PM mass data. Seasonality was controlled for in the time-series analyses using a 3 month span smooth of the

data, rather than the more commonly employed one month or less span. Thus, residual seasonality may have been a factor in this study's $PM_{2.5-10}$ results. Both bidirectional case-crossover and time-series analyses revealed that coarse PM ($PM_{10-2.5}$) averaged over 5-6 days was significantly associated with asthma hospitalization in both males and females. The magnitude of this effect appeared to increase with increasing number of days of exposure averaging for most models, with the relative risk estimates stabilizing at about 6 days. Using a bidirectional case-crossover analysis, the estimated relative risks were 1.14 (CI: 1.02, 1.28) for males and 1.18 (CI: 1.02, 1.36) for females, for an increment of 8.4 $\mu g/m^3$ in 6-day averages of $PM_{10-2.5}$. The corresponding relative risk estimates were 1.10 and 1.18, respectively, from the time-series analysis. The effect of $PM_{10-2.5}$ remained positive after adjustment for the effects of gaseous pollutants CO, NO_2, SO_2, and O_3. They did not find significant effects of fine PM ($PM_{2.5}$) or of thoracic PM (PM_{10}) on asthma hospitalizations, except in the unidirectional case-cross-over analyses. Seasonal-specific results were not presented. The paper's discussion ignores previous results by Thurston et al. (1994), which provided results during summers in the same time range (1986 to 1988) that are in direct conflict with respect to the significance of $PM_{2.5}$. That study used daily direct measurements of size fractionated PM in analysis for those three summers and found significant effects for summertime $PM_{2.5}$. Seasonality of data analysis may therefore be a factor in the differences between these two Toronto hospital admissions studies regarding the health effects of fine PM. Overall, this new study suggests that coarse particle mass can also be a risk factor in children's asthma hospital admissions.

There have also been numerous new time-series studies examining associations between air pollution and respiratory-related hospital admissions in Europe, as summarized in Appendix 8B, Table 8B-2, but most of these studies relied primarily on black smoke (BS) as their PM metric. BS is a particle reflectance measure that provides an indicator of PM blackness and is highly correlated with airborne carbonaceous particle concentrations (Bailey and Clayton, 1982). In the U.S., Coefficient of Haze (CoH) is a metric of particle transmittance that similarly most directly represents a metric of particle blackness and ambient elemental carbon levels (Wolff et al., 1983) and has been found to be highly correlated with BS ($r = 0.9$; Lee et al., 1972). However, the relationship between airborne carbon and total mass of overall aerosol

(PM) composition varies over time and from locality to locality, so the BS-mass ratio is less reliable than the BS-carbon relationship (Bailey and Clayton, 1982). This means that the BS-mass relationship is likely to be very different between Europe and the United States, largely due to differences in local PM source characteristics (e.g., percentages of diesel powered motor vehicles). Therefore, while these European BS-health effects studies may be of qualitative interest for evaluating the PM-health effects associations, they are not as useful for quantitative assessment of PM effects relevant to the United States.

Probably the most extensive and useful recent European air pollution health effects analyses have been conducted as part of the APHEA multicity study, which evaluated 15 European cities from 10 different countries with a total population of over 25 million. All studies used a standardized data collection and analysis approach, which included consideration of the same suite of air pollutants (BS, SO_2, NO_2, SO_2, and O_3) and the use of time-series regression addressing seasonal and other long-term patterns; influenza epidemics; day of the week; holidays; weather; and autocorrelation (Katsouyanni et al., 1996). The general coherence of the APHEA results with other results gained under different conditions strengthens the argument for causality in the air pollution-health effects association. In earlier studies, the general use of the less comparable suspended particle (SPM) measures and BS as PM indicators in some of the APHEA locations and analyses lessens the quantitative usefulness of such analyses in evaluating associations between PM and health effects most pertinent to the U.S. situation. However, Atkinson et al. (2001) report results of PM_{10} analyses in a study of eight APHEA cities.

As for other single-city European studies of potential interest here, Hagen et al. (2000) compared the association of PM_{10} and co-pollutants with hospital admissions for respiratory causes in Drammen, Norway during 1994 to 1997. Respiratory admissions averaged only 2.2 per day; so, the power of this analysis is weaker than studies looking at larger populations and longer time periods. The NMMAPS modeling approach was employed. While a significant association was found for PM_{10} as a single pollutant, it became nonsignificant in multiple pollutant models. In two pollutant models, the associations and effect size of pollutants were generally diminished, and when all eight pollutants were considered in the model, all pollutants

became nonsignificant. These results are typical of the problems of analyzing and interpreting the coefficients of multiple pollutant models when the pollutants are even moderately intercorrelated over time. A unique aspect of this work was that benzene was considered in this community to be strongly affected by traffic pollution. In two pollutant models, benzene was most consistently still associated. The authors conclude that PM is mainly an indicator of air pollution in this city and emissions from vehicles seem most important for health effects. Thompson et al. (2001) report a similar result in Belfast, Northern Ireland, where, after adjusting for multiple pollutants, only the benzene level was independently associated with asthma emergency department (ED) admissions.

8.3.2.4 Key New Respiratory Medical Visits Studies

As noted above, medical visits include both hospital ED and doctors' office visits. As in the past, most newly available morbidity studies in Table 8B-3, Appendix 8B and in Table 8-24 below are of ED visits and their associations with air pollution. These studies collectively confirm the results provided in the 1996 PM AQCD, indicating a positive and generally statistically significant association between ambient PM levels and increased respiratory-related hospital visits.

Of the medical visit and hospital admissions studies since the 1996 PM AQCD, among the most informative are those that evaluate health effects at relatively low PM concentrations. As for U.S. studies, Tolbert et al. (2000b) reported a significant PM_{10} association with pediatric ED visits in Atlanta where mean PM_{10} = 39 $\mu g/m^3$ and maximum PM_{10} = 105 $\mu g/m^3$. The Lipsett et al. (1997) study of winter air pollution and asthma emergency visits in Santa Clara Co, CA, may provide insight where one of the principal sources of PM_{10} is residential wood combustion (RWC). Their results demonstrate an association between PM_{10} levels and asthma. Also of interest, Delfino et al. (1997a) found significant PM_{10} and $PM_{2.5}$ associations for respiratory ED visits among older adults in Montreal when mean PM_{10}=21.7 $\mu g/m^3$ and mean $PM_{2.5}$ = 12.2 $\mu g/m^3$. Hajat et al. (1999) also reported significant PM_{10} associations with asthma doctor's visits for children and young adults in London when mean PM_{10} = 28.2 $\mu g/m^3$ and the PM_{10} 90th percentile was only 46.4 $\mu g/m^3$. Overall, then, several new medical visits studies indicate

TABLE 8-24. SUMMARY OF UNITED STATES PM_{10}, $PM_{2.5}$, AND $PM_{10-2.5}$ ASTHMA MEDICAL VISIT STUDIES

Reference	Outcome Measures	Mean Levels ($\mu g/m^3$)	Co-Pollutants Measured	Lag	Method	Effect Estimate* (95% CL)
PM_{10}						
Choudhury et al. (1997)	Asthma	41.5	Not considered	0	GLM	20.9 (11.8, 30.8)
Lipsett et al. (1997)	Asthma	61.2	NO_2, O_3	2	GLM	34.7 (16, 56.5) at 20 °C
Tolbert et al. (2000b)	Asthma	38.9	O_3	1	GEE	13.2 (1.2, 26.7)
Tolbert et al. (2000a)**	Asthma	29.1	NO_2, O_3, CO, SO_2	0-2	GLM	8.8 (−8.7, 54.4)
$PM_{2.5}$						
Tolbert et al. (2000a)**	Asthma	19.4	NO_2, O_3, CO, SO_2	0-2	GLM	2.3 (−14.8, 22.7)
$PM_{10-2.5}$						
Tolbert et al. (2000a)**	Asthma	9.39	NO_2, O_3, CO, SO_2	0-2	GLM	21.1 (−18.2, 79.3)

* Effect estimates derived from single-pollutant models.
**Preliminary results based on emergency department visit data from 18 of 33 participating hospitals.

PM-health effects associations at lower $PM_{2.5}$ and PM_{10} levels than those from previous publications.

8.3.2.4.1 Scope of Medical Visit Morbidity Effects

Several newer medical visit studies consider a new endpoint for comparison with ED visits: visits in the primary care setting. In particular, key studies showing PM associations for this health outcome include: the study by Hajat et al. (1999) that evaluated the relationship between air pollution in London, UK; and daily General Practice (GP) doctor consultations for asthma and other lower respiratory disease (LRD); the study by Choudhury et al. (1997) of private asthma medical visits in Anchorage, Alaska; and the study by Ostro et al. (1999b) of daily visits by young children to primary care health clinics in Santiago, Chile for upper or lower respiratory symptoms.

While limited in number, the above studies collectively provide new insight into the fact that there is a broader scope of morbidity associated with PM air pollution exposure than previously documented. As the authors of the London study note: "There is less information about the effects of air pollution in general practice consultations but, if they do exist, the public health impact could be considerable because of their large numbers." Indeed, the London study of doctors' GP office visits indicates that the effects of air pollution, including PM, can affect many more people than indicated by hospital admissions alone.

These new studies also provide indications as to the quantitative nature of medical visits effects, relative to those for hospital admissions. In the London case, comparing the number of admissions from the authors' earlier study (Anderson et al., 1996) with those for GP visits in the 1999 study (Hajat et al., 1999) indicates that there are ~24 asthma GP visits for every asthma hospital admission in that city. Also, comparing the PM_{10} coefficients indicates that the all-ages asthma effect size for the GP visits (although not statistically different) was about 30% larger than that for hospital admissions. Thus, these new studies suggest that looking at only hospital admissions and emergency hospital visit effects may greatly underestimate the overall numbers of respiratory morbidity events due to acute ambient PM exposure.

8.3.2.4.2 Factors Potentially Affecting Respiratory Medical Visit Study Outcomes

Some newly available studies have examined certain factors that might extraneously affect the outcomes of PM-medical visit studies. Stieb et al. (1998a) examined the occurrence of bias and random variability in diagnostic classification of air pollution and daily cardiac or respiratory ED visits, such as for asthma, COPD, respiratory infection, etc. They concluded that there was no evidence of diagnostic bias in relation to daily air pollution levels. Also, Stieb et al. (1998b) reported that for a population of adults visiting an emergency department with cardiorespiratory disease, fixed site sulfate monitors appear to accurately reflect daily variability in average personal exposure to particulate sulfate, whereas acid exposure was not as well represented by fixed site monitors. Another study investigated possible confounding of respiratory visit effects due to pollens and mold spores (Steib et al, 2000). Aeroallergen levels did not influence the results, similar to asthma panel studies described below in Section 8.3.3.

In London, Atkinson et al. (1999a) studied the association between the number of daily ED visit for respiratory complaints and measures of outdoor air pollution for PM_{10}, NO_2, SO_2 and CO. They examined different age groups and reported strongest associations for children for visits for asthma, but were unable to separate PM_{10} and SO_2 effects.

8.3.2.5 Identification of Potential Susceptible Subpopulations

Associations between ambient PM measures and respiratory admissions have been found for all age groups, but older adults and children generally have been indicated by hospital admissions studies to exhibit the most consistent PM-health effects associations. As reported in previous PM AQCDs, numerous studies of older adults (e.g., those 65+ years of age) have related acute PM exposure with an increased incidence of hospital admissions (e.g., see Anderson et al, 1998). However, only a limited number have specifically studied children as a subgroup. Burnett et al. (1994) examined the differences in air pollution-hospital admissions associations as a function of age in Ontario, reporting that the largest percentage increase in admissions was found among infants (neonatal and postneonatal, one year or less in age).

Further efforts have aimed at identifying and quantifying air pollution effects among potentially especially susceptible subpopulations of the general public. Some new studies have further investigated the hypothesis that the elderly are especially affected by air pollution. Zanobetti et al. (2000a) examined PM_{10} associations with hospital admissions for heart and lung disease in ten U.S. cities, finding an overall association for COPD, pneumonia, and CVD. They found that these results were not significantly modified by poverty rate or minority status in this population of Medicare patients. Ye et al. (2001) examined emergency transports to the hospital. Both PM_{10} and $N0_2$ levels were significantly associated with daily hospital transports for angina, cardiac insufficiency, myocardial infarction, acute and chronic bronchitis, and pneumonia. The pollutant effect sizes were generally found to be greater in men than in women, except those for angina and acute bronchitis, which were the same across genders. Thus, in these various studies, cardiopulmonary hospital visits and admissions among the elderly were seen to be consistently associated with PM levels across numerous locales in the U.S. and abroad, generally without regard to race or income; but sex was sometimes an effect modifier.

Several new studies of children's morbidity also support the indication of air pollution effects among children. Pless-Mulloli et al. (2000) evaluated children's respiratory health and air pollution near opencast coal mining sites in a cohort of nearly 5,000 children aged 1 to 11 years in England. Mean PM levels were not high (mean < 20 $\mu g/m^3$ PM_{10}), but statistically significant PM_{10} associations were found with respiratory symptoms. A roughly 5% increase of General Practitioner medical visits was also noted, but was not significant. Ilabaca et al. (1999) also found an association between levels of fine PM and ED visits for pneumonia and other respiratory illnesses among children < 15 years old in Santiago, Chile, where the levels of $PM_{2.5}$ were very high (mean = 71.3 $\mu g/m^3$) during 1995 to 1996. The authors found it difficult to separate out the effects of various pollutants, but concluded that PM (especially the fine component) is associated with the risk of these respiratory illnesses. Overall, these new studies support past assertions that children, and especially neo-natal infants, are especially susceptible to the health effects of air pollution.

The respiratory-related hospital admissions studies summarized in Appendix 8B reveal that the PM RR's for all children (e.g., 0 to 18 years old) are not often notably larger than those for adults, but such comparisons of RR's must adjust for differences in baseline risks for each group. For example, if hospital admissions per 100,000 per day for young children are double the rate for adults, then they will have a pollution relative risk (RR) per $\mu g/m^3$ that is half that of the adults given the exact same impact on admissions/100,000/$\mu g/m^3$/day. Thus, it is important to adjust RR's or Excess Risks (ER's) for each different age groups' baseline, but this information is usually not available (especially regarding the population catchment for each age group in each study). One of the few indications that is notable when comparing children with other age group effect estimates in Table 8B-2 is the higher excess risk estimate for infants (i.e., the group < 1 year of age) in the Gouveia and Fletcher (2000) study, an age group that has estimated risk estimate roughly twice as large as for other children or adults.

8.3.2.6 Summary of Salient Findings on Acute Particulate Matter Exposure and Respiratory-Related Hospital Admissions and Medical Visits

The results of new studies discussed above are generally consistent with and supportive of findings presented in the 1996 PM AQCD (U.S. Environmental Protection Agency, 1996a),

with regard to ambient PM associations of short-term exposures with respiratory-related hospital admissions/medical visits. Figure 8-12 summarizes results for maximum excess risk of respiratory-related hospital admission and visits per 50 μg/m^3 PM_{10} based on single-pollutant models for selected U.S. cities. The excess risk estimates fall most consistently in the range of 5 to 20% per 50 μg/m^3 PM_{10} increments, with those for asthma visits and hospital admissions generally somewhat higher than for COPD and pneumonia hospital admissions. More limited new evidence both (a) substantiates increased risk of respiratory-related hospital admissions due to ambient fine particles ($PM_{2.5}$, $PM_{1.0}$, etc.) and also (b) points towards such admissions being associated with ambient coarse particles ($PM_{10-2.5}$). Excess risk estimates tend to fall in the range of ~5.0 to 15.0% per 25 μg/m^3 $PM_{2.5}$ or $PM_{10-2.5}$ for overall respiratory admissions or for COPD admissions, whereas larger estimates are found for asthma admissions.

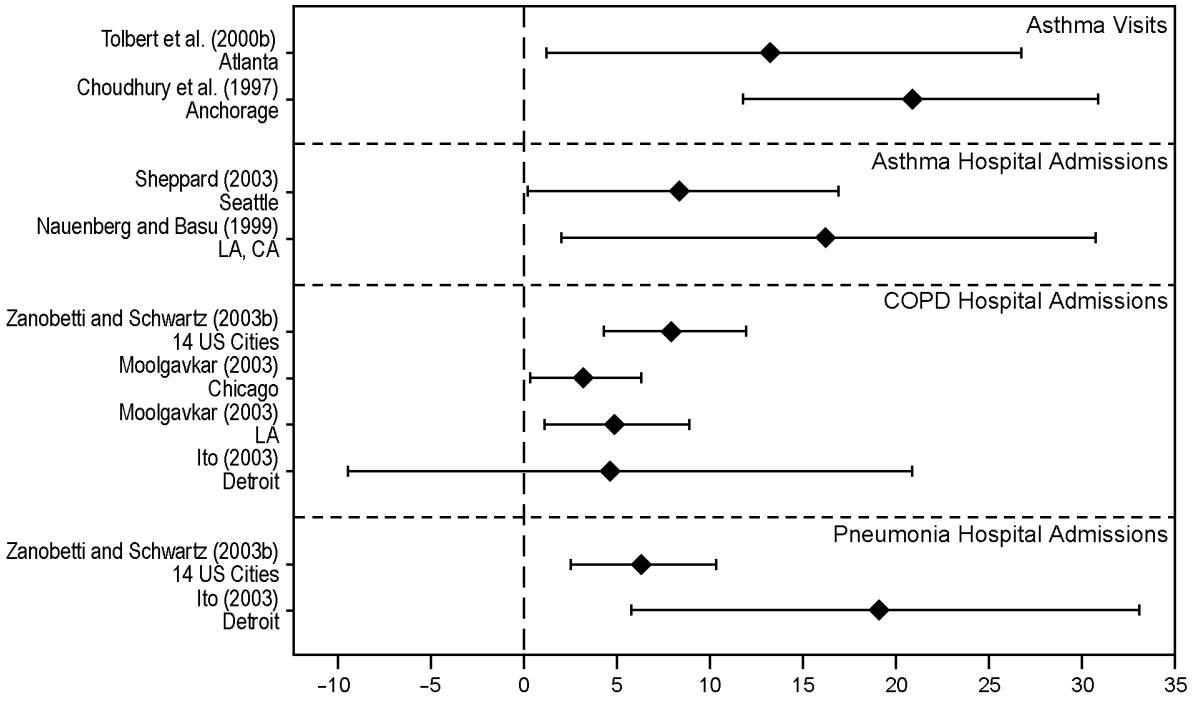

Figure 8-12. Maximum excess risk of respiratory-related hospital admissions and visits per 50 μg/m^3 PM_{10} increment in studies of U.S. cities based on single-pollutant models.

Various new medical visits studies (including nonhospital physician visits) indicate that the use of hospital admissions alone can greatly understate the total clinical morbidity effects of air pollution. Thus, these results support the hypothesis that considering only hospital admissions and ED visit effects may greatly underestimate the numbers of medical visits occurring in a population as a result of acute ambient PM exposure. Those groups identified in these morbidity studies as most strongly affected by PM air pollution are older adults and the very young.

8.3.3 Effects of Particulate Matter Exposure on Lung Function and Respiratory Symptoms

In the 1996 PM AQCD, the available respiratory studies used a wide variety of designs examining pulmonary function and respiratory symptoms in relation to ambient concentrations of PM_{10}. The populations studied included several different subgroups (e.g., children, asthmatics, etc.); and the models used for analysis varied, but did not include GAM use. The pulmonary function studies were suggestive of short-term effects resulting from ambient PM exposure. Peak expiratory flow rates showed decreases in the range of 2 to 5 l/min per 50 $\mu g/m^3$ increase in 24-h PM_{10} or its equivalent, with somewhat larger effects in symptomatic groups, e.g., asthmatics. Studies using FEV_1 or FVC as endpoints showed less consistent effects. The chronic pulmonary function studies, less numerous than the acute studies, had inconclusive results.

8.3.3.1 Effects of Short-Term Particulate Matter Exposure on Lung Function and Respiratory Symptoms

The available acute respiratory symptom studies discussed in the 1996 PM AQCD included several different endpoints, but typically presented results for upper respiratory symptoms, lower respiratory symptoms, or cough. These respiratory symptom endpoints had similar general patterns of results. The odds ratios were generally positive, the 95% confidence intervals for about half of the studies being statistically significant (i.e., the lower bound exceeded 1.0).

The earlier studies of morbidity health outcomes of PM exposure on asthmatics were limited in terms of conclusions that could be drawn because of the few available studies on asthmatic subjects. Lebowitz et al. (1987) reported a relationship with TSP exposure and

productive cough in a panel of 22 asthmatics but not for peak flow or wheeze. Pope et al. (1991) reported on respiratory symptoms in two panels of Utah Valley asthmatics. The 34 asthmatic school children panel yielded estimated odd ratios of 1.28 (1.06, 1.56) for lower respiratory illness (LRI) and the second panel of 21 subjects aged 8 to 72 years for LRI of 1.01 (0.81, 1.27) for exposure to PM_{10}. Ostro et al. (1991) reported no association for $PM_{2.5}$ exposure in a panel of 207 adult asthmatics in Denver; but, for a panel of 83 asthmatic children age 7 to 12 years in central Los Angeles, found a relationship of shortness of breath to O_3 and PM_{10}, but could not separate effects of the two pollutants (Ostro et al., 1995). These few studies did not indicate a consistent relationship for PM_{10} exposure and health outcome in asthmatics.

Numerous new studies of short-term PM exposure effects on lung function and respiratory symptoms published since 1996 were identified by an ongoing Medline search. Most of these followed a panel of subjects over one or more time periods and evaluated daily lung function and/or respiratory symptom in relation to changes in ambient PM_{10}, $PM_{10-2.5}$, and/or $PM_{2.5}$. Some used other measures of airborne particles, e.g., ultrafine PM, TSP, BS, and sulfate fraction of ambient PM. Lung function was usually measured daily, with most studies including forced expiratory volume (FEV), forced vital capacity (FVC) and peak expiratory flow rate (PEF), measured both in the morning and afternoon. Various respiratory symptoms were measured, e.g., cough, phlegm, difficulty breathing, wheeze, and bronchodilator use. Detailed summaries of these studies are presented in Appendix 8B. Data on physical and chemical aspects of ambient PM levels (especially for PM_{10}, $PM_{10-2.5}$, $PM_{2.5}$, and smaller size fractions) are of particular interest, as are new studies examining health outcome effects and/or exposure measures not much studied in the past.

Specific studies were selected for summarization based on the following criteria:

- Peak flow was used as the primary lung function measurement of interest.
- Cough, phlegm, difficulty breathing, wheeze, and bronchodilator use were summarized as measures of respiratory symptoms when available.
- Quantitative relationships were estimated using PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, and/or smaller PM as independent variables.
- Analyses used in the study were done such that each individual served as their own control.

8.3.3.1.1 Lung Function and Respiratory Symptom Effects in Asthmatic Subjects

Appendix B Tables 8B-4 and 8B-5 summarize salient features of new studies of short-term PM exposure effects on lung function and respiratory symptoms, respectively, in asthmatic subjects; and key quantitative results are summarized in Table 8-25 for PM_{10} and Table 8-26 for $PM_{2.5}$. The peak flow analyses results for asthmatics tend to show small decrements for PM_{10} and $PM_{2.5}$ as seen in studies by Gielen et al. (1997), Peters et al. (1997c), Romieu et al. (1997), and Pekkanen et al. (1997).

For PM_{10}, the available point estimates for morning PEF lagged one day showed decreases, but the majority of the studies were not statistically significant (as per Table 8-25 and as shown in Figure 8-13 as an example of PEF outcomes). Lag 1 may be more relevant for morning measurement of asthma outcome from the previous day. The figure presents studies which provided such data. The results were consistent for both AM and PM peak flow analyses. Effects using two- to five-day lags averaged about the same as did the zero to one-day lags, but had wider confidence limits. Similar results were found for the fewer $PM_{2.5}$ studies. Of these, Pekkanen et al. (1997) and Romieu et al. (1996) found similar results for $PM_{2.5}$ and PM_{10}, while the study of Peters et al. (1997b) found slightly larger effects for $PM_{2.5}$.

Pekkanen et al. (1997) also reported changes in peak flow to be related to several sizes of PM. The authors reported morning PEF changes of −0.970 (SE = 0.502) l(cm^3) for particle number count (0.032 - 0.10 in size), −0.901 (0.536) for $PM_{1.0-3.2}$, and −1.13 (SE = 0.478) for PM_{10}. Peters et al. (1997c) report that the strongest effects on peak flow were found with ultrafine particles: $PM_{MC\ 0.01-0.1}$: −1.21 (−2.13, −0.30); $PM_{MC0.01-2.5}$: −1.01 (−1.92, −0.11); and PM_{10}: −1.30 (−2.36, −0.24). Penttinen et al. (2001) using biweekly spirometry over 6 months on a group of 54 adult asthmatics found that FVC, FEV_1, and spirometric PEFR were inversely, but mostly nonsignificantly-associated with ultrafine particle concentrations. Compared to the effect estimates for self-monitored PEFR, the effect estimates for spirometric PEFR tended to be larger. The strongest associations were observed in the size range of 0.1 to 1 μm. In a further study, von Klot et al. (2002) evaluated 53 adult asthmatics in Erfurt, Germany in the winter of 1996-1997. Relationships were estimated from generalized estimating equations, adjusting for autocorrelation. Asthma symptoms were related to small

TABLE 8-25. SUMMARY OF QUANTITATIVE PFT CHANGES IN ASTHMATICS PER 50 µg/m^3 PM_{10} INCREMENT

Reference Citation, Location, etc.	Outcome Measure	Mean Particulate Levels (Range) µg/m^3	Co-Pollutants Measured	Lag Structure	Effect Measures Standardized to 50 µg/m^3 PM_{10}
Asthma Studies					
Pekkanen et al. (1997)	Morning PEFR	14 (10, 23)	NO_2	0 day	−2.71 (−6.57, 1.15)
Gielen et al. (1997)	Morning PEFR	30.5 (16, 60)	Ozone	1 day	1.39 (−0.57, 3.35)
Romieu et al. (1996)	Morning PEFR	166.8 (29, 363)	Ozone	1 day	−4.70 (−7.65, -1.70)
Romieu et al. (1997)	Morning PEFR	(12, 126)	Ozone	1 day	−0.65 (−5.32, 3.97)
Peters et al. (1997a)	Morning PEFR	47 (29, 73)	SO_2, sulfate, H^+	1 day	−0.84 (−1.62, −0.06)
Peters et al. (1997b)	Morning PEFR	55 (?, 71)	SO_2, sulfate, H^+	1 day	−1.30 (−2.36, −0.24)
Gielen et al. (1997)	Morning PEFR	30.5 (16, 60)	Ozone	2 day	0.34 (−1.78, 2.46)
Romieu et al. (1996)	Morning PEFR	166.8 (29, 363)	Ozone	2 day	−4.90 (−8.40, -1.50)
Romieu et al. (1997)	Morning PEFR	(12, 126)	Ozone	2 day	2.47 (−1.75, 6.75)
Gielen et al. (1997)	Evening PEFR	30.5 (16, 60)	Ozone	0 day	−0.30 (−2.24, 1.64)
Romieu et al. (1996)	Evening PEFR	166.8 (29, 363)	Ozone	0 day	−4.80 (−8.00, -1.70)
Romieu et al. (1997)	Evening PEFR	(12, 126)	Ozone	0 day	−1.32 (−6.82, 4.17)
Pekkanen et al. (1997)	Evening PEFR	14 (10, 23)	NO_2	0 day	−0.35 (−4.31, 3.61)
Peters et al. (1996)	Evening PEFR	112	SO_2, sulfate, PSA	0 day	−1.03 (−1.98, −0.08)
Peters et al. (1997a)	Evening PEFR	47 (29, 73)	SO_2, sulfate, H^+	0 day	−0.92 (−1.96, 0.12)
Peters et al. (1997b)	Evening PEFR	55 (?, 71)	SO_2, sulfate, H^+	0 day	−0.37 (−1.82, 1.08)
Timonen & Pekkanen (1997) Urban	Evening PEFR	18 (?, 60)	NO_2, SO_2	0 day	−1.10 (−5.20, 3.00)
Timonen & Pekkanen (1997) Suburban	Evening PEFR	13 (?, 37)	NO_2, SO_2	0 day	−1.66 (−8.26, 4.94)
Gielen et al. (1997)	Evening PEFR	30.5 (16, 60)	Ozone	2 day	−2.32 (−5.36, 0.72)
Romieu et al. (1996)	Evening PEFR	166.8 (29, 363)	Ozone	2 day	−3.65 (−7.20, 0.03)
Romieu et al. (1997)	Evening PEFR	(12, 126)	Ozone	2 day	−0.04 (−4.29, 4.21)
Segala et al. (1998)	Morning PEFR	34.2 (9, 95)	SO_2, NO_2	2 day	−0.62 (−1.52, 0.28)
Pekkanen et al. (1997)	Evening PEFR	14 (10, 23)	NO_2	2 day	0.14 (−6.97, 7.25)

TABLE 8-25 (cont'd). SUMMARY OF QUANTITATIVE PFT CHANGES IN ASTHMATICS PER 50 µg/m^3 PM_{10} INCREMENT

Reference Citation, Location, etc.	Outcome Measure	Mean Particulate Levels (Range) µg/m^3	Co-Pollutants Measured	Lag Structure	Effect Measures Standardized to 50 µg/m^3 PM_{10}
Asthma Studies (cont'd)					
Peters et al. (1997b)	Evening PEFR	55 (?, 71)	SO_2, sulfate, H^+	2 day	−2.31 (−4.53, −0.10)
Timonen & Pekkanen (1997) Urban	Evening PEFR	18 (?, 60)	NO_2, SO_2	2 day	−1.13 (−4.75, 2.52)
Timonen & Pekkanen (1997) Suburban	Evening PEFR	13 (?, 37)	NO_2, SO_2	2 day	0.38 (−6.37, 7.13)
Peters et al. (1996)	Evening PEFR	112	SO_2, sulfate, PSA	5 day	−1.12 (−2.13, −0.10)
Peters et al. (1997a)	Evening PEFR	47 (29, 73)	SO_2, sulfate, H^+	1-5 day	−1.34 (−2.83, 0.15)
Timonen & Pekkanen (1997) Urban	Evening PEFR	18 (?, 60)	NO_2, SO_2	1-4 day	−0.73 (−7.90, 6.44)
Timonen & Pekkanen (1997) Suburban	Evening PEFR	13 (?, 37)	NO_2, SO_2	1-4 day	−4.18 (−20.94, 12.58)
Hiltermann et al. (1998)	Ave. AM & PM	39.7 (16, 98)	Ozone, NO_2, SO_2	1 day	−0.90 (−3.84, 2.04)
Hiltermann et al. (1998)	Ave. AM & PM	39.7 (16, 98)	Ozone, NO_2, SO_2	2 day	−0.50 (−4.22, 3.22)
Hiltermann et al. (1998)	Ave. AM & PM	39.7 (16, 98)	Ozone, NO_2, SO_2	1-7 day	−2.20 (−10.43, 6.03)
Vedal et al. (1998)	Ave. AM & PM	19.1 (1, 159)	None	1-4 day	−1.35 (−2.70, −.05)

TABLE 8-26. SUMMARY OF PFT CHANGES IN ASTHMATICS PER 25 µg/m^3 $PM_{2.5}$ INCREMENT

Reference Citation, L:ocation, etc.	Outcome Measure	Mean Particulate Levels (Range) µg/m^3	Co-Pollutants Measured	Lag Structure	Effect Measures Standardized to 25 µg/m^3 $PM_{2.5}$
Romieu et al. (1996)	Morning PEFR	85.7 (23, 177)	Ozone	1 day	−3.65 (−8.25, 1.90)
Peters et al. (1997b)	Morning PEFR	50.8 (9, 347)	SO_2, sulfate, H^+	1 day	−0.71 (−1.30, 0.12)
Romieu et al. (1996)	Morning PEFR	85.7 (23, 177)	Ozone	2 day	−3.68 (−9.37, 2.00)
Peters et al. (1997c)	Morning PEFR	50.8 (9, 347)	SO_2, sulfate, H^+	1-5 day	−1.19 (−1.18, 0.57)
Romieu et al. (1996)	Evening PEFR	85.7 (23, 177)	Ozone	0 day	−4.27 (−7.12, -0.85)
Peters et al. (1997b)	Evening PEFR	50.8 (9, 347)	SO_2, sulfate, H^+	0 day	−0.75 (−1.66, 0.17)
Romieu et al. (1996)	Evening PEFR	85.7 (23, 177)	Ozone	2 day	−2.55 (−7.84, 2.740
Peters et al. (1997b)	Evening PEFR	50.8 (9, 347)	SO_2, sulfate, H^+	1-5 day	−1.79 (−2.64, -0.95)

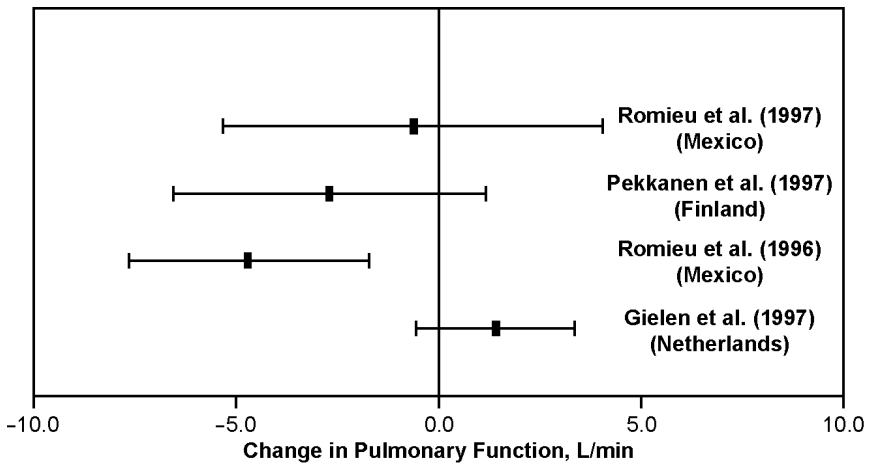

Figure 8-13. Illustrative acute pulmonary function change studies of asthmatic children. Effect of 50 μg/m^3 PM_{10} on morning peak flow lagged one-day.

particles ($PM_{MC0.1-05}$, $PM_{MC0.01-2.5}$) and $PM_{2.5-10}$. The strongest relations were for 14 day mean PM levels, especially for the smaller particles ($PM_{MC0.01-2.5}$).

Overall, then, PM_{10} and $PM_{2.5}$ both appear to affect lung function in asthmatics, but there is only limited evidence for a stronger effect of fine versus coarse fraction particles; nor do ultrafine particles appear to have any notably stronger effect than other larger-diameter fine particles. Also, of the studies provided, few if any analyses were able to clearly separate out the effects of PM_{10} and $PM_{2.5}$ from other pollutants.

The effects of PM_{10} on respiratory symptoms in asthmatics tended to be positive, although they are somewhat less consistent than PM_{10} effects on lung function. Most studies showed increases in cough, phlegm, difficulty breathing, and bronchodilator use, although these increases were generally not statistically significant for PM_{10} (see Tables 8-27, 8-28, 8-29, and 8-30; and, for cough as an example, see Figure 8-14). Vedal et al. (1998) reported that (a) increases in PM_{10} were associated with increased reporting of cough, phlegm production, and sore throat and (b) children with diagnosed asthma are more susceptible to the effects than are other children. Similarly, in the Gielen et al. (1997) study of a panel of children, most of whom had asthma, low levels of PM increased symptoms and medication use. The Peters et al. (1997b)

TABLE 8-27. SUMMARY OF ASTHMA PM_{10} COUGH STUDIES

Reference Citation, Location, etc.	Outcome Measure	Mean Particulate Levels (Range) µg/m^3	Co-Pollutants Measured	Lag Structure	Effect Measures Standardized to 50 µg/m^3 PM_{10}
Asthma Studies					
Vedal et al. (1998)	OR cough	19.1 (1, 159)	None	0 day	1.40 (1.04, 1.88)
Gielen et al. (1997)	OR cough	30.5 (16, 60)	Ozone	0 day	2.19 (0.77, 6.20)
Hiltermann et al. (1998)	OR cough	39.7 (16, 98)	Ozone, NO_2, SO_2	0 day	0.93 (0.83, 1.04)
Peters et al. (1997b)	OR cough	55 (?, 71)	SO_2, sulfate, H^+	0 day	1.32 (1.16, 1.50)
Peters et al. (1997c)	OR cough	47 (29, 73)	SO_2, sulfate, H^+	0 day	1.01 (0.97, 1.07)
Romieu et al. (1997)	OR cough	(12, 126)	Ozone	0 day	1.21 (1.10, 1.33)
Romieu et al. (1996)	OR cough	166.8 (29, 363)	Ozone	0 day	1.27 (1.16, 1.42)
Vedal et al. (1998)	OR cough	19.1 (1, 159)	None	2 day	1.40 (1.13, 1.73)
Gielen et al. (1997)	OR cough	30.5 (16, 60)	Ozone	2 day	2.19 (0.47, 10.24)
Segala et al. (1998)	OR nocturnal cough	34.2 (9, 95)	SO_2, NO_2	2 day	(values not given because not significant)
Neukirch et al. (1998)	OR nocturnal cough	34.2 (9, 95)	SO_2, NO_2	3 day	(values not given because not significant)
Romieu et al. (1996)	OR cough	166.8 (29, 363)	Ozone	2 day	1.27 (1.07, 1.50)
Romieu et al. (1997)	OR cough	(12, 126)	Ozone	2 day	1.00 (0.92, 1.10)
Ostro et al. (2001)	OR cough	47 (11, 119) 24 hr	Ozone, NO_2	3 day	1.32 (1.12, 1.55)
Hiltermann et al. (1998)	OR cough	39.7 (16, 98)	Ozone, NO_2, SO_2	1-7 day	0.94 (0.82, 1.08)
Peters et al. (1997b)	OR cough	55 (?, 71)	SO_2, sulfate, H^+	1-5 day	1.30 (1.09, 1.55)
Peters et al. (1997c)	OR cough	47 (29, 73)	SO_2, sulfate, H^+	1-5 day	1.10 (1.04, 1.17)
Ostro et al. (2001)	OR cough	102 (47, 360) 1 hr max	ozone, NO_2	3 day	1.05 (1.02, 1.18)

TABLE 8-28. SUMMARY OF ASTHMA PM_{10} PHLEGM STUDIES

Reference Citation, Location, etc.	Outcome Measure	Mean Particulate Levels (Range) µg/m³	Co-Pollutants Measured	Lag Structure	Effect Measures Standardized to 50 µg/m³ PM_{10}
Vedal et al. (1998)	OR phlegm	19.1 (1, 159)	None	0 day	1.28 (0.86, 1.89)
Peters et al. (1997c)	OR phlegm	47 (29, 73)	SO_2, sulfate, H^+	0 day	1.13 (1.04, 1.23)
Romieu et al. (1997)	OR phlegm	(12, 126)	Ozone	0 day	1.05 (0.83, 1.36)
Romieu et al. (1996)	OR phlegm	166.8 (29, 363)	Ozone	0 day	1.21 (1.00, 1.48)
Vedal et al. (1998)	OR phlegm	19.1 (1, 159)	None	2 day	1.40 (1.03, 1.90)
Romieu et al. (1997)	OR phlegm	(12, 126)	Ozone	2 day	1.00 (0.86, 1.16)
Romieu et al. (1996)	OR phlegm	166.8 (29, 363)	Ozone	2 day	1.16 (0.91, 1.49)
Peters et al. (1997c)	OR phlegm	47 (29, 73)	SO_2, sulfate, H^+	1-5 day	1.17 (1.09, 1.27)

TABLE 8-29. SUMMARY OF ASTHMA PM_{10} LOWER RESPIRATORY ILLNESS (LRI) STUDIES

Reference Citation, Location, etc.	Outcome Measure	Mean Particulate Levels (Range)	Co-Pollutants Measured	Lag Structure	Effect Measures Standardized to 50 µg/m³ PM_{10}
Vedal et al. (1998)	LRI	19.1 (1, 159)	None	0 day	1.10 (0.82, 1.48)
Gielen et al. (1997)	LRI	30.5 (16, 60)	Ozone	0 day	1.26 (0.94, 1.68)
Romieu et al. (1997)	LRI	(12, 126)	Ozone	0 day	1.00 (0.95, 1.05)
Romieu et al. (1996)	LRI	166.8 (29, 363)	Ozone	0 day	1.21 (1.10, 1.42)
Vedal et al. (1998)	LRI	19.1 (1, 159)	None	2 day	1.16 (1.00, 1.34)
Gielen et al. (1997)	LRI	30.5 (16, 60)	Ozone	2 day	1.05 (0.74, 1.48)
Segala et al. (1998)	LRI	34.2 (9, 95)	SO_2, NO_2	2 day	1.66 (0.84, 3.30)
Romieu et al. (1997)	LRI	(12, 126)	Ozone	2 day	1.00 (0.93, 1.08)
Romieu et al. (1996)	LRI	166.8 (29, 363)	Ozone	2 day	1.10 (0.98, 1.24)
Delfino et al. (1998a)	LRI	24 h 26 (6, 51) 8-h 43 (23-73) 1-h 57 (30-108)	Ozone Ozone Ozone	0 day 0 day 0 day	1.47 (0.90 - 2.39) 2.17 (1.33 - 3.58) 1.78 (1.25 - 2.53)

TABLE 8-30. SUMMARY OF ASTHMA PM_{10} BRONCHODILATOR USE STUDIES

Reference Citation, Location, etc.	Outcome Measure	Mean Particulate Levels (Range) µg/m³	Co-Pollutants Measured	Lag Structure	Effect Measures Standardized to 50 µg/m³ PM_{10}
Gielen et al. (1997)	OR bronchodilator use	30.5 (16, 60)	Ozone	0 day	0.94 (0.59, 1.50)
Hiltermann et al. (1998)	OR bronchodilator use	39.7 (16, 98)	Ozone, NO_2, SO_2	0 day	1.03 (0.93, 1.15)
Peters et al. (1997c)	OR bronchodilator use	47 (29, 73)	SO_2, sulfate, H^+	0 day	1.06 (0.88, 1.27)
Gielen et al. (1997)	OR bronchodilator use	30.5 (16, 60)	Ozone	2 day	2.90 (1.81, 4.66)
Hiltermann et al. (1998)	OR bronchodilator use	39.7 (16, 98)	Ozone, NO_2, SO_2	1-7 day	1.12 (1.00, 1.25)
Peters et al. (1997c)	OR bronchodilator use	47 (29, 73)	SO_2, sulfate, H^+	1-5 day	1.23 (0.96, 1.58)

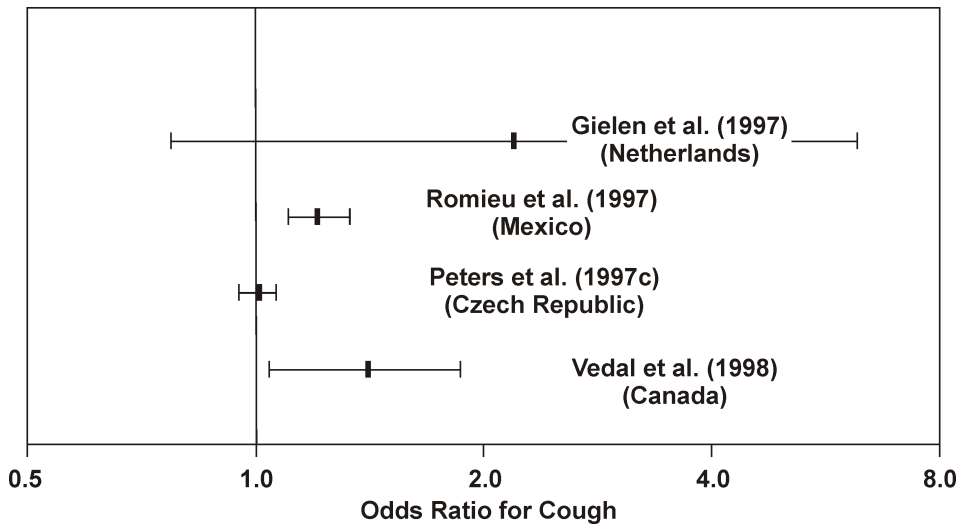

Figure 8-14. Odds ratios with 95% confidence interval for cough per 50-µg/m^3 increase in PM_{10} for illustrative asthmatic children studies at lag 0.

study of asthmatics examined particle effects by size and found that fine particles were associated with increases in cough, of which MC 0.01-2.5 was the best predictor.

Delfino et al. (1998a) used an asthma symptom score to evaluate the effects of acute air pollutant exposures. The 1- and 8-h PM_{10} maximum concentrations had larger effects than the 24-h mean. Subgroup analyses showed effects of current day PM maxima to be strongest in the 10 more frequently symptomatic children; the odds ratios for symptoms were 2.24 (1.46, 3.46) for 47 µg/m^3 1-h PM_{10}; 1.82 (1.18, 2.8) for 36 µg/m^3 8-h PM_{10}, and 1.50 (0.80-2.80) for 25 µg/m^3 24-h PM_{10}. Analyses suggested that effects of O_3 and PM_{10} were largely independent. Delfino et al. (2002) also studied 22 asthmatic children aged 9 to 19 years in March and April 1996. Associations were evaluated by generalized estimating equations, adjusting for autocorrelation. The endpoint was symptoms interfering with daily activities. This endpoint was associated with PM_{10}, NO_2, and O_3 and there was a positive interaction effect of PM_{10} and NO_2 jointly. Both of these studies also reported significant associations with fungal spores, but not pollens; no significant interactions were found between aeroallergens and air pollutants.

Romieu et al. (1996) found children with mild asthma to be more strongly affected by high ambient levels of PM (mean PM_{10} = 166.8 µg/m^3) observed in northern Mexico City than

in a study (Romieu et al., 1997) conducted in a nearby area with lower PM_{10} levels (mean PM_{10} = 54.2 μg/m^3). Yu et al. (2000) reported estimates of odds ratios for asthma symptoms and 10 μg/m^3 increments in PM_{10} and $PM_{1.0}$ values of 1.18 (1.05, 1.33) and 1.09 (1.01, 1.18), respectively. Multipollutant models with CO and SO_2 yielded 1.06 (0.95, 1.19) for PM_{10}, and 1.11 (0.98, 1.26) for $PM_{1.0}$, thus showing a lower value for PM_{10} and a loss of significance for both PM_{10} and $PM_{1.0}$. The correlation between CO and $PM_{1.0}$ and PM_{10} was 0.82 and 0.86. Ostro et al. (2001) studied a panel of inner-city African American children using a GEE model with several measures of PM, including PM_{10} (both 24-h average and 1-h max.) and $PM_{2.5}$, demonstrating positive associations with daily probability of shortness of breath, wheeze, and cough.

Desqueyroux et al. (2002) studied 60 adult severe asthmatics from November 1995 to November 1996. Relationships were estimated from generalized estimating equations adjusting for autocorrelation. Each asthma exacerbation was confirmed by a physician, and each of the cases were followed for a sufficient length of time to allow investigations of any lagged associations with air pollution. Statistical analysis that accounted for temporal, meteorological, and aerobiological variables and some individual characteristics revealed significant associations between PM_{10}, O_3, and incident asthma attacks. Odds Ratio (OR) for an increase of 10 μg/m^3 of PM_{10} was 1.41 (CI: 1.16, 1.71). PM_{10} was not related to incident asthma attacks using lags of 1 or 2 days; but PM_{10} associations for 3, 4, and 5 day lags were significant. PM_{10} remained significant even after adjusting for other pollutants including O_3, SO_2, and NO_2.

Just et al. (2002) also studied 82 asthmatic children for 3 months during spring and early summer in Paris. Relationships were estimated from generalized estimating equations adjusting for autocorrelation. No significant relationships were found between PM_{13} and lung function or respiratory symptoms. For $PM_{2.5}$ results, see Table 8-31. All showed positive associations (several being clearly significant at $p < 0.05$) between $PM_{2.5}$ and increased cough, phlegm, or LRI.

Of studies that included two indicators for PM (PM_{10}, $PM_{2.5}$) in their analyses, the study of Peters et al. (1997b) found similar effects for the two PM measures, whereas the Romieu et al. (1996) study found slightly larger effects for $PM_{2.5}$.

TABLE 8-31. SUMMARY OF ASTHMA $PM_{2.5}$ RESPIRATORY SYMPTOM STUDIES

Reference Citation, Location, etc.	Outcome Measure	Mean Particulate Levels (Range) µg/m^3	Co-Pollutants Measured	Lag Structure	Effect Measures Standardized to 25 µg/m^3 $PM_{2.5}$
Peters et al. (1997c)	OR cough	50.8 (9, 347)	SO_2, sulfate, H^+	0 day	1.22 (1.08, 1.38)
Romieu et al. (1996)	OR cough	85.7 (23, 177)	Ozone	0 day	1.27 (1.08, 1.42)
Tiittanen et al. (1999)	OR cough	15 (3, 55)	NO_2, SO_2, CO, ozone	0 day	1.04 (0.86, 1.20)
Romieu et al. (1996)	OR cough	85.7 (23, 177)	Ozone	2 day	1.16 (0.98, 1.33)
Tittanen et al. (1999)	OR cough	15 (3, 55)	NO_2, SO_2, CO, ozone	2 day	1.24 (1.02, 1.51)
Ostro et al. (2001)	OR cough	40.8 (4, 208)	Ozone, NO_2	3 day	1.02 (0.98, 1.06)
Peters et al. (1997c)	OR cough	50.8 (9, 347)	SO_2, sulfate, H^+	1-5 day	1.02 (0.90, 1.17)
Romieu et al. (1996)	OR Phlegm	85.7 (23, 177)	Ozone	0 day	1.21 (0.98, 1.48)
Romieu et al. (1996)	OR Phlegm	85.7 (23, 177)	Ozone	2 day	1.16 (0.99, 1.39)
Romieu et al. (1996)	OR LRI	85.7 (23, 177)	Ozone	0 day	1.21 (1.05, 1.42)
Romieu et al. (1996)	OR LRI	85.7 (23, 177)	Ozone	2 day	1.16 (1.05, 1.42)

Two asthma studies, both in the United States, examined PM indicators by 1 h averages as well as by 24 h averages. The PM_{10} 1 h outcome was larger than the 24 h outcome for lower respiratory illness in one study (Delfino et al., 1998a) but was lower for cough in the other study (Ostro et al., 2001).

Several of the studies reviewed above (Delfino et al., 1998a, 2002; Ostro et al., 2001; Yu et al., 2000; Mortimer et al., 2002; Vedal et al., 1998) that were conducted in the United States and Canada found positive associations between various health endpoints for asthmatics and ambient PM exposure (indexed by PM_{10}, $PM_{2.5}$, or $PM_{10-2.5}$). The endpoints included PEF decrements, various individual respiratory symptoms, and combinations of respiratory symptoms. The various endpoints each represent effects on respiratory health.

8.3.3.1.2 Lung Function and Respiratory Symptom Effects in Nonasthmatic Subjects

Results for PM_{10} peak flow analyses in non-asthmatic studies (summarized in Appendix 8B Table 8B-6) were inconsistent, with fewer studies reporting results in the same manner as for the asthmatic studies. Many of the point estimates showed increases rather than decreases (see Table 8-32). The effects on respiratory symptoms in nonasthmatics (see Appendix 8B Table 8B-7) were similar to those in asthmatics. Most studies showed that PM_{10} increases cough, phlegm, difficulty breathing, and bronchodilator use, although these were generally not statistically significant (Table 8-33). Vedal et al. (1998) reported no consistent evidence for adverse health effects in a nonasthmatic control group.

Results of the $PM_{2.5}$ peak flow and symptom analyses in nonasthmatic studies (see Appendix 8B Table 8B-8, Table 8-34) were similar to PM_{10} results discussed above.

Three authors, Schwartz and Neas (2000), Tiittanen et al. (1999) and Neas et al. (1999), used $PM_{10-2.5}$ as a coarse fraction particulate measure (Table 8-35). Schwartz and Neas (2000) found that $PM_{10-2.5}$ was significantly related to cough. Tiittanen found that one day lag of $PM_{10-2.5}$ was related to morning PEF, but there was no effect on evening PEF. Neas et al. found no effects of $PM_{10-2.5}$ on PEF.

The Schwartz and Neas (2000) reanalyses allows comparison of fine and coarse particle effects on healthy school children using two pollutant models of fine and coarse PM. CM was estimated by subtracting $PM_{2.1}$ from PM_{10} data. For reanalysis of the Harvard Six City Diary

TABLE 8-32. SUMMARY OF NON-ASTHMA PM_{10} PFT STUDIES

Reference Citation, Location, etc.	Outcome Measure	Mean Particulate Levels (Range) µg/m³	Co-Pollutants Measured	Lag Structure	Effect Measures Standardized to 50 µg/m³ PM_{10}
Gold et al. (1999)	Morning PEFR	51 (23, 878)	Ozone	1 day	−0.20 (−0.47, 0.07)
Tiittanen et al. (1999)	Morning PEFR	28 (5, 122)	NO_2, SO_2, CO, ozone	0 day	1.21 (−0.43, 2.85)
Neas et al. (1999)	Morning PEFR	32	Ozone	1-5 day	2.64 (−6.56, 11.83)
Tiittanen et al. (1999)	Morning PEFR	28 (5, 122)	NO_2, SO_2, CO, ozone	1-4 day	−1.26 (−5.86, 3.33)
Boezen et al. (1999)	OR > 10% AM PEFR Decr.	42 (5, 146)	NO_2, SO_2	1 day	1.04 (0.95, 1.13)
Boezen et al. (1999)	OR > 10% AM PEFR Decr.	42 (5, 146)	NO_2, SO_2	2 day	1.02 (0.93, 1.11)
Boezen et al. (1999)	OR > 10% AM PEFR Decr.	42 (5, 146)	NO_2, SO_2	1-5 day	1.05 (0.91, 1.21)
Neas et al. (1999)	Morning PEFR	32	Ozone	0 day	−8.16 (−14.81, −1.55)
Harré et al. (1997)	% change in morning PEFR	(not given)	NO_2, SO_2, CO	1 day	0.07 (−0.50, 0.63)
Neas et al. (1999)	Evening PEFR	32	Ozone	0 day	−1.44 (−7.33, 4.44)
Schwartz & Neas (2000) Uniontown	Evening PEFR	(not given)	Sulfate fraction	0 day	−1.52 (−2.80, −0.24)
Schwartz & Neas (2000) State College	Evening PEFR	(not given)	Sulfate fraction	0 day	−0.93 (−1.88, 0.01)
Tiittanen et al. (1999)	Evening PEFR	28 (5, 122)	NO_2, SO_2, CO, ozone	0 day	0.72 (−0.63, 1.26)
Tiittanen et al. (1999)	Evening PEFR	28 (5, 122)	NO_2, SO_2, CO, ozone	0 day	2.33 (−2.62, 7.28)
Gold et al. (1999)	Evening PEFR	51 (23, 878)	Ozone	0 day	−0.14 (−0.45, 0.17)
Neas et al. (1999)	Evening PEFR	32	Ozone	1-5 day	1.47 (−7.31, 10.22)
Boezen et al. (1999)	OR > 10% PM PEFR Decr.	42 (5, 146)	NO_2, SO_2	0 day	1.17 (1.08, 1.28)
Boezen et al. (1999)	OR > 10% PM PEFR Decr.	42 (5, 146)	NO_2, SO_2	2 day	1.08 (0.99, 1.17)
Boezen et al. (1999)	OR > 10% PM PEFR Decr.	42 (5, 146)	NO_2, SO_2	1-5 day	1.16 (1.02, 1.33)
Van der Zee et al. (1999)	OR > 10% PM PEFR Decr.	34 (?, 106)	NO_2, SO_2, sulfate	0 day	1.44 (1.02, 2.03)
Van der Zee et al. (1999)	OR > 10% PM PEFR Decr.	34 (?, 106)	NO_2, SO_2, sulfate	2 day	1.14 (0.83, 1.58)
Van der Zee et al. (1999)	OR > 10% PM PEFR Decr.	34 (?, 106)	NO_2, SO_2, sulfate	1-5 day	1.16 (0.64, 2.10)
Harré et al. (1997)	% change in evening PEFR	(not given)	NO_2, SO_2, CO	1 day	−0.22 (−0.57, 0.16)

TABLE 8-33. SUMMARY OF NON-ASTHMA PM_{10} RESPIRATORY SYMPTOM STUDIES

Reference Citation, Location, etc.	Outcome Measure	Mean Particulate Levels (Range) µg/m^3	Co-Pollutants Measured	Lag Structure	Effect Measures Standardized to 50 mg/m^3 PM_{10}
Schwartz & Neas (2000)	OR cough – no other symptoms	(not given)	Sulfate fraction	0 day	1.20 (1.07, 1.35)
Boezen et al. (1998)	OR cough	42 (5, 146)	NO_2, SO_2	0 day	1.06 (0.93, 1.21)
Van der Zee et al. (1999) Urban areas	OR cough	34 (?, 106)	NO_2, SO_2, sulfate	0 day	1.04 (0.95, 1.14)
Tiittanen et al. (1999)	OR cough	28 (5, 122)	NO_2, SO_2, CO, ozone	0 day	1.00 (0.87, 1.16)
Van der Zee et al. (1999) Urban areas	OR cough	34 (?, 106)	NO_2, SO_2, sulfate	2 day	0.94 (0.89, 1.06)
Van der Zee et al. (1999) Urban areas	OR cough	34 (?, 106)	NO_2, SO_2, sulfate	1-5 day	0.95 (0.80, 1.13)
Tiittanen et al. (1999)	OR cough	28 (5, 122)	NO_2, SO_2, CO, ozone	1-4 day	1.58 (0.87, 2.83)
Boezen et al. (1998)	OR phlegm	42 (5, 146)	NO_2, SO_2	0 day	1.11 (0.91, 1.36)
Tiittanen et al. (1999)	OR phlegm	28 (5, 122)	NO_2, SO_2, CO, ozone	2 day	Positive but not significant
Schwartz & Neas (2000)	LRI	(not given)	Sulfate fraction	0 day	
Van der Zee et al. (1999) Urban areas	LRI	34 (?, 106)	NO_2, SO_2, sulfate	0 day	0.98 (0.89, 1.08)
Van der Zee et al. (1999) Urban areas	LRI	34 (?, 106)	NO_2, SO_2, sulfate	2 day	1.01 (0.93, 1.10)

TABLE 8-34. SUMMARY OF NON-ASTHMA $PM_{2.5}$ RESPIRATORY OUTCOME STUDIES

Reference Citation, Location, etc.	Outcome Measure	Mean Particulate Levels (Range) µg/m³	Co-Pollutants Measured	Lag Structure	Effect Measures Standardized to 25 µg/m³ $PM_{2.5}$
Gold et al. (1999)	Morning PEFR	30.3 (9, 69)	Ozone	1 day	−0.22 (−0.46, 0.01)
Tiittanen et al. (1999)	Morning PEFR		NO_2, SO_2, CO, ozone	0 day	1.11 (−0.64, 2.86)
Tiittanen et al. (1999)	Morning PEFR		NO_2, SO_2, CO, ozone	1-4 day	−1.93 (−7.00, 3.15)
Neas et al. (1999)	Morning PEFR	24.5 (?, 88)	Ozone	1-5 day	2.64 (−6.56, 11.83)
Schwartz & Neas (2000) Uniontown	Evening PEFR	(not given)	Sulfate fraction	0 day	−1.52 (−2.80, −0.24)
Schwartz & Neas (2000) State College	Evening PEFR	(not given)	Sulfate fraction	0 day	−0.93 (−1.88, 0.01)
Tiittanen et al. (1999)	Evening PEFR		NO_2, SO_2, CO, ozone	0 day	0.70 (−0.81, 2.20)
Tiittanen et al. (1999)	Evening PEFR		NO_2, SO_2, CO, ozone	0 day	1.52 (−3.91, 6.94)
Gold et al. (1999)	Evening PEFR	30.3 (9, 69)	Ozone	0 day	−0.10 (−0.43, 0.22)
Neas et al. (1999)	Evening PEFR	24.5 (?, 88)	Ozone	1-5 day	1.47 (−7.31, 10.22)
Tiittanen et al. (1999)	OR cough	15 (3, 55)	NO_2, SO_2, CO, ozone	0 day	1.04 (0.86, 1.20)
Tiittanen et al. (1999)	OR cough	15 (3, 55)	NO_2, SO_2, CO, ozone	2 day	1.24 (1.02, 1.51)
Schwartz & Neas (2000)	OR LRS	(not given)	Sulfate fraction	0 day	1.61 (1.19, 2.14)

TABLE 8-35. SUMMARY OF NON-ASTHMA COARSE FRACTION STUDIES OF RESPIRATORY ENDPOINTS

Reference Citation, Location, etc.	Outcome Measure	Mean Particulate Levels (Range) µg/m^3	Co-Pollutants Measured	Lag Structure	Effect Measures Standardized to 25 µg/m^3 $PM_{10-2.5}$
Tiittanen et al. (1999)	Morning PEFR	8 (.2, 67)	NO_2, SO_2, CO, ozone	1 day	−1.26 (−2.71, 0.18)
Neas et al. (1999)	Morning PEFR	8.3	Ozone	1 day	−4.31 (−11.43, 2.75)
Tiittanen et al. (1999)	Morning PEFR	8 (.2, 67)	NO_2, SO_2, CO, ozone	2 day	0.51 (−0.77, 2.16)
Tiittanen et al. (1999)	Morning PEFR	8 (.2, 67)	NO_2, SO_2, CO, ozone	1-4 day	−0.57 (−1.96, 0.81)
Neas et al. (1999)	Morning PEFR	8.3	Ozone	1-5 day	−6.37 (−21.19, 8.44)
Tiittanen et al. (1999)	Evening PEFR	8 (.2, 67)	NO_2, SO_2, CO, ozone	0 day	0.66 (−0.33, 1.81)
Neas et al. (1999)	Evening PEFR	8.3	Ozone	1 day	1.88 (−4.75, 8.44)
Tiittanen et al. (1999)	Evening PEFR	8 (.2, 67)	NO_2, SO_2, CO, ozone	2 day	0.03 (−1.41, 1.47)
Tiittanen et al. (1999)	Evening PEFR	8 (.2, 67)	NO_2, SO_2, CO, ozone	1-4 day	2.37 (−1.69, 4.96)
Neas et al. (1999)	Evening PEFR	8.3	Ozone	1-5 day	5.94(−7.00, 18.94)
Tiittanen et al. (1999)	OR cough	8 (.2, 67)	NO_2, SO_2, CO, ozone	0 day	0.99 (0.87, 1.12)
Tiittanen et al. (1999)	OR cough	8 (.2, 67)	NO_2, SO_2, CO, ozone	2 day	1.23 (1.06, 1.42)
Tiittanen et al. (1999)	OR cough	8 (.2, 67)	NO_2, SO_2, CO, ozone	1-4 day	1.31 (0.81, 2.11)
Schwartz & Neas (2000)	OR cough without other symptoms	(not given)	Sulfate fraction	0 day	1.77 (1.24, 2.55)
Schwartz & Neas (2000)	OR LRS	(not given)	Sulfate fraction	0 day	1.51 (0.94, 4.87)

Study in the two PM pollutant model, they report for cough a $PM_{2.5}$ OR of 1.07 (0.90, 1.26; per 15 μg/m^3 increment) and a $PM_{10-2.5}$ OR of 1.18 (1.04, 1.34); per 8 μg/m^3 increment in contrast to lower respiratory symptom results of a $PM_{2.5}$ OR of 1.29 (1.06, 1.57) and a $PM_{10-2.5}$ OR of 1.05 (0.9, 1.23). In the Uniontown reanalysis, peak flow for $PM_{2.1}$ (for a 14 μg/m^3 increment) was −0.91 1/m (−1.14, −1.68) and for $PM_{10-2.1}$ (for a 15 μg/m^3 increment) was +1.04 1/m (−1.32, +3.4). For State College, peak flow for $PM_{2.1}$ was −0.56 (−1.13, +0.01), and for $PM_{10-2.1}$ it was −0.17 (−2.07, +1.72).

Coull et al. (2001) reanalyzed data from the Pope et al. (1991) study of PM effects on pulmonary function of children in the Utah Valley, using additive mixed models which allow for assessment of heterogeneity of response or the source of heterogeneity. These additive models describe complex covariate effects on each child's peak expiratory flow while allowing for unexplained population heterogeneity and serial correlation among repeated measurements. The analyses indicate heterogeneity among that population with regard to PM_{10} (i.e., specifically that there are three subjects in the Utah Valley study who exhibited a particularly acute response to PM_{10}). However the limited demographic data available in the Utah Valley Study does not explain the heterogeneity in PM sensitivity among the school children population.

Two studies examined multipollutant models. The Jalaludin et al. (2000) analyses used a multipollutant model that evaluated PM_{10}, O_3, and NO_2. They found in metropolitan Sydney that ambient PM_{10} and O_3 concentrations are poorly correlated (r = 0.13). For PEFR the β (SE) for PM_{10} only was 0.0045 (0.0125), p = 0.72; and for PM_{10} and O_3, 0.0051 (0.0124), p = 0.68. Ozone was also unchanged in the one- and two-pollutant models. Gold et al. (1999) attempted to study the interaction of $PM_{2.5}$ and O_3 on PEF in Mexico City children (age = 8 to 12 years). The authors found independent effects of the two pollutants, but the joint effect was slightly less than the sum of the independent effects.

8.3.3.2 Long-Term Particulate Matter Exposure Effects on Lung Function and Respiratory Symptoms

8.3.3.2.1 Summary of 1996 Particulate Matter Air Quality Criteria Document Key Findings

In the 1996 PM AQCD, the available long-term PM exposure-respiratory disease studies were limited in terms of conclusions that could be drawn. At that time, three studies based on a

similar type of respiratory symptom questionnaire administered at three different times as part of the Harvard Six-City and 24-City Studies provided data on the relationship of chronic respiratory disease to PM. All three studies suggest a long-term PM exposure effect on chronic respiratory disease. The analysis of chronic cough, chest illness and bronchitis tended to be significantly positive for the earlier surveys described by Ware et al. (1986) and Dockery et al. (1989). Using a design similar to the earlier one, Dockery et al. (1996) expanded the analyses to include 24 communities in the United States and Canada. Bronchitis was found to be higher (OR = 1.66) in the community with the highest particle strong acidity when compared with the least polluted community. Fine particulate sulfate was also associated with higher reporting of bronchitis (OR = 1.65, 95% CI 1.12, 2.42).

Interpretation of such studies requires caution in light of the usual difficulties ascribed to cross-sectional studies. That is, evaluation of PM effects is based on variations in exposure determined by a different number of locations. In the first two studies, there were six locations and, in the third, twenty-four. The results seen in all studies were consistent with a PM gradient, but it was not readily possible to separate out clear effects of PM from other factors or pollutants having the same gradient.

Chronic pulmonary function studies by Ware et al. (1986), Dockery et al. (1989), and Neas et al. (1994) had good monitoring data and well-conducted standardized pulmonary function testing over many years, but showed no effect for children from airborne particle pollution indexed by TSP, PM_{15}, $PM_{2.5}$ or sulfates. In contrast, the Raizenne et al. (1996) study of U.S. and Canadian children found significant associations between FEV_1 and FVC and acidic particles (H^+). Overall, the available studies provided only limited evidence suggestive of pulmonary lung function decrements being associated with chronic exposure to PM indexed by various measures (TSP, PM_{10}, sulfates, etc.). However, it was noted that cross-sectional studies require very large sample sizes to detect differences because they cannot eliminate person to person variation, which is much larger than the within person variation. There may be so much noise in the large variability that one cannot observe the exposure - effect signal.

8.3.3.2.2 New Studies of Respiratory Effects of Long-Term Particulate Matter Exposure

Several studies published since 1996 evaluated effects of long-term PM exposure on lung function and respiratory illness (see Appendix 8B, Table 8B-8). The new studies examining PM_{10} and $PM_{2.5}$ in the United States include McConnell et al. (1999), Abbey et al. (1998), Berglund et al. (1999), Peters et al. (1999a,b), and Avol et al. (2001), all of which examined effects in California cohorts but produced variable results. McConnell et al. (1999) noted that, as PM_{10} increased across communities, the bronchitis risk per interquartile range also increased, results consistent with those reported by Dockery et al. (1996). However, the high correlation of PM_{10}, acid, and NO_2 precludes clear attribution of the McConnell et al. bronchitis effects specifically to PM alone. Avol et al. (2001) reported that, for 110 children who moved to other locations, those subjects who moved to areas of lower PM_{10} showed increased growth in lung function and subjects who moved to communities with higher PM_{10} showed slowed lung function growth.

Gauderman et al. (2000, 2002) presented results from a study that is both a cohort and a cross-sectional study. This unique design followed two cohorts of southern California children who were fourth graders in 1993 and 1996 respectively. The cohorts, located in 12 communities, were followed for 4 years. A three stage model which allowed for individual slopes, within community covariates, and community-wide air pollution averages, was fitted using SAS Proc MIXED. Pulmonary function measurements included FVC, FEV1, MMEF, and PEFR, all of which gave similar results for both $PM_{2.5}$ and PM_{10}. In the first cohort, PM_{10} showed a significant 1.3% decrease in annual growth rates for a 51.5 $\mu g/m^3$ difference in PM_{10}. This difference was only 0.4% in the second cohort; however, the two were not significantly different from each other. The effect for $PM_{2.5}$ was slightly less for a difference of 22.2 $\mu g/m^3$. In an earlier cross-sectional analysis, Peters et al. (1999b) studied the prevalence of respiratory symptoms in 12 southern California communities in 1993. To estimate the relationship between symptoms and pollutants a two-stage regression approach was used. The first stage estimated community-specific rates adjusted for individual covariates. The second stage regressed these rates on pollutant averages from 1986 to 1990, finding no significant relationships between respiratory symptoms and average PM_{10} levels.

In a non-U.S. PM_{10} study, Horak et al. (2002) conducted a combined cohort and cross-sectional study similar in design to that of Gauderman et al. (2000). The cohorts were taken from 975 school children in 8 communities in lower Austria between 1994 and 1997. Relationships were estimated from generalized estimating equations adjusting for autocorrelation, and adjustments were made for sex, atopy, ETS, baseline lung function, height, and site. Growth in FVC and MEF were significantly related to winter PM_{10} levels.

Gehring et al. (2002) enrolled 1,756 newborn children in the Munich area. Individual $PM_{2.5}$ and NO_2 levels were estimated from actual measurements at 40 sites combined with a GIS predictor model. $PM_{2.5}$ levels ranged from 11.9 to 21.9 $\mu g/m^3$. The incidence (in the first two years of life) of cough without infection and dry cough at night were related to $PM_{2.5}$ levels. Wheeze, bronchitis, respiratory infections, and runny nose were not related to $PM_{2.5}$ levels.

Other non-U.S. studies examined PM measures such as TSP and BS in European countries. In Germany, Heinrich et al. (2000) reported a cross-sectional survey of children, conducted twice (with the same 971 children included in both surveys). TSP levels decreased between surveys, as did the prevalence of all respiratory symptoms (including bronchitis). Also, Krämer et al. (1999) reported a study in six East and West Germany communities, which found decreasing yearly TSP levels to be related to ever-diagnosed bronchitis from 1991 to 1995. Lastly, Jedrychowski et al. (1999) reported an association between both BS and SO_2 levels in various areas of Krakow, Poland, and slowed lung function growth (FVC and FEV_1).

Leonardi et al. (2000) studied a different health outcome measure as part of the Central European Air Quality and Respiratory Health (CESAR) study. Blood and serum samples were collected from school children ages 9 to 11 years in each of 17 communities in Central Europe (n = 10 to 61 per city). Numbers of lymphocytes increased as PM concentrations increased across the cities. Regression slopes, adjusted for confounder effects, were larger and statistically significant for $PM_{2.5}$, but small and nonsignificant for $PM_{10-2.5}$. A similar positive relationship was found between IgG concentration in serum and $PM_{2.5}$ gradient, but not for PM_{10} or $PM_{10-2.5}$.

8.3.3.2.3 Summary of Long-Term Particulate Matter Exposure Respiratory Effects

The methodology used in the long-term studies varies much more than the methodology in the short-term studies. Some studies reported highly significant results (related to one or another ambient PM indicator), whereas others reported no significant results. The cross-sectional studies are often confounded, in part, by unexplained differences between geographic regions. The studies that looked for a time trend are also confounded by other conditions that were changing over time. The newer cohort studies provide the best evidence bearing on chronic PM exposure effects. The Gauderman et al. (2000, 2002) cohort studies found significant decreases in lung function growth among southern California school children to be related to PM_{10} levels, but the Peters et al. (1999b) cross-sectional study of the children in the Gauderman et al. cohorts found no relationship between respiratory symptoms and annual average PM_{10} levels in 12 southern California communities. In addition, the well-conducted cross-sectional studies by Dockery et al. (1996) and Raizenne et al. (1996), assessed earlier in the 1996 PM AQCD, found differences in peak flow and bronchitis rates associated with fine particle sulfate and acidity, and they remain among the more credible available studies of long-term PM exposure effects on respiratory function symptoms.

8.3.4 Ambient PM Impacts on Fetal and/or Early Postnatal Development/Mortality

Some older cross-sectional mortality studies reviewed in the 1996 PM AQCD suggested that the young may represent a susceptible subpopulation for PM-related mortality. Lave and Seskin (1977), for example, found significant associations of TSP mortality among those 0-14 years of age. Also, Bobak and Leon (1992) studied neonatal (ages < 1 mo) and postneonatal mortality (ages 1-12 mo) in the Czech Republic and reported significant associations between PM_{10} and postneonatal mortality, even after considering other pollutants. Postneonatal respiratory mortality showed highly significant associations for all pollutants considered, but only PM_{10} remained significant in multipollutant models. The exposure duration was longer than a few days, but shorter than in adult chronic PM exposure prospective cohort studies. Thus, the few available studies reviewed in the 1996 PM AQCD suggested an association between ambient PM concentrations and infant mortality, especially among

postneonatal infants. More recent studies have focused on ambient PM relationships (a) with intrauterine mortality and morbidity and (b) with early post neonatal infant mortality.

8.3.4.1 PM Effects on Intrauterine Fetal Morbidity/Mortality

During the past decade or so, increasing attention has begun to be focused on the evaluation of possible effects or prenatal exposures to ambient PM and other "criteria air pollutants" on fetal growth and development. Concerns about these possible air pollution impacts, as indexed by measures such as low birth weight (LBW) or preterm births, are prompted by studies indicating that both preterm births and low birth weights are important predictors of infant mortality, childhood morbidity, and perhaps even adult morbidity (Barker et al., 1993; Spinello et al., 1995; Joseph and Kramer, 1996). In evaluating possible pollutant effects, a number of variables with well-established links to fetal growth and development must be taken into account, e.g., maternal and paternal weight and height, gestational weight gain, maternal smoking and alcohol consumption, the infant's sex and racial/ethnic background, etc. (Kramer, 1987; Berkowitz and Papiernik, 1993; Divon et al., 1994).

In one large-scale U.S. study, Ritz et al (2000) evaluated the effects of ambient PM_{10}, CO, NO_2, SO_2, and O_3 exposures during pregnancy on the occurrence of preterm births among a cohort of 97,518 neonates born in the South Coast Air Basin (SoCARB) of California. Pollutant values measured at the closest of 17 air-monitoring stations (within 2 mi. radius of residential zip code on birth certificate) were averaged over the entire pregnancy or distinct periods during pregnancy for each birth in nondesert portions of Los Angeles, San Bernardino, Riverside, and Orange Counties (which comprise the SoCARB district) during 1989 to 1993. Adjusting for various factors known to be related to occurrence of premature births (e.g., maternal age, race, smoking during pregnancy, etc.), the effects of the different air pollutants on preterm birth risk were analyzed by means of both single-pollutant and multiple pollutant logistic regression models. A 16% increase in preterm birth risk was estimated per 50 $\mu g/m^3$ increment in PM_{10} concentrations averaged over the first month of pregnancy (RR = 1.20; CI: 1.06, 1.26) and a 20% increase per 50 $\mu g/m^3$ PM_{10} averaged over 6 weeks prior to birth. The effects sizes varied only slightly between single and multiple pollutant molds or with adjustments for other risk factors.

Significant associations were also found for CO, but inclusion of other pollutants or covariates in the model caused CO effect estimates to fluctuate. For both PM_{10} and CO, the most precise effects estimates (with narrowest CI) were found for exposures averaged over 6 weeks prebirth.

In another large U.S. study, Maisonet et al. (2001) evaluated associations between low birth weight (LBW, ≤ 2,500 g at birth) and daily average PM_{10}, SO_2, and CO levels, based on every sixth day ambient 24-h PM_{10} monitor readings and 24-h averages of hourly SO_2 and CO readings at community monitoring stations in six Northeastern U.S. cities (Boston, MA; Hartford, CT; Philadelphia, PA; Pittsburgh, PA; Springfield, MA; Washington, DC). Using air pollution data from U.S. EPA, average trimester exposures were estimated for PM_{10}, SO_2, and CO based on 3 to 4 PM_{10}, 1 to 4 SO_2, and 2 to 4 CO monitors per city. Based on NCHS data sets, information on numerous covariates (e.g., gestational age, gender, maternal age, maternal race/ethnicity, maternal prenatal smoking, alcohol consumption, etc.) was included in a logistic regression model to generate adjusted odds ratios (AOR) and 95% CI for LBW, and then linear regression models were used to assess reductions in birth weight (in grams) in relation to each air pollution variable. Ranges of exposure categories were defined for each air pollutant as percentiles of the exposure distribution (< 25th percentile; 25 to 50th; 50th to 75th; 75th to 95th; and ≥ 95th). Of 130,465 live singleton births during 1994 to 1996, after exclusions for several reasons, 89,557 (68.6%) of infants were included in the final analyses. There were no statistically significant ($p < 0.05$) associations between LBW and PM_{10} percentile groups ≥ 25th versus < 25th percentile or for continuous (10 $\mu g/m^3$) PM_{10} and LBW during any of the prenatal trimesters among white or African-American infants. However, first trimester ambient PM_{10} levels were associated with increased risk for full-term LBW among Hispanics (AOR 1.36; CI: 1.06, 1.75). Much more consistent increases in AOR for LBW were found for various trimesters of CO and/or SO_2 exposure. The authors concluded that, overall, LWB was not associated with PM_{10} exposure during pregnancy.

Rogers et al. (2000) reported results of another, much smaller, population-based case-control study of possible associations between exposures to ambient TSP and SO_2 (using a combined TSP SO_2 index) and risk of having a very low birth weight (VLBW) baby (i.e., weighing < 1,500 g at birth) among women residing in Atlanta, Savannah, or other areas in

Georgia Health Care District 9 during 1986 to 88. Environmental transport models were used to estimate TSP SO_2 exposures at the birth homes of study subjects, and exposures ≤ 9.94 μg/m^3, the median of TSP and SO_2 exposures for the control subjects were used as referent exposures. The controls included 202 mothers of babies weighing 1,500 g or more at birth for comparison versus 143 mothers of VLBW babies. A distinct trend suggesting a relationship between TSP/SO_2 exposure and increased risk for VLBW was reported. However, the results, while suggestive of possible ambient TSP and/or SO_2 effects on VLBW at high exposure levels (frequency distributions for cases and controls began to separate at ~55 μg/m^3 TSP SO_2), are not based on direct TSP or SO_2 monitoring data and should not be accorded much weight unless confirmed by other studies using better more directly measured air pollution exposure indices.

With regard to new non-U.S. studies of prenatal PM exposure effects on intrauterine morbidity/mortality, Dejmek et al. (1999) evaluated possible impacts of ambient PM_{10} and $PM_{2.5}$ exposure (monitored by EPA-developed VAPS methods) during pregnancy on risk for intrauterine growth retardation (IUGR) in the highly polluted Teplice District of Northern Bohemia in the Czech Republic during 1993 to 1996. Mean levels of pollutants (PM, NO_2, SO_2) were calculated for each month of gestation and three concentration intervals (low, medium, high) were derived for each pollutant. Preliminary analyses found significant associations of IUGR with PM_{10} and SO_2 early in pregnancy but not with NO_2. Odds ratios for IUGR for PM_{10} and $PM_{2.5}$ levels were determined by logistic regressions for each month during gestation, after adjusting for potential confounding factors (e.g., maternal smoking, alcohol consumption during pregnancy, etc.). Definition of an IUGR birth was any one for which the birth weight fell below the 10th percentile by gender and age for live births in the Czech Republic (1992-93). The ORs for IUGR were significantly related to PM_{10} during the first month gestation: that is, as compared to low PM_{10}, the medium level PM_{10} OR = 1.47 (CI: 0.99, 2.16) and the high level PM_{10} OR = 1.85 (CI: 1.29, 2.66). $PM_{2.5}$ levels were highly correlated with PM_{10} (r = 0.98) and manifested similar patterns (OR = 1.16, CI: 0.08, 0.69 for medium $PM_{2.5}$ level; OR = 1.68, CI: 1.18, 2.40 for high $PM_{2.5}$ level). These results suggest effects of PM exposures (probably including fine particles such as sulfates, acid aerosols, and PAHs in the Teplice ambient mix) early in pregnancy (circa embryo implantation) on fetal growth and development.

In broader further analyses of the same data set from which the above Czech study results were derived, Dejmek et al. (2000) evaluated relationships between IUGR and exposures to PM_{10}, $PM_{2.5}$ and PAHs during early pregnancy among women residing in the highly polluted Teplice area or in Prachatice (an area with similarly high PAH but low particle concentrations). Mean PM_{10}, $PM_{2.5}$ and c-PAH exposures during 9 gestation months (GMs) were estimated for each mother and regressed (controlling for several potential covariates, e.g., maternal age, smoking, alcohol consumption, parental education, etc.) in logistic regression models against data for all European-origin live births during 1993 to 1998 in Teplice (n = 3,378) and Prachatice (n = 1,505). The adjusted odds ratio (AOR) for IURG confirmed the previously published findings noted above for increased risk of IURG being associated with ambient particle exposures in Teplice during the first GM, but not in Prachatice (the lower particle area). Adjusted odds ratios calculated for low, medium, and high c-PAH levels (L = < 15, M = 15-30, M ≥ 30 ng/m^3) for fetuses from Teplice during the first GM were 1.60 (CI: 1.06, 2.15) and 2.15 (CI: 2.7, 3.6), respectively, for medium and high c-PAHs versus the low c-PAH exposure group. Similar associations were reported for the medium and high PAH exposures (during first GM) in Prachatice even in the presence of low overall particle levels, prompting the authors to hypothesize a likely important role for PAHs.

8.3.4.2 PM Effects on Postneonatal Infant Mortality

Results suggestive of possible early postnatal PM exposure effects on neonatal infant mortality have also emerged from some other new studies. Woodruff et al. (1997), for example, used cross-sectional methods to evaluate possible associations between postneonatal infant mortality and ambient PM_{10} pollution in U.S. urban areas. This study involved an analysis of a cohort of ~4 million infants born during 1989 to 1991 in 86 U.S. metropolitan statistical areas (MSAs). Data from the National Center for Health Statistics-linked birth/infant death records were combined at the MSA level with PM_{10} data from EPA's Aerometric database. Infants were categorized as having low, medium, or high exposures based on tertiles of PM_{10} averaged over the first 2 postnatal months. Relationships between this early neonatal PM_{10} exposure and total and cause-specific postneonatal mortality rates (from 1 mo to 1 year of age) were examined

using logistic regression analyses, adjusting for demographic and environmental factors. Overall postneonatal mortality rates per 1,000 live births were 3.1 among infants in areas with low PM_{10} exposures, 3.5 among infants with medium PM_{10} exposures, and 3.7 among high PM_{10} exposed infants. After adjustment for covariates, the OR and 95% confidence intervals for total postneonatal mortality for the high versus the low exposure group was 1.10 (CI: 1.04, 1.16). For normal birth weight infants, high PM_{10} exposure was associated with mortality for respiratory causes (OR = 1.40, CI: 1.05, 1.85) and sudden infant death syndrome (OR = 1.26, CI: 1.14, 1.39). Among low birth weight babies, high PM_{10} exposure was positively (but not significantly) associated with mortality from respiratory causes (OR = 1.18, CI: 0.86, 1.61). However, other pollutants (e.g., CO) were not considered as possible confounders, and this lack of consideration of other air pollutants as potential confounders in this new study introduces uncertainty in attribution of observed effects to PM.

Lipfert et al. (2000c) used a modeling approach similar to that of Woodruff et al. (1997), but used annual-average PM_{10} air quality data for one year (1990) instead of PM_{10} averaged over the first two postnatal months during 1989 to 1991. The quantitative relationship between the individual risk of infant mortality did not differ among infant categories (by age, by birthweight, or by cause), but PM_{10} risks for SIDs deaths were higher for babies of smoking mothers. SO_4^{2-} was a strong negative predictor of SIDs mortality for all age and birth weight categories. The authors (a) noted difficulties in ascribing the reported PM_{10} and SO_4^{2-} associations to effects of the PM pollutants per se versus the results possibly reflecting interrelationships between the air pollution indices, a strong well-established east-west gradient in U.S. SIDS cases, and/or underlying sociodemographic factors (e.g., the socioeconomic or education level of parents) and (b) hypothesized that a parallel gradient in use of wood burning in fireplaces or woodstoves and consequent indoor wood smoke exposure might explain the observed cross-sectional study results. Lipfert et al. (2000c) also raised questions as to whether the findings of Woodruff et al. (1977) could be due to confounding factors.

The study by Loomis et al. (1999) of infant mortality in Mexico City during 1993-1995 provides interesting information pointing towards possible fine particle effects on infant mortality. That is, in Mexico City (where mean 24-h $PM_{2.5}$ = 27.4 $\mu g/m^3$), infant mortality was

found to be associated with $PM_{2.5}$, NO_2, and O_3 in single pollutant GAM Poisson models, but much less consistently with NO_2 and O_3 than $PM_{2.5}$ in multipollutant models. The estimated excess risk for $PM_{2.5}$-related infant mortality lagged 3 to 5 days was 18.2% (CI = 6.4, 30.7) per 25 $\mu g/m^3$ $PM_{2.5}$. The extent to which such a notable increased risk for infant mortality might be extrapolated to U.S. situations is not clear, however, due to possible differences in prenatal maternal or early postnatal infant nutritional status.

Bobak and Leon (1999) conducted a matched population-based case-control study covering all births registered in the Czech Republic from 1989 to 1991 that were linked to death records. They used conditional logistic regression to estimate the effects of suspended particles and nitrogen oxides on risk of death in the neonatal and early postneonatal period, controlling for maternal socioeconomic status and birth weight, birth length, and gestational age. The effects of all pollutants were strongest in the postneonatal period and specific for respiratory causes. Only PM showed a consistent association when all pollutants were entered in one model. Thus, in this study, long-term exposure to PM was the air pollutant metric most strongly associated with excess postneonatal deaths.

8.3.4.3 Summary of Saliant Points on PM Effects on Fetal and/or Early Postnatal Development/Mortality

A few older cross-sectional studies reviewed in the 1996 PM AQCD reported findings suggestive of (a) possible TSP relationship to increased postnatal mortality among U.S. infants, children, and adolescents (aged 0 to 14 years) and (b) possible associations between early postnatal mortality among Czech infants (1 to 12 mo). Several more recent studies conducted in the U.S. have focused on the possible effects of air pollution exposures during pregnancy on the occurrence of preterm or low birth weight births, both of these being risk factors for a myriad of later health problems (childhood morbidity/mortality; possible adult morbidity). One study found results suggestive of prenatal PM_{10} exposures during the 1st month of pregnancy or averaged over 6 weeks prior to birth being associated with increased risk of preterm birth, even in multipollutant models. However, another large scale U.S. study found little evidence indicative of prenatal PM_{10} exposures being related to increased risk of low birth weight, whereas a new Czech study did find evidence indicative of interuterine growth retardation

(leading to low birth weight) being related to $PM_{2.5}$ exposures during the first gestational month. Similarly, analogously mixed results were reported for some new studies that evaluated ambient PM relationships to early postnatal mortality among U.S., Czech, and Mexican infants. These results, overall, highlight the need for more research to elucidate potential ambient PM effects on fetal development/mortality and for postnatal morbidity/mortality.

8.4 INTERPRETIVE ASSESSMENT OF THE EPIDEMIOLOGIC EVIDENCE

8.4.1 Introduction

Numerous PM epidemiology studies assessed in the 1996 PM AQCD implicated ambient PM as a likely contributor to mortality and morbidity effects associated with ambient air pollution exposures. Since preparation of the 1996 PM AQCD, the epidemiologic evidence concerning ambient PM-related health effects has vastly expanded. Past regulatory decisions have been important in the selection of PM indices and evolution of PM epidemiologic literature. That is, the adoption of PM_{10} standards in 1987 and of $PM_{2.5}$ standards in 1997 have generated ambient air concentration databases that have made it possible for research to address many previously unresolved issues regarding potential linkages between airborne PM and human health; and the newly implemented nationwide network of speciation samplers holds promise for further advances regarding identification of the most influential specific components of the ambient air pollution mixture and their sources.

As was discussed in Sections 8.2 and 8.3, numerous new PM epidemiology studies have evaluated health effects associated with short or long-term ambient PM exposure. Most have found positive associations (many being statistically significant) between (a) excess risks for various mortality and/or morbidity endpoints in many U.S. cities and elsewhere and (b) ambient PM indexed by a variety of ambient community monitoring methods. Some other new studies have found positive, but nonsignificant associations with PM, and a few have reported negative (usually nonsignificant) associations with ambient PM and/or more robust gaseous co-pollutant effects. Several issues and attendant uncertainties continue to be important in assessing and

interpreting the overall PM epidemiology database and its implications for estimating risks associated with exposure to ambient PM concentrations in the United States. These include issues concerning: (1) approaches to model specification to take into account important effect modifiers (such as weather) and to control for potential confounding of PM effects by co-pollutants (especially major gaseous pollutants such as O_3, CO, NO_2, SO_2); (2) temporal relationships between exposure and effect (lags); (3) potential consequences of measurement error; (4) attribution of various types of health effects to specific PM components (e.g., PM_{10}, $PM_{10-2.5}$, $PM_{2.5}$, ultrafines, sulfates, metals, etc.) or to source-oriented indicators (motor vehicle emissions, vegetative burning, etc.); (5) the general shape of exposure-response relationship(s) between PM and/or other pollutants and observed health effects (e.g., potential indications of thresholds); (6) geographic homogeneity / heterogeneity of PM exposure-health risk relationships; and (7) implications of PM-related mortality effects (e.g., mortality displacement; life shortening). All of these issues are of much importance for characterizing and interpreting ambient PM-health effects associations.

Assessing the above uncertainties in relation to the PM epidemiology data base remains a challenge. The basic issue is that there are an extremely large number of possible models, any of which may turn out to give the best statistical "fit" of a given set of data, and only some of which can be dismissed a priori as biologically or physically illogical or impossible, except that putative cause clearly cannot follow effect in time. Most of the models for daily time-series studies are fitted by adjusting for changes over long time intervals and across season, by day of week, weather, and climate. Many of the temporal and weather variable models have been fitted to data using semi-parametric methods such as spline functions or local regression smoothers (LOESS). The goodness of fit of these base models has been evaluated by criteria suitable for GLM with Poisson or hyper-Poisson responses (number of events) with a log link function, particularly the Akaike Information Criterion (AIC) and the more conservative Bayes Information Criterion (BIC) which adjust for the number of parameters estimated from the data. The Poisson over-dispersion index and the autocorrelation of residuals are also often used. However, if high correlations between PM and one or more gaseous pollutants emitted from a

common source (e.g., motor vehicles) exist in a given area, then disentangling their relative individual partial contributions to observed health effects associations becomes very difficult.

Testing numerous models or model specifications (e.g., including single versus various combinations of multiple air pollutants, varying numbers and combinations of meteorological variables, varying numbers of knots in splines, varying degrees of freedom, etc.) can yield a widely varying array of results; and approaches to selection of "best fit" models and to characterizing uncertainties associated with modeling outcomes remain controversial issues. In an effort to address such issues, Dominici et al. (2003) used a uniform approach (same variables and smoothing functions) in the NMMAPS 90 city study. This approach reduces the uncertainty associated with multiple testing, but at the cost of possibly not identifying the best model in each city. Lumley and Sheppard (2000) used different control variables to check the bias in model identification. They found that the bias was small, but of the same magnitude as the estimated health impacts. Another approach is to use one set of data for model identification, and a second set of data for model fitting. Cross validation also shields light on this issue.

Testing many models to identify the model with the best fit can lead to an under-estimation of uncertainty. Bayesian model averaging, or BMA, used in other fields (e.g., econometrics) as a formalized means for conducting model search strategies and providing an approach to account for modeling uncertainties (Hoeting et al., 1999), has begun to be employed in the late 1990's in air pollution epidemiologic analyses. Among the first and best known applications of the BMA approach to evaluation of air pollution effects are the studies by Clyde (1999), Clyde (2000), and Clyde et al. (2000).

As discussed earlier (in Section 8.2.2), Clyde (1999) employed BMA techniques in an analysis of PM_{10}-mortality relationships among the elderly ($\geq$ 65 years old) in Chicago and Cook County, IL during 1985 to 1990, using daily PM_{10} data from one monitoring site and daily averages of one-in-six day PM_{10} data from subsets of 6 of 20 other monitoring sites. Using principal component analyses involving combinations of meteorological factors and allowing for both linear models and nonlinear relationships of mortality to PM_{10} variations, Clyde (1999) reported a very high overall model averaging probability (near one) for the existence of a particulate matter effect. Based on the results, she noted that the prediction interval suggests that

the overall reduction in deaths among the elderly (> 65 years) in Chicago would be 91 to 300 deaths per year for a 10 $\mu g/m^3$ decrease in PM. However, Clyde (1999) also noted the preliminary nature of her Chicago/Cook County analyses and that the results needed to be caveated (as per discussion in Section 8.2.2).

A more extensive systematic evaluation of model choice was subsequently carried out by Clyde (2000), using Bayesian Model Averaging for the same Birmingham, AL, data as was analyzed earlier by Smith et al. (1999). In the Clyde (2000) study, several different calibrated information criterion priors were tried in which models with large numbers of parameters are penalized to various degrees. After taking out a baseline trend (estimated using a GLM estimate with a 30-knot thin-plate smoothing spline), 7,860 models were selected for use in model averaging. These included lags 0 to 3 days of a daily monitor PM_{10}, an area-wide average PM_{10} value with the same lags, temperature (daily extremes and average) lagged 0 to 2 days, humidity (dewpoint, relative humidity min and max, average specific humidity) lagged 0 to 2 days, and atmospheric pressure, lagged 0 to 2 days. The model choice is sensitive to the specification of calibrated information criterion priors, in particular disagreeing as to whether different PM_{10} variables should be included or not. For example, one or another PM_{10} variable was included in all the top 25 AIC models, but only in about 1/3 of the top BIC models. The two approaches yielded relative risk estimates per 100 $\mu g/m^3$ PM_{10} increment of about 1.05 for AIC, with 95% probability (confidence) intervals of (0.94, 1.17) for the AIC prior, and of 1.1015 (0.99, 1.11) for the BIC prior. A validation study in which randomly selected data were predicted using the different priors favored Bayesian model averaging with BIC prior over model selection (picking the best model) with BIC or any approach with AIC. This type of modeling may represent another type of multipollutant modeling approach in addition to more typical hypotheses-driven model construction and interpretation that draws more on external information (e.g., exposure, dosimetric, toxicologic relationships) in specifying models and interpreting their results. However, it should be noted that the 95% probability (confidence) intervals for estimates derived for both the AIC and BIC priors encompass relative risk (RR) estimates derived for PM_{10}-mortality associations in Birmingham by more widely-used conventional methods. That is, RR estimates for PM_{10}-elderly mortality in Birmingham of 1.11 derived by Poisson regression GEE

(Schwartz, 1993) and 1.09 derived by a linear model using square roots of the daily death counts as the dependant variable (Smith, 1999) fall within the 95% probability intervals derived by the Clyde (2000) BMA approach.

In most of this document, confidence intervals, or credible intervals for Bayesian analyses, are reported in order to emphasize that the effect size is not known with certainty, but some values are more nearly consistent with the data than effect size values outside the interval. P-values or t-values are implicitly associated with a null hypothesis of no effect. A nominal significance level of $p \leq 0.05$ or 5% (i.e., a 95% confidence interval) is usually used as a guide for the reader, but P-values should not be used as a rigid decision-making tool. If the observed confidence intervals were arrived at by a number of prior model specification searches, eliminating some worse fitting models, the true interval may well be wider.

Given the now extremely large number of published epidemiologic studies of ambient PM associations with health effects in human populations and the considerably wide diversity in applications of even similar statistical approaches (e.g., "time-series analyses" for short-term PM exposure effects), it is neither feasible nor useful here to try to evaluate the methodological soundness of every individual study. Rather, a four-pronged approach is likely to yield useful evaluative information: (1) an overall characterization of evident general commonalities (and/or notable marked differences) among findings from across the body of studies dealing with particular PM exposure indices and types of health outcomes, looking for convergence (and/or divergence) of evidence regarding types of effects and effect-sizes attributable to ambient PM indices across various geographic locations based on various methodologically acceptable analyses; (2) thorough, critical assessment of newly published multicity analyses of PM effects, assuming that greater scientific weight is generally ascribable to their results than those of smaller-sized studies (often of individual cities) yielding presumably less precise effect size estimates; (3) evaluation of, albeit at times less precise, single city results; and (4) evaluation of coherence of the findings with other types of pertinent biological information (e.g., exposure, dosimetry, toxicity, etc.).

In the sections that follow, issues noted above are critically discussed. First follows a discussion of the GAM issue and a summary of some key findings emerging from the short communications and peer-review commentary published by HEI (2003b).

8.4.2 GAM Issue and Reanalyses Studies

As discussed earlier, Dominici et al. (2002) reported that the default convergence criteria used in the S-Plus function GAM may not guarantee convergence to the best unbiased estimate in all cases. The actual importance of this effect has begun to be quantified, with the results of the reanalyses of a number of important studies described in short communications published in the HEI (2003c) Special Report being especially helpful in this regard. As for the net outcome of these reanalyses efforts, HEI (2003c) summarizes it well, as follows:

> "Overall, the revised analyses using GAM with more stringent convergence criteria and iterations and GLM-natural splines resulted in lower estimates, but largely confirmed the effect of exposure to particulate matter on mortality (Burnett and Goldberg, 2003; Dominici et al., 2003; Katsouyanni et al., 2003; Samoli et al. ,2003; Schwartz, 2003b; Zanobetti and Schwartz, 2003b) and morbidity, especially for hospitalizations for cardiovascular and respiratory diseases (Atkinson et al., 2003; Fairley, 2003; Gold et al., 2003; Hoek, 2003; Ito, 2003; Le Tertre et al., 2003; Ostro et al., 2003; Schwartz, 2003a; Sheppard, 2003; Zanobetti and Schwartz, 2003a). As in earlier analyses, the effect was more pronounced among individuals 65 years of age and older (Fairley; Gold et al.; Goldberg and Burnett; Ito; Le Tertre et al.; Mar et al.; Moolgavkar; Schwartz a). The impact of various sensitivity analyses, when these were performed, differed across the studies. No significant impacts were seen in some (Ostro et al.), whereas in others, alternative modeling of time (Klemm and Mason; Moolgavkar) and weather factors (Goldberg and Burnett; Ito) resulted in substantial changes."

The following discussion elaborates in more detail the nature and extent of potential problems in various studies that have used the GAM default algorithm, but which have also had their analyses redone using alternative methods in order to address this convergence issue.

8.4.2.1 Impact of Using the More Stringent GAM Model on PM Effect Estimates for Mortality

Many of the reanalysis studies analyzed associations between PM_{10} and mortality, allowing evaluation of the impact of the GAM convergence problem on this PM index. Table 8-36 and Figure 8-15 show the percent excess total nonaccidental mortality (unless noted otherwise) risk

TABLE 8-36. PM_{10} EXCESS RISK ESTIMATES FROM REANALYSIS STUDIES FOR TOTAL NONACCIDENTAL MORTALITY PER 50 µg/m^3 INCREASE IN PM_{10}

Study	GAM-Default	GAM-Stringent	GLM
Multi-Cities Analyses			
NMMAPS 90-cities; Dominici et al. (2002)	2.1 (1.6, 2.6)	1.4 (0.9, 1.9)	1.1 (0.5, 1.7)
Harvard 6-cities; Klemm and Mason (2003)	4.1 (2.8, 5.4)	3.6 (2.1, 5.0)	2.0 (0.3, 3.8)
US 10 cities; Schwartz (2003b)	3.4 (2.7, 4.1)	3.3 (2.6, 4.1)	2.8 (2.0, 3.6)
8 Canadian cities; Burnett and Goldberg (2003)	4.5 (2.2, 6.7)	3.6 (1.4, 5.8)	2.7 (−0.1, 5.5)
APHEA2; Katsouyanni et al. (2003)	3.5 (2.9, 4.1)	3.3 (2.8, 3.9)	2.1 (1.5, 2.8)
Single-Cities Analyses			
Santa Clara Co.; Fairley (2003)	8.0**	7.8 (2.8, 13.1)	8.3 (2.9, 13.9)
Coachella Valley; Ostro et al. (2003)*	5.6 (1.7, 9.6)	5.5 (1.6, 9.5)	5.1 (1.2, 9.1)
Los Angeles Co.; Moolgavkar (2003)	2.4 (0.5, 4.4)	2.4 (0.5, 4.3)	2.3 (0.1, 4.5)
Cook Co.; Moolgavkar (2003)	2.4 (1.3, 3.5)	2.6 (1.6, 3.6)	2.6 (1.5, 3.7)
Phoenix, AZ; Mar et al. (2003)*	9.9 (1.9, 18.4)	9.7 (1.7, 18.3)	9.5 (0.6, 19.3)
Detroit, '85-'90; Ito (2003)	1.7 (0.2, 3.2)	0.9 (−0.5, 2.4)	0.7 (−0.8, 2.1)
Detroit, '92-'94; Ito (2003)	4.4 (−1.0, 10.1)	3.3 (−2.0, 8.9)	3.1 (−2.2, 8.7)
The Netherlands; Hoek (2003)	0.9 (0.1, 1.7)	0.9 (0.2, 1.7)	0.9 (0.1, 1.7)
Erfurt, Germany; Stolzel et al. (2003)	6.4 (0.3, 12.9)	6.2 (0.1, 12.7)	5.3 (−1.8, 12.9)

*Cardiovascular Mortality
**No CI interval given

estimates per 50 µg/m^3 increase in PM_{10} derived from the reanalysis studies for (1) GAM with default convergence criteria; (2) GAM with stringent convergence criteria; and, (3) GLM with natural splines that approximate the original GAM model. The table and figure show results only from the studies that used all of the three alternative models for PM_{10}. It can be seen that most, but not all, reanalyses resulted in reductions in PM_{10} risk estimates when more stringent convergence criteria were used in GAM models. Using GLM with natural splines resulted in additional reduction in PM_{10} risk estimates for most, but not all, cases. The extent of reduction in PM_{10} risk estimates seen with use of GAM with more stringent convergence criteria or GLM

with natural splines was generally proportionally greater for the larger-scale multicity studies than for the single-city analyses. The decreases in PM_{10} effect size estimates for the multicity studies can be seen in Table 8-36 to fall rather evenly across the range of −3 to −33% for the GAM-stringent and from −18 to −52% for the GLM reanalyses values. In contrast, the single-city reanalyses yielded PM_{10} effect size estimates that were generally little changed from the original estimates (varying by ±10% for 7 of 9 GAM-stringent and for 6 of 9 GLM reanalyses, with the others decreasing by 17 to 59%). The relative percent reduction is greater for the studies that had smaller PM_{10} risk estimates in the original analyses (e.g., NMMAPS U.S. 90 cities analyses). It can also be seen in Figure 8-15 that the extent of reduction in PM_{10} risk estimates is smaller than the variability of PM_{10} risk estimates across the studies. Thus, the effect of the GAM convergence problem does not appear, in most cases, to be substantial. Several of the reanalysis reports also analyzed $PM_{2.5}$ and $PM_{10-2.5}$. Generally, the pattern and extent of reductions in mortality risk estimates were similar to those for PM_{10}. The results for $PM_{2.5}$ and $PM_{10-2.5}$ mortality risk estimates are compared in a later section.

Dominici et al. (2002) also illustrated that GAM models, even with stringent convergence criteria, still result in biased (downward) standard errors of regression coefficients. This was the main reason for the use of GLM with natural splines in the reanalysis studies. As can be seen from Figure 8-15, the 95% confidence bands are somewhat wider for GLM results than for GAM results in some, but not all cases. However, the extent of wider confidence bands is not substantial in most cases (the bias ranged from a few percent to ~15% in most cases). It should be noted that, while a GLM model with natural splines provides correct standard error of regression coefficient, it is not equivalently as flexible as LOESS or smoothing splines. Unlike LOESS or smoothing splines, natural splines fit linearly at both ends of the data span. Natural splines therefore may not be an ideal model option for temperature effects, for which the slopes are likely nonlinear (especially at the higher end). Goldberg and Burnett (2003), in their reanalysis of Montreal data, discussed related issues. In their reanalysis, the originally reported risk estimates of PM indices (CoH, extinction coefficient, predicted $PM_{2.5}$, and sulfate) were greatly attenuated in the GLM model with natural splines. One of the alternative explanations for these results was that the natural spline does not fit the possibly nonlinear (threshold) effect

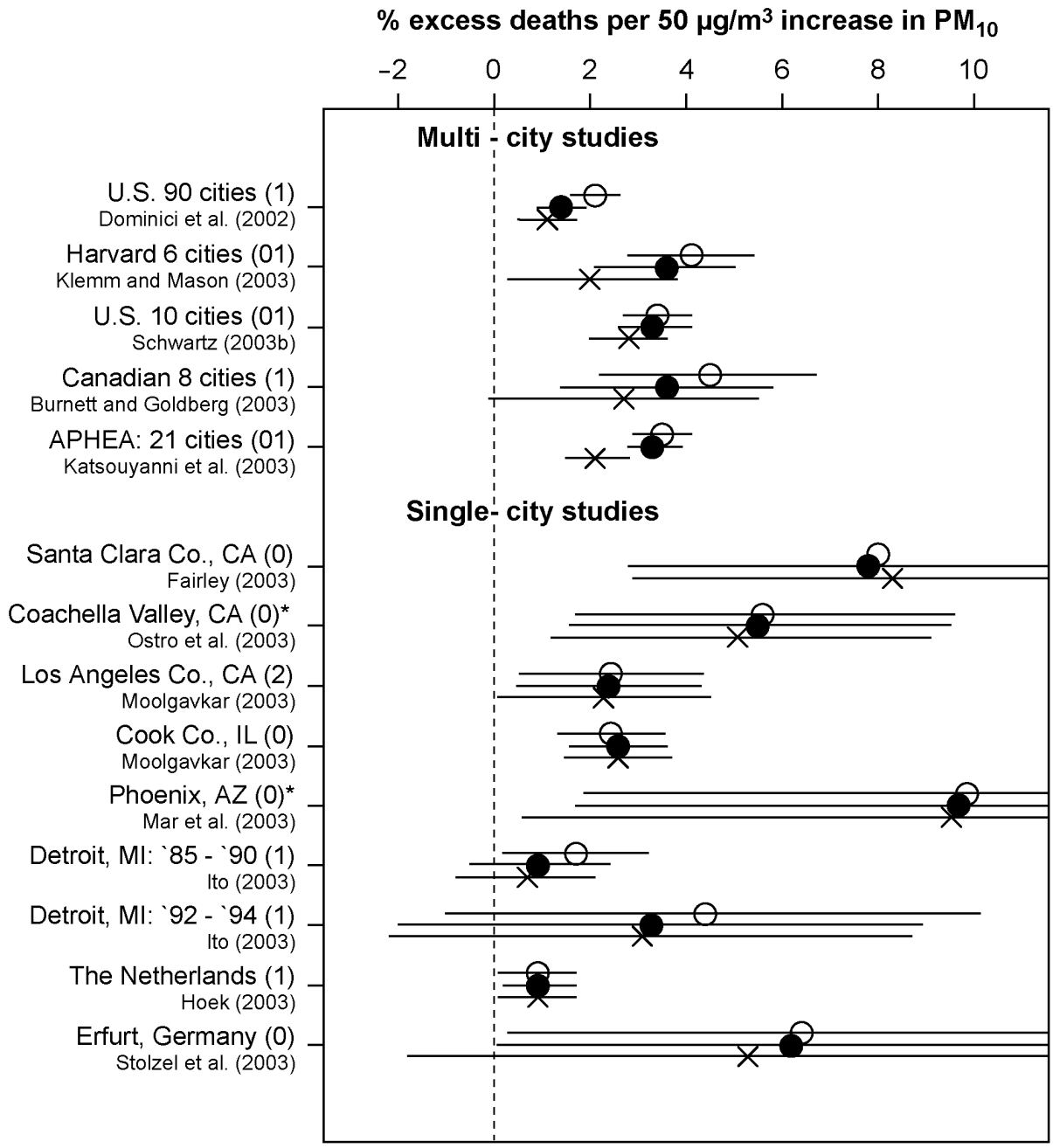

Figure 8-15. PM_{10} excess risk estimates for total nonaccidental mortality for numerous locations (and for cardiovascular mortality[*] for Coachella Valley, CA and Phoenix, AZ), using: (1) GAM with default convergence criteria (white circle); (2) GAM with stringent convergence criteria (black circle); and, (3) GLM/natural splines (x) that approximate the original GAM model from the GAM reanalysis studies. The numbers in parenthesis indicate lag days used ("01" is average of 0- and 1-day lags).

of temperature as well as nonparametric smoothers. Hoek (2003), in his reanalysis of the Netherlands data, also showed that, compared to GAM models, GLM/natural spline models resulted in larger deviance, indicating poorer fits. Thus, there are remaining issues regarding the trade-off between GAM/nonparametric smoothers and GLM/parametric smoothers. The GLM/natural splines may produce correct standard errors but cannot guarantee "correct" model specifications. More recently, Domimici et al. (2003) developed and published a GAM routine for SPlus that gives correct standard errors, but it was not developed in time to be used for the GAM reanalysis effects reported on in HEI (2003c).

Three reanalysis reports applied alternative smoothing approaches (e.g., penalized splines) that, as with GLM/natural splines, did not have the problem of biased standard error. These studies were: reanalyses of Harvard six cities data by Schwartz (2003a); reanalysis of 10 U.S. cities data by Schwartz (2003b); and reanalysis of APHEA2 by Katsouyanni et al. (2003). Generally, as with GLM/natural splines, the use of alternative smoothing approaches resulted in smaller PM risk estimates than GAM with stringent convergence criteria. In the reanalysis of APHEA2 study, the PM_{10} risk estimates from penalized splines were smaller than those from GAM, but larger than those from natural splines. Three alternative smoothing approaches (B-splines, penalized splines, and thin-plate splines) used in the reanalysis of Harvard six cities $PM_{2.5}$ data resulted in generally smaller risk estimates than those from natural splines. As was expected, all of these alternative smoothing approaches resulted in standard errors that were comparable to those from natural splines but larger than those from GAM models.

Several of the GAM reanalysis reports included additional sensitivity analyses which provided useful information. These sensitivity analyses included examinations of the effect of changing degrees of freedom for smoothing of temporal trends and weather variables (Dominici et al. [2002]; Ito [2003]; Klemm and Mason [2003]; Moolgavkar [2003]; and Burnett and Goldberg [2003]). In these analyses, changing the degrees of freedom for smoothing of temporal trends or weather effects often resulted in change of PM coefficients to a similar or even greater extent than those caused by the GAM convergence problem. A distinctly less well investigated issue is the effect of the use of different weather model specifications (i.e., how many and which weather variables and their lags are included). In a limited examination of this

issue in the reanalysis of Detroit data (Ito, 2003), a weather model specification similar to that used in the NMMAPS U.S. 90 cities study consistently yielded smaller PM_{10} risk estimates than a weather model similar to that used in the Harvard six cities study.

In summary, the results from the GAM reanalysis studies indicate that PM risk estimates from GAM models were often, but not always, reduced when more stringent convergence criteria were used. However, the extent of the reduction was not substantial in most cases. The variability of PM risk estimates due to the model specification, including the number of weather terms and extent of smoothing, is likely larger than the effect of the GAM convergence problem. The extent of downward bias in standard errors reported for these data (a few percent to ~15%) also appears not to be very substantial, especially when compared to the range of standard errors across studies due to differences in population size and numbers of days available. Nevertheless, this chapter mainly considers results of the reanalyzed studies or of other originally published studies that did not use GAM with default convergence criteria, because the extent of the effect of this problem is not generally predictable in each individual study.

8.4.2.2 Impact of Using the More Stringent GAM Model on PM Effect Estimates for Respiratory Hospital Admissions

The NMMAPS multicity study (Samet et al., 2000a,b) of PM_{10} concentrations and hospital admissions used the default GAM model specification with multiple smooths. The changes derived from use of the more stringent GAM convergence criteria are illustrated by the results of reanalyses by Zanobetti and Schwartz (2003a). Their results indicate that there was only about a 14% decline in the effect estimates associated with use of the more appropriate stringent convergence requirement. The two estimates were well within the 95% confidence interval of each other. Also, in comparing the difference in the estimates between each of the six pairs of estimates by a two-sided z-statistic, all the p-values are > 0.5, indicating that the two convergence requirements gave insignificant differences in estimates.

To examine the potential influence of the GAM convergence specification on the results of the original Detroit data analysis by Lippmann et al. (2000), the associations between PM components and daily mortality/morbidity were re-examined by Ito (2003) using more stringent convergence criteria, as well as by applying a GLM that approximated the original GAM

models. Generally, the GAM models with stringent convergence criteria and GLM models resulted in somewhat smaller estimated relative risks than those reported in the original study, averaging 17% less for the stringent GAM case versus the default case. For COPD, the decrease associated with the more stringent convergence criteria was larger (averaging 30%). Overall, for all types of hospital admissions (including pneumonia, COPD and ischemic heart disease) the change to the more stringent GAM convergence criteria gave an average decrease of 20 percent, while a switch to the GLM model specification gave an average 29% decrease in estimated PM effect size.

As discussed earlier, Sheppard (2003) recently conducted a reanalysis of their non-elderly hospital admissions data for asthma in Seattle, WA, in order to evaluate the effect of the fitting procedure on their previously published analyses. A lag of 1 day was used for all PM models. As shown in Table 8-37, the results were provided in the manuscript to only one significant figure (to the nearest whole percent), making the calculation of percent changes between models problematic, since the rounding of the effect estimates are nearly on the order of the size of the effect estimate changes. However, it can be seen that the pattern of changes in effects estimates and 95% CI values is very similar to that seen in other studies.

TABLE 8-37. COMPARISON OF MAXIMUM SINGLE DAY LAG EFFECT ESTIMATES FOR $PM_{2.5}$, $PM_{10-2.5}$, and PM_{10} FOR SEATTLE ASTHMA HOSPITAL ADMISSIONS BASED ON ORIGINAL GAM ANALYSES USING DEFAULT CONVERGENCE CRITERIA VERSUS REANALYSES USING GAM WITH MORE STRINGENT CONVERGENCE CRITERIA AND GLM

	Original Default GAM Model* % Increase/IQR (95% CI)	Reanalysis Stringent GAM % Increase/IQR (95% CI)	Reanalysis GLM (Natural Spline) % Increase/IQR (95% CI)
$PM_{2.5}$	4 (2, 7)	4 (1, 6)	3 (1, 6)
$PM_{2.5-10}$	4 (1, 7)	2 (0, 5)	2 (−1, 4)
PM_{10}	5 (2, 8)	4 (1, 7)	3 (0, 6)

*$PM_{2.5}$ IQR = 11.8 ug/m^3; $PM_{2.5-10}$ IQR = 9.3 ug/m^3; PM_{10} IQR = 19 ug/m^3.

Source: Derived from Sheppard (2003).

Further evidence of the relatively small effect of the default convergence criteria issue in most applications is the recent work by Moolgavkar (2003), in which he reanalyzed his earlier GAM analyses of hospital admissions for COPD (Moolgavkar, 2000c) for the cities of Los Angeles (Los Angeles County) and Chicago (Cook County). In his original publication, Moolgavkar found ~5.0% excess risk for COPD hospital admissions among the elderly (64+ years old) in Los Angeles to be significantly related to both $PM_{2.5}$ and $PM_{10-2.5}$ in one pollutant models. In the same study, similar magnitudes of excess risk (i.e., in the range of ~4 to 7%) were found in one-pollutant models to be associated with $PM_{2.5}$ or $PM_{10-2.5}$ for other age groups (0 to 19 years; 20 to 64 years) in Los Angeles, as well. In his reanalyses of these GAM results using the more stringent convergence criteria, however, Moolgavkar (2003) combined all three Los Angeles age groups into one analysis, providing greater power, but also complicating before/after comparisons as to the actual effect on the results of using the more stringent convergence criteria. In the case of the Cook County analyses, the author changed other model parameters (i.e., the number of degrees of freedom in the model smooths) at the same time as implementing the more stringent convergence criteria, so direct before/after comparisons were not possible for Moolgavkar's Chicago reanalyses.

Therefore, in order to provide a one-to-one comparison for Los Angeles, the original age-specific GAM analyses have been pooled using inverse variance weighting and are presented along with Moolgavkar's (2003) reanalyses results (in terms of a % increase per 10 $\mu g/m^3$ mass increase for both $PM_{2.5}$ and PM_{10}) in Table 8-38. As shown in that table, the Moolgavkar Los Angeles results for all-age COPD admissions for the original and the more stringent convergence criteria GAM cases (using the same degrees of freedom) are very similar, with the effects estimate either decreasing (for $PM_{2.5}$) or increasing (for PM_{10}) very slightly. In those cases where a much larger number of degrees of freedom were used with either the more stringent GAM model or a natural spline GLM model, larger reductions in effects estimates were seen as compared to the original GAM model. For the same number of degrees of freedom, the natural spline model gave either a slightly larger (for $PM_{2.5}$) or a slightly smaller (for PM_{10}) effects estimate than the stringent GAM model. Thus, the reanalyses indicate that use of more stringent GAM convergence criteria results in minimal changes in PM effect size estimates in

TABLE 8-38. COMPARISON OF LOS ANGELES COPD HOSPITAL ADMISSIONS MAXIMUM SINGLE DAY LAG EFFECT ESTIMATES FOR $PM_{2.5}$ and PM_{10} FROM THE ORIGINAL GAM ANALYSES USING DEFAULT CONVERGENCE CRITERIA VERSUS EFFECT ESTIMATES DERIVED FROM REANALYSES USING MORE STRINGENT CONVERGENCE CRITERIA AND FOR MODELS SMOOTHED WITH MORE DEGREES OF FREEDOM

	Original Default GAM Model* (30 df) % Increase/10 µg/m^3 (95% CI)	Reanalysis Stringent GAM (30 df) % Increase/10 µg/m^3 (95% CI)	Reanalysis Stringent GAM (100 df) % Increase/10 µg/m^3 (95% CI)	Reanalysis Natural Spline (100 df) % Increase/10 µg/m^3 (95% CI)
$PM_{2.5}$	1.90 (0.97-2.84)**	1.85 (0.82-2.89)**	1.38(0.51-2.25)***	1.49(0.41-2.58)***
PM_{10}	1.43 (0.85-2.02)**	1.51 (0.85-2.18)**	1.08 (0.50-1.66)**	0.98 (0.24-1.72)**

*Original GAM estimates derived for "all ages" from original analyses by age subgroups using inverse variance weights.
**For (maximum) lag case = 2 days.
***For (maximum) lag case = 0 days.

Source: Derived from Moolgavkar (2000c) and Moolgavkar (2003).

this case, as compared to those obtained using the default GAM model; whereas the number of degrees of freedom used with either GAM or GLM models can result in much larger changes in the PM effect size estimates and broader confidence intervals.

These various reanalyses results therefore confirm that the PM effect estimates generally do decline somewhat when using the more stringent convergence criteria, as compared to the default GAM, with the new estimates being well within the confidence intervals of the original estimates. However, the effect of using more stringent convergence criteria was seen to have less influence on the effect estimate than investigator-to-investigator variations in model specifications (e.g., the extent of smoothing). Overall, then the absolute impact was relatively small and the basic direction of effect and conclusions regarding the significance of the PM effect on hospital admissions remained unchanged in these analyses when more stringent GAM convergence criteria were used.

8.4.2.3 HEI Commentaries

The HEI Special Report (2003a,c) presents the HEI Special Panel's reviews of both the Revised Analyses of the National Morbidity, Mortality, and Air Pollution Study (NMMAPS), Part II and the Revised Analyses of Selected Time-Series Studies, which includes short communication reports presenting results from other revised analyses of original articles and reports. Beyond looking at the results of reanalyses designed specifically to address problems associated with the use of default convergence criteria in the S-Plus GAM function, the reviews also identified issues associated with the sensitivity of study findings to the use of alternative modeling approaches that some investigators employed in their reanalyses. In general, the Special Panel concluded that the original PM effects estimates were more sensitive to the modeling approach used to account for temporal effects and weather variables than to the convergence criteria used in the GAM model.

A modeling issue of particular importance highlighted by HEI (2003c) is the sensitivity of all models (e.g., GAM, GLM-natural splines, GLM-penalized splines) to the degrees of freedom allotted to potentially confounding weather variables and time. The commentary discusses the trade-off involved in selecting the number of degrees of freedom for time and weather variables, while recognizing that there remains no altogether satisfactory way to choose the most appropriate degrees of freedom. For example, in considering the effect of temperature, if the degrees of freedom in the smoothing function for temperature are overly restricted, some actual nonlinear effects of temperature would be falsely ascribed to the pollution variable. To avoid this, the analyst is tempted to afford many degrees of freedom to temperature or other potentially confounding variables. However, if more degrees of freedom are allotted than needed, such that the temperature smooth function is more "wiggly" than the true dose response function, then the result will be a much less efficient estimate of the pollutant effect. This would have the effect of incorrectly ascribing part of the true pollution effect to the temperature variable, which would compromise our ability to detect a true but small pollution effect. The commentary notes that the empirical data cannot determine the optimal trade-off between these conflicting needs, and it is difficult to use an a priori biological or meteorologic knowledge to determine the optimal trade-off. Thus, the Special Panel generally recommended further exploration of the sensitivity

of these studies both to a wider range of alternative degrees of smoothing and to alternative specifications of weather variables in time-series models.

More specifically, the HEI Special Panel offered the conclusions and recommendations for NMMAPS and other revised analyses highlighted below:

NMMAPS Revised Analyses

Dominici et al. (2002) conducted a range of revised analyses, applying alternative methods to correct shortcomings in the S-Plus GAM programming. HEI's Special Panel review (HEI, 2003a) of this revised analyses yielded the following conclusions:

- While estimates of effect are quantitatively smaller than those in the original studies, a statistically significant overall effect of PM_{10} on mortality remains, and the qualitative conclusions that were initially drawn from NMMAPS remain unchanged.
- While the alternative approaches used to model temporal effects in the revised NMMAPS analyses addressed the problems of obtaining incorrect effect estimates and standard errors when using the preprogrammed GAMs software, no models can be recommended at this time as being strongly preferred over another for use in this context.
- While formal tests of PM effect across cities did not indicate evidence of heterogeneity because of the generally large individual-city effect standard errors, the power to assess the presence of heterogeneity was low. The possibility of heterogeneity still exists.
- The appropriate degree of control for time in these time-series analyses has not been determined. Thus, the impact of more aggressive control for time should continue to be explored and studies to evaluate bias related to the analytic approach to smoothing and the degree of smoothing should be encouraged.
- Weather continues to be a potential confounder of concern, such that further work should be done on modeling weather-related factors.

Revised Analyses for Other Short Communications

Based on its review, the HEI Special Panel (HEI, 2003c) reached the following conclusions:

- As was the case with the findings of the original studies, the revised findings will continue to help inform regulatory decisions regarding PM.
- The PM effect persisted in the majority of studies; however, the number of studies showing an adverse effect of PM was slightly smaller.

- In some of the large number of studies in which the PM effect persisted, the estimates of PM effect were substantially reduced.
- In the few studies in which further sensitivity analyses were performed, some showed marked sensitivity of the PM effect estimate to the degree of smoothing and/or the specification of weather.
- The use of more appropriate convergence criteria on the estimates of PM effect in the revised analyses produced varied effects across the studies. In some studies, stricter convergence criteria had little impact, and in a few the impact was substantial. No study's conclusions changed in a meaningful way by the use of stricter criteria compared to the original analyses.
- In most studies, parametric smoothing approaches used to obtain correct standard errors of the PM effect estimates produced slightly larger standard errors than the GAM. However, the impact of these larger standard errors on level of statistical significance of the PM effect was minor.
- For the most part, the original PM effect estimates were more sensitive to the method used to account for temporal effects than to changing the convergence criteria.
- Even though the alternative approaches used to model temporal effects in the revised analyses addressed the problems of obtaining incorrect effect estimates and standard errors when using the GAMs software, none can be recommended at this time as being strongly preferred over another for use in this context.
- Neither the appropriate degree of control for time nor the appropriate specification of the effects of weather in these time-series analyses has been determined. This awareness introduces a degree of uncertainty that has not been widely appreciated previously, such that the sensitivity of these studies to a wider range of alternative degrees of smoothing and alternative specifications of weather variables in time-series models should continue to be explored.

8.4.3 Assessment of Confounding by Co-Pollutants and Adjustments for Meteorological Variables

8.4.3.1 Introduction to Assessment of Confounding by Co-Pollutants

Airborne particles are found among a complex mixture of atmospheric pollutants, some of which are widely measured (such as gaseous criteria co-pollutants O_3, CO, NO_2, SO_2) and others which are not routinely measured. Determining the extent to which observed ambient PM-health effects associations can be attributed to airborne particles acting alone or in combination with other air pollutants or may be due to confounding by other pollutants is one of the more difficult

issues encountered in assessing PM-related epidemiologic evidence. Because (a) many of the pollutants are closely correlated due to emissions by common sources and dispersion by common meteorological factors and (b) some are in the pathway of formation of other pollutants (e.g., NO → NO_2 → NO_3^- → Particle Mass), it may be difficult to disentangle their effects (as noted in Section 8.1.1).

It is widely accepted that some PM metrics are associated with health effects, and that PM has effects independent of the gaseous co-pollutants. The extent to which ambient gaseous co-pollutants have health effects independent of PM is important in considering the extent to which health effects attributed to PM may actually be due in part to co-pollutants or to some other environmental factors, and vice versa. EPA produces Air Quality Criteria Documents for four gaseous pollutants: CO, NO_2, SO_2, and O_3 (U.S. Environmental Protection Agency, 1982, 1993, 1996b, 2000b). Health effects of the gaseous pollutants exerted independently from PM, and in some cases jointly with PM, are discussed in those documents. They are also considered to some extent in this section and elsewhere in this document because they may affect quantitative assessments of the effects of various PM metrics when these other pollutants are also present in the atmosphere. The gaseous pollutants may also be of interest as PM effect modifiers or through interactions with PM.

Co-pollutant models have received a great deal of attention in the last several years because there exist improved statistical methods for estimating PM effects by analyses of daily time-series of mortality (Schwartz and Marcus, 1990; Schwartz, 1991) or hospital admissions (Schwartz, 1994a,b) and/or in prospective cohort studies (Dockery et al., 1993). A number of studies using such methods have not only found significant positive relationships between mortality and one or more PM indicators, but also with one or another of the four gaseous criteria pollutants (O_3, NO_2, CO, SO_2) in daily time-series studies, and between SO_2 and mortality in the reanalyses of two large prospective cohort studies (Krewski et al., 2000). In the daily time-series studies, the estimated PM effect is relatively stable when the co-pollutant is included in the model in some cities, whereas the estimated PM effect in other cities changes substantially when certain co-pollutants are included. In interpreting the results of any of these

studies, it is reasonable to consider the biological plausibility of a given pollutant being likely to affect the particular health endpoint.

Some gaseous co-pollutants (e.g., CO, SO_2 and NO_2) may be acting as indicators of distinct emission sources and/or as indicators of PM from these sources. Concentrations of such gaseous co-pollutants may therefore be correlated with total PM mass or even more strongly correlated with specific PM constituents (due to their emission from a common source). Thus, one or another specific gaseous co-pollutant may serve as an indicator of the day-to-day variation in the contribution of a distinct emission source and to the varying concentrations of airborne PM. In a model with total PM mass, then, a gaseous co-pollutant may well actually be serving as a surrogate for the source-apportioned contribution to ambient air PM. Or, PM could also act as an indicator for emission sources or gaseous co-pollutants. It would be interesting to evaluate models that include both source-relevant particle components and gaseous pollutants derived from common sources (e.g., those attributable to motor vehicles, coal combustion, oil combustion, etc.). The closest approach thus far has been Model II in Burnett et al. (2000), a default GAM analysis.

The role of gaseous pollutants as surrogates for source-apportioned PM may be distinct from confounding. The true health effect may be independently associated with a particular ambient PM constituent that may be more or less toxic than the particle mix as a whole. Thus, a gaseous co-pollutant may give rise to the appearance of confounding in a regression model. If it were to serve as an indicator of the more toxic particles, the gaseous co-pollutant could greatly diminish the coefficient for total particle mass. In such a model, the coefficient for total particle mass would most properly be interpreted as an indicator of the other, less-toxic particles.

8.4.3.2 Statistical Issues in the Use of Multipollutant Models

Multipollutant models may be useful tools for assessing whether the gaseous co-pollutants may be *potential* confounders of PM effects, but cannot determine if in fact they are. Variance inflation and effect size instability can occur in nonconfounded multipollutant models as well as in confounded models. Our usual regression diagnostic tools can only determine whether there is a potential for confounding. In PM epidemiology studies, the gaseous pollutants, except O_3,

frequently have a high degree of positive linear correlation with PM metrics, a condition known as multicolinearity; therefore, although multicolinearity leading to effect size estimate instability and variance inflation are necessary conditions for confounding, they are not sufficient in and of themselves to determine whether confounding exists.

The most commonly used methods include multipollutant models in which both the putative causal agent (PM) and one or more putative co-pollutants are used to estimate the health effect of interest. If the effect size estimate for PM is "stable," then it is often assumed that the effects of confounding are minimal. "Stable" is usually interpreted as meaning that the magnitude of the estimated effect is similar in models with PM alone and in models with PM and one or more co-pollutants, and the statistical significance or width of the confidence interval for the PM effect is similar for all models, with or without co-pollutants. These criteria (usually unquantified) diagnose confounding in a narrow sense, interpreted as synonymous with multicolinearity, not as a failure of the study design or other forms of model mis-specification.

Beyond the conceptual issues discussed above that arise in assessing confounding, a number of technical issues arise in the use of statistical models, as discussed below.

(a) Model mis-specification assumes many forms. The omission of predictive regressors ("underfitting", defined by Chen et al., 2000) may produce biased estimates of the effects of truly predictive regressors that are included in the model. Inclusion of unnecessary or nonpredictive regressors along with all truly predictive regressors ("over-fitting") will produce unbiased estimates of effect, but may increase the estimated standard error of the estimated effect if it is correlated with other predictors. Omitting a truly predictive regressor while including a correlated but noncausal variable ("mis-fitting") will attribute the effect of the causal regressor to the noncausal regressor. Interaction terms are candidates for omitted regressor variables. It is important to avoid the "mis-fitting" scenario. Assuming that there is a linear relationship when the true concentration-response function is nonlinear will produce a biased estimate of the effect size, high or low, at different concentrations. One of the most common forms of model mis-specification is to use the wrong set of multiday lags, which could produce any of the consequences described as "under-fitting" (e.g., using single-day lags when a

multiday or distributed lag model is needed), "over-fitting" (e.g., including a longer span of days than is needed), or "mis-fitting" (e.g., using a limited set of lags while the effects are in fact associated with different set of lags). Different PM metrics and gaseous pollutants may have different lag structures, so that in a multipollutant model, forcing both PM and gases to have the same lag structure is likely to yield "mis-fitting." Finally, classical exposure measurement errors (from use of proxy variables) attenuates (biases) effect size estimates under most assumptions about correlations among regressors and among their measurement errors (Zeger et al., 2000).

(b) Bias: All of the mis-specifications listed in (a) can bias the effect size estimate except for "over-fitting" and measurement error of Berkson type. The estimates of the standard error of the effect size estimate under "over-fitting" or Berkson error cases are inflated, however; and result in broader confidence intervals than would otherwise occur with a more appropriately specified model and/or one with less Berkson type measurement error.

(c) Effect size standard error estimates are usually sensitive to model mis-specification. When all truly predictive regressors are added to an "underfit" model, the reduction in uncertainty is almost always sufficient to be reflected by the standard errors of estimated effect size being reduced ("variance deflation"). On the other hand, adding correlated noncausal variables to "over-fitted" or "mis-fitted" models further increases estimated standard errors ("variance inflation"). Variance inflation can occur whenever a covariate is highly correlated with the regressor variable that is presumably the surrogate for the exposure of interest. Confounding with the regressor variable can occur only when the covariate is correlated (a) with the regressor variable proxy for the exposure of interest and (b) with the outcome of interest in the absence of the exposure of interest.

(d) Mis-specification errors may compound each other. If the underlying concentration-response function is nonlinear but there is measurement error in the exposure metrics used, then different subpopulations may actually have greater or smaller risk than assigned by a linear model. Consider the hypothetical case of a "hockey-stick" model with a threshold. If there was

no exposure measurement error, then those in the population with measured concentrations above the threshold would have excess risk, whereas those below would not. However, if exposures were measured with error, even if the measured concentration were above the threshold, some people could experience actual exposures that are, in fact, below the threshold and, therefore, pose no excess risk. Conversely, if the measured (with error) concentration fell below the threshold, some people could actually experience concentrations above the threshold and could be at excess risk. The flattening of a nonlinear concentration-response curve by measurement error is a well known phenomenon detectable by standard methods (Cakmak et al., 1999).

(e) Whether effect size estimates and their standard errors are really significantly different among models is a question not usually addressed quantitatively. Some authors report various goodness-of-fit criteria such as AIC, BIC, deviance, or over-dispersion index (e.g., Chock et al., 2000; Clyde et al., 2000), but this is not yet so wide-spread as to assist in analyses of secondary data for use in this document. Variance inflation may also happen with a correctly specified model when both pollutants are causal and highly correlated, compared to a model in which only one pollutant is causal and the noncausal pollutant is omitted. The situation where the variance or standard error decreases when an additional variable is added (variance deflation) suggests that the model with the covariate is more nearly correct and that the standard errors of all covariates may decrease. Statistical significance is a concept of limited usefulness in assessing or comparing results of many models from the same data set. Still, it is a familiar criterion, and one addressed here by using a nominal two-sided 5% significance level for all tests and 95% confidence intervals for all estimates, acknowledging their limitations. There is at present no consensus on what clearly constitutes "stability" of a model estimate effect size, e.g., effect sizes that differ by no more than 20% (or some other arbitrary number) from the single-pollutant models. Simple comparison of the overlap of the confidence intervals of the models is not used because the model estimates use the same data, and the confidence intervals for effect size in different models are more-or-less correlated. In analyses with missing days of data for different pollutants, comparisons must also incorporate differences in sample size or degrees of freedom.

In any case, statistical comparisons alone cannot fully resolve questions about either conceptual or statistical issues in confounding via considerations about statistical significance. If the model is mis-specified in any of the numerous ways described above, then effect size estimates and/or their estimated standard errors are likely biased.

The most commonly used approach to diagnose potential confounding is fitting multipollutant models and evaluating the stability of the estimated particle effect sizes against inclusion of co-pollutants. If an additional covariate is added to a baseline model (e.g., with PM alone) and the model predicts the outcome better with the covariate, then the reduction in variance (or deviance for generalized linear or additive models [GLM or GAM]) outweighs the loss of degrees of freedom for variability. Although not always true, it is reasonable to expect a decrease in the estimated asymptotic standard error of the effect size estimate ("variance deflation"), but improved goodness-of-fit may not reduce the standard errors of all parameters in equal proportion because introducing the new covariate modifies the covariate variance-covariance matrix. The weighted inverse covariance matrix provides an exact estimate for standard errors in ordinary linear regression models, and approximately so in GLM or GAM. The effects on other parameter estimates are rarely reported.

"Variance inflation" may occur under several circumstances, including "under-fitting" and "mis-fitting" in which a truly predictive covariate is omitted or replaced by a correlated proxy, and "over-fitting" in which a nonpredictive covariate correlated with the PM metric is also included in the model. The potential for over-fitting can be diagnosed by evaluating the eigenvalues of the correlation matrix of the predictors, with very small values identifying near-colinearity. However, the complete covariate correlation matrix is almost never reported, including all weather variables and nonlinear functions entered separately as covariates. Nonetheless, even a correlation matrix among all pollutants would be informative. Furthermore, composite correlation matrices in multicity studies may conceal important differences among the correlation matrices.

Multipollutant models may be sensitive to multicolinearity (high correlations among particle and gaseous pollutant concentrations) and to so-called "measurement errors", possibly associated with spatial variability. Combining multipollutant models across several cities may

not improve the precision of the mean combined PM effect-size estimate, if the differences among the cities are as large or larger in the multipollutant models as in the single-pollutant PM model. Second-stage regressions have been useful in identifying effect modifiers in the NMMAPS and APHEA 2 studies, but may not, in general, provide a solution to the problem in that confounding of effects is a within-city phenomenon.

Three promising alternative approaches versus simple reliance on multipollutant modeling have begun to be used to evaluate more fully the likelihood that exposures to gaseous co-pollutants can account for the ambient PM-health effects associations now having been reported in numerous published epidemiology studies. The first is based on evaluation of personal exposures to particles and gases, as was done for three panels of participants in Baltimore, MD (Sarnat et al., 2000, 2001). This study (discussed in detail in Chapter 5) directly addressed the premise that if individuals are not exposed to a potential confounder, then there is a lower probability that the potential confounder contributes to the observed effect. The Sarnat results support the conclusion that personal exposure to sulfates, fine particles, and PM_{10} are well correlated with their ambient concentrations measured at corresponding fixed sites, but the correlations are much lower for $PM_{10-2.5}$, O_3, and NO_2. There is, however, a great deal of variation for one of three two-week panels from one season to the next. The sample size was small (n = 56), but marginally significant associations were detected between personal and ambient NO_2 for the personal-ambient correlation but was much lower than for particles. There were, however, some residences in which personal and ambient NO_2 were highly correlated. This has been seen when residences are close to a major road, which was the case for several members in each of the three studied cohorts (i.e., healthy elderly adults, adults with COPD, and children 9 to 13 years).

Another promising approach is the use of principal component or factor analysis to determine which combinations of gaseous criteria pollutants and PM size fractions or chemical constituents together cannot be easily disentangled, and which pollutants are substantially independent of the linear combinations of the others. For example, the source-oriented factor analysis study of Mar et al. (2000) produced evidence suggesting independent effects of regional

sulfate, motor vehicle-related particles, particles from vegetive burning, and PM_{10-25} for cardiovascular mortality in Phoenix (as discussed in Section 8.2.2.4.3).

There are also now available some recent examples of a third promising approach, i.e., the use of so-called "intervention studies." Interesting evidence for ambient PM effects are beginning to emerge from some such studies, which relate changes (decreases in health risk outcomes) to decreases in airborne particles due to deliberate reductions in pollutant emissions from sources that ordinarily contribute to elevated ambient PM levels in a given locale. As described before (Section 8.2.3.4), some health outcome changes occurred in some studies in the presence of low levels of ambient gaseous co-pollutants or little change in at least some of the co-pollutants in the presence of reduced concentrations of PM mass or constituents.

8.4.3.3 Multipollutant Modeling Outcomes

As stated in the introduction to this chapter, ambient PM exists as a component of a complex air pollution mixture that includes other criteria pollutants, as well as many other airborne contaminants that may convey risks to health. Particulate matter is of both primary and secondary origin, and two of the gaseous criteria pollutants (sulfur dioxide and nitrogen dioxide) contribute to the formation of secondary particles. Because of shared sources, concentrations of ambient PM, SO_2, and NO_2 may be correlated to a moderate degree in urban areas. Generally, concentrations of PM and other monitored pollutants are imperfect measures of personal exposures and the extent of measurement error likely varies among the pollutants and also among population subgroups. In interpreting the findings of multipollutant models, there are several alternative explanations for observed associations that need to be considered based on the above points, as follows:

- An effect estimated for PM reflects a "true effect" of particulate matter (causal interpretation).
- An effect estimated for PM reflects the total effect of the overall air pollution mixture (PM is an indicator of mixture toxicity).
- An effect estimated for PM reflects confounding (at least to a degree) by another pollutant (PM effect is confounded).

- An effect estimated for PM may be modified by levels of other pollutants (there is effect modification).
- An effect estimated for PM may be an underestimate of the true effect because of the inclusion in a model of other criteria air pollutants (e.g., SO_2, NO_2) which are contributors to the PM levels observed. This latter effect can be interpreted as the estimated effect of PM on health not mediated by contributions to PM.

As also stated previously, multipollutant modeling has been one commonly-used method employed for assessing potential confounding by co-pollutants. Figures 8-16 through 8-19 present results derived from multipollutant models in studies that either did not use GAM originally or were reanalyzed using GLM.

As shown in Figure 8-16, the single-pollutant PM effect size estimates for total mortality (with PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$) in most of the studies did not change much across the various individual co-pollutants and combinations of co-pollutants as they were added into multipollutant models, e.g., in the multicity studies by Dominici et al. (2003b) and Schwartz (2003b) or the single-city studies by Ito (2003), Fairley (2003), and Morgan et al. (1998). One notable exception is the study by Moolgavkar (2003) in Los Angeles Co., in which the PM effect estimates were substantially reduced with the inclusion of CO in the model. On the other hand, in the study in Pittsburgh by Chock et al. (2000), the PM_{10} effect estimates remained little changed or were somewhat increased with the inclusion of CO and the other co-pollutants. For cardiovascular mortality and morbidity (Figure 8-17), in many cases the PM effect estimates were again little changed when various individual and combinations of co-pollutants were added to the models, although the pattern seems to be somewhat more variable for cardiovascular-related effects than for total mortality. For example, in Toronto, PM effects estimates for cardiovascular hospital admissions for all three PM indicators were appreciably reduced with the inclusion of NO_2, but not CO; the inclusion of all four gaseous co-pollutants showed the most substantial reductions in the PM effect estimates for each indicator (Burnett et al., 1997a). Ito (2003) presents results for cardiovascular mortality and hospital admissions in Detroit and, in most cases, PM effect estimates are similar in models with and without co-pollutants; some variability is seen across these results, however, with the cardiovascular mortality effect estimates showing a decrease with the inclusion of either CO or NO_2, especially

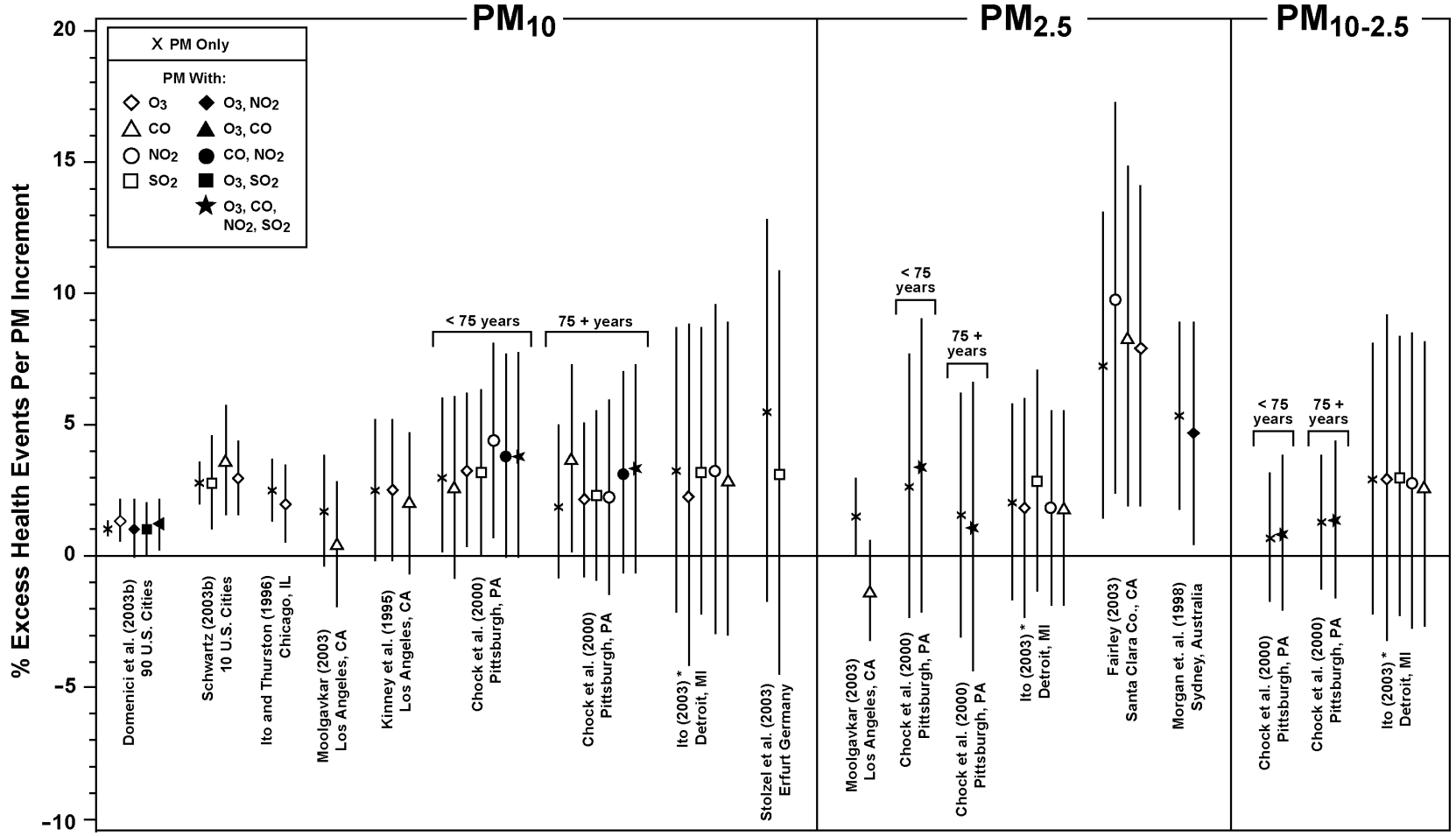

Figure 8-16. Excess risk estimates for total nonaccidental mortality in single-pollutant (PM only) and multipollutant models. PM increments: 50 µg/m^3 for PM_{10} and 25 µg/m^3 for $PM_{2.5}$ and $PM_{10-2.5}$. Results presented from time-series studies that did not use GAM or were reanalyzed using GLM.

*Estimates for multipollutant models in Ito (2003) obtained from the author via personal communication (November, 2003).

8-248

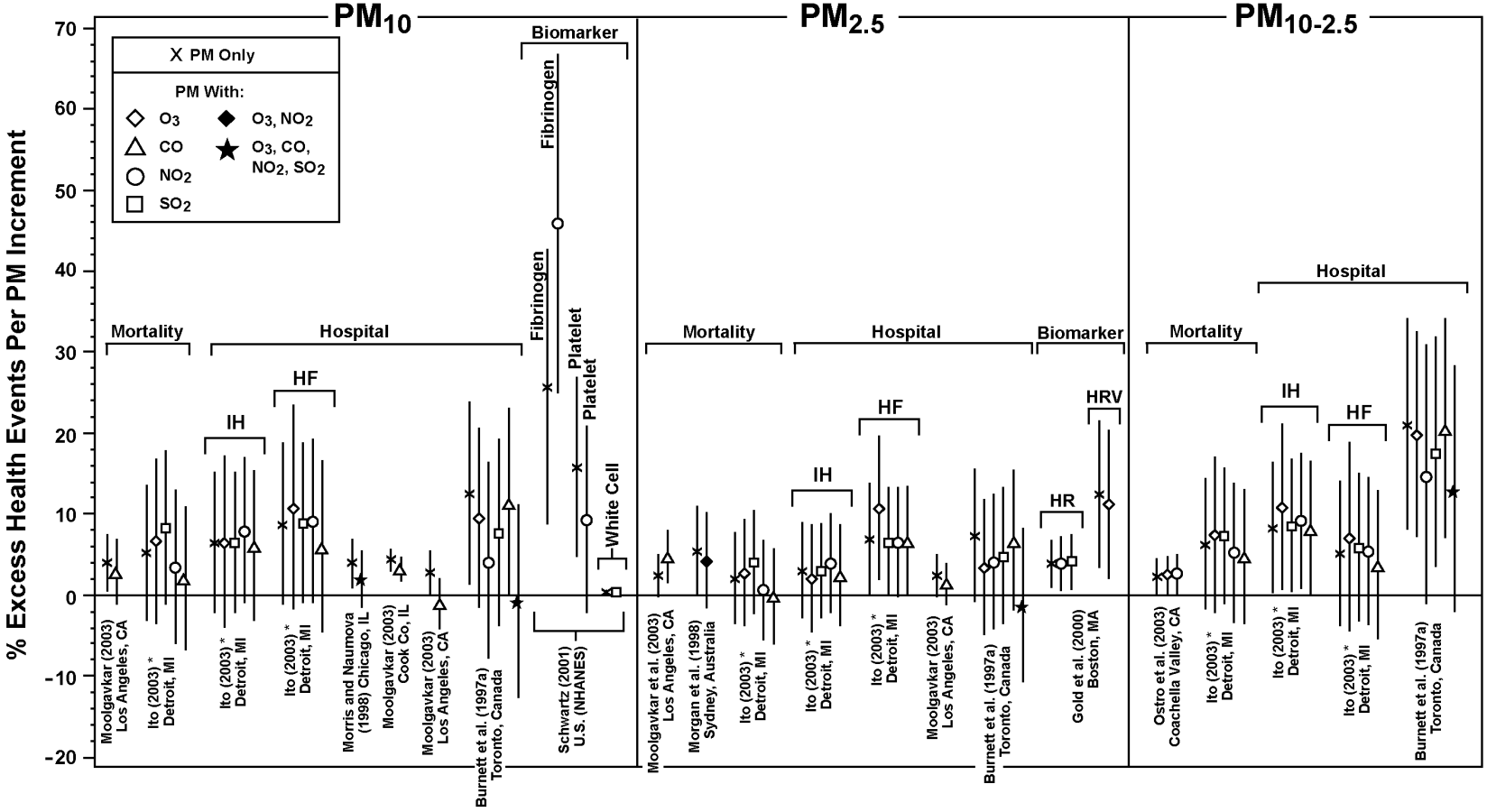

Figure 8-17. Excess risk estimates for cardiovascular-related effects, including mortality, hospital admissions, and changes in biomarkers (e.g., increases in blood parameters or decreases in heart rate variability measures) in single-pollutant (PM only) and multipollutant models. PM increments: 50 µg/m^3 for PM_{10} and 25 µg/m^3 for $PM_{2.5}$ and $PM_{10-2.5}$. Results presented from time-series studies that did not use GAM or were reanalyzed using GLM. IH = ischemic heart disease; HF = heart failure; HR = heart rate; HRV = heart rate variability.

*Estimates for multipollutant models in Ito (2003) obtained from the author via personal communication (November, 2003).

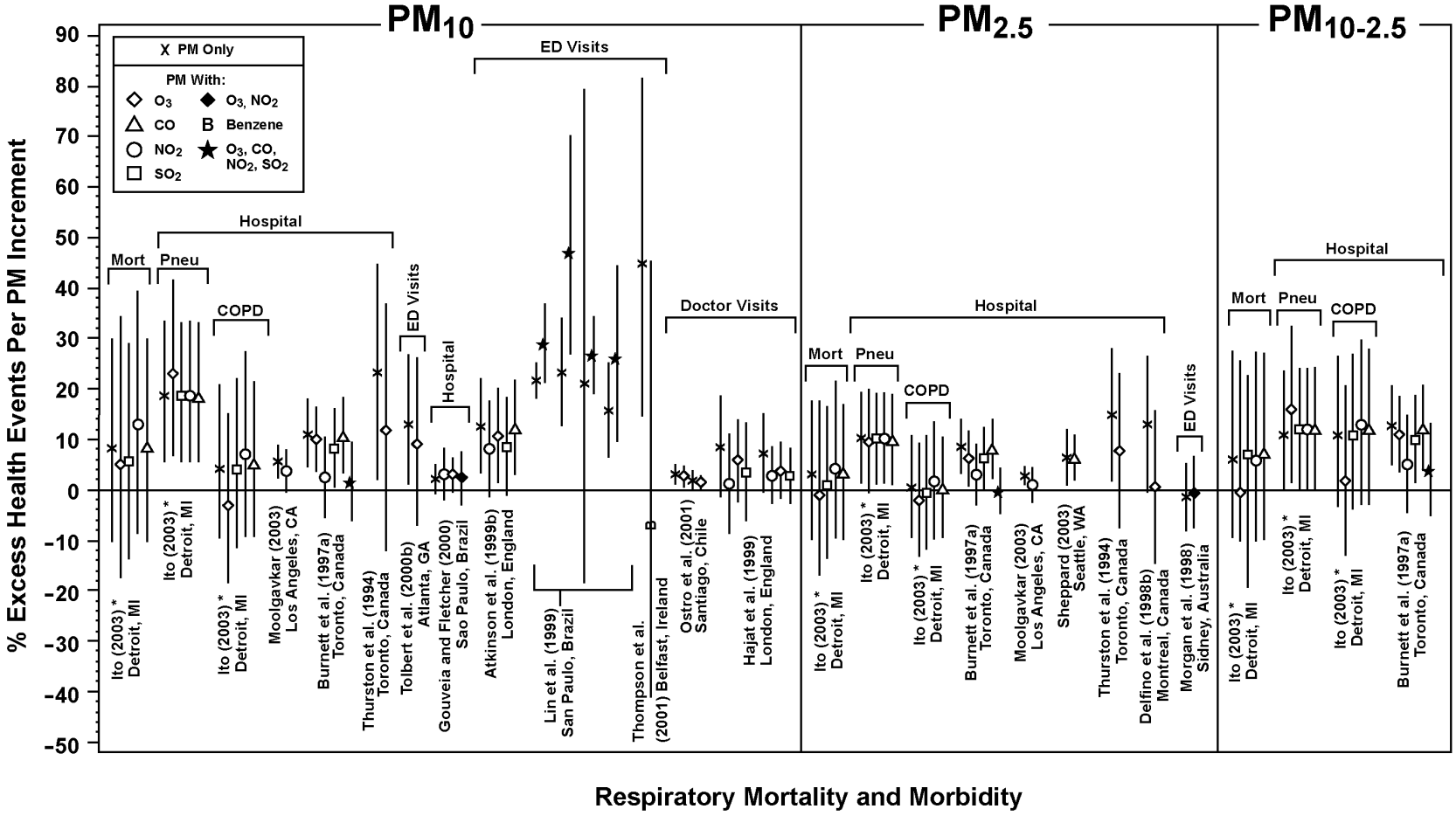

Figure 8-18. Excess risk estimates for respiratory-related effects, including mortality, hospital admissions and medical visits in single-pollutant (PM only) and multipollutant models. PM increments: 50 µg/m^3 for PM_{10} and 25 µg/m^3 for $PM_{2.5}$ and $PM_{10-2.5}$. Results presented from time-series studies that did not use GAM or were reanalyzed using GLM. Mort = mortality; Pneu = pneumonia; COPD = chronic obstructive pulmonary disease.

*Estimates for multipollutant models in Ito (2003) obtained from the author via personal communication (November, 2003).

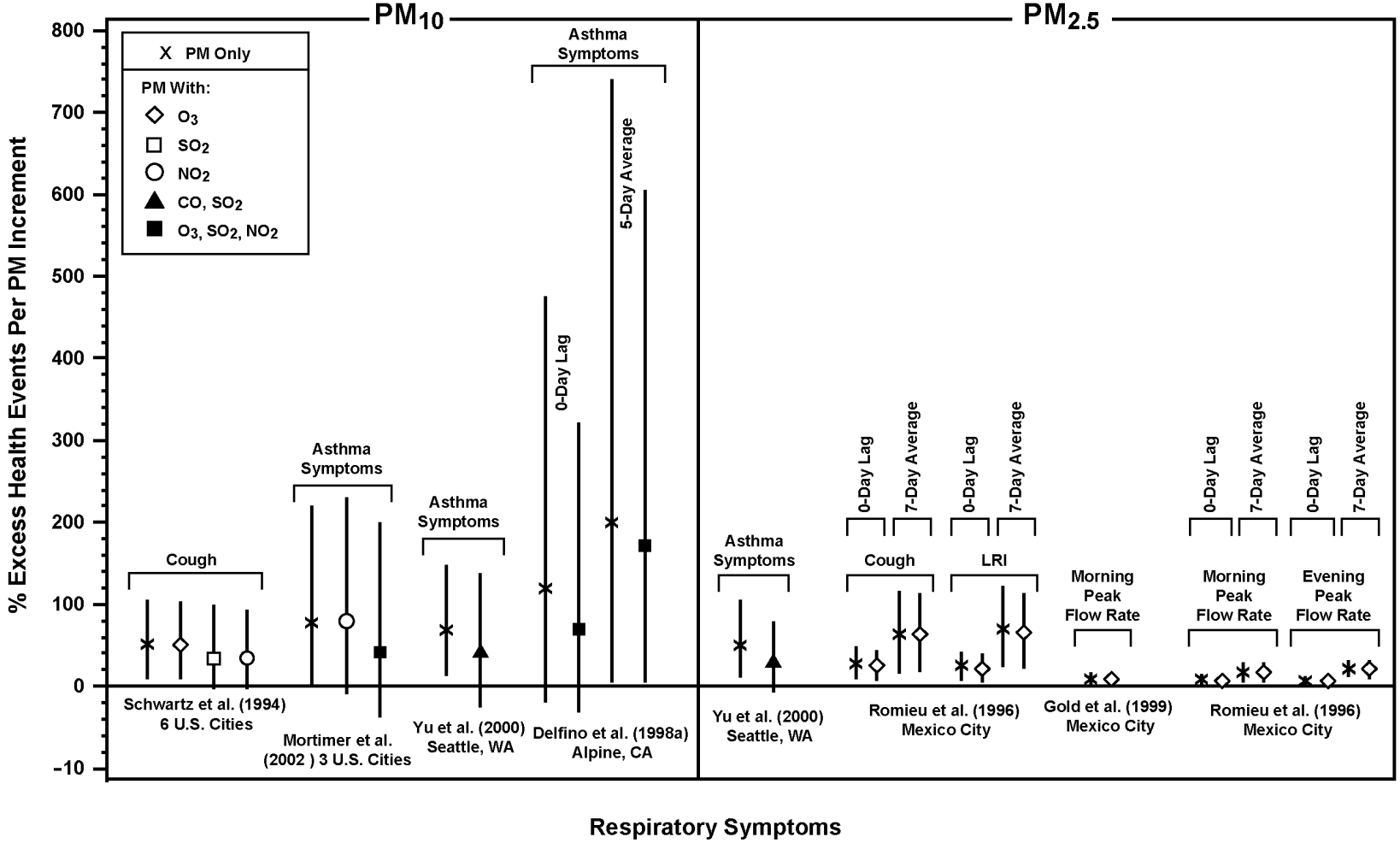

Figure 8-19. Excess risk estimates for increases in respiratory symptoms or decreases in lung function measures in single-pollutant (PM only) and multipollutant models. PM increments: 50 µg/m^3 for PM_{10} and 25 µg/m^3 for $PM_{2.5}$ and $PM_{10-2.5}$. Results presented from time-series studies that did not use GAM or were reanalyzed using GLM.

for PM_{10}. In Moolgavkar (2003), the inclusion of CO resulted in variable reductions in the PM_{10} effect estimates for cardiovascular mortality (L.A. Co.) and hospital admissions (Cook Co.), although the PM_{10} estimate for hospital admissions in Cook County remained significant.

As held for cardiovascular-related effects, the PM effect estimates for respiratory-related mortality and morbidity effects also did not show much change in many cases when various individual and combinations of co-pollutants were added to the models (Figure 8-18). However, for some endpoints, PM effect estimates are changed substantially with the addition of specific co-pollutants, most notably with O_3 or NO_2. For example, in the Toronto study by Burnett et al.(1997a), PM effect estimates for respiratory hospital admissions for all three PM indicators are appreciably reduced with the inclusion of NO_2, but not O_3; and an even larger reduction was seen with the inclusion of all four gaseous co-pollutants, as was seen in this study for cardiovascular hospital admissions. Other Canadian studies of respiratory hospital admissions or medical visits show appreciable reductions in PM_{10} and/or $PM_{2.5}$ effects estimates with the inclusion of O_3 (Thurston et al., 1994; Delfino et al., 1998b). In Detroit (Ito, 2003), the COPD hospital admissions effect estimates for PM_{10} and $PM_{10-2.5}$ were reduced in models with O_3, as was the respiratory mortality effect estimate for $PM_{10-2.5}$; whereas the PM effect estimates for pneumonia hospital admissions were either unchanged or somewhat increased for all three indicators. As for results of studies on respiratory symptoms and lung function changes (Figure 8-19), the PM effect estimates were generally robust to adjustment for O_3, though somewhat reduced in a study conducted in Alpine, CA (Delfino et al., 1998b). Effect estimates for asthma symptoms were also somewhat reduced in models that included both CO and SO_2 in Seattle (Yu et al., 2000) and in models that included O_3, SO_2, and NO_2 in a 3-city study by Mortimer et al. (2002).

In addition to the above studies, a number of others only qualitatively reported results for multipollutant models, but did not provide quantitative results and are thus not included in Figures 8-16 through 8-19. From this group of studies, some reported that PM effect estimates remained significant with adjustment for gaseous co-pollutants (e.g., Ostro et al., 2003; Cifuentes et al., 2000; Sunyer and Basagaña, 2001; Lipsett et al., 1997; Desqueyroux et al., 2002), while others reported more robust associations with gaseous pollutants (e.g., Lipfert et al.,

2000a; Stieb et al., 2000; Peters et al., 2000a). Beyond the quantitative results presented above, Moolgavkar (2003) also describes additional results of multipollutant models in which PM effects may or may not be robust to the inclusion of gaseous co-pollutants, depending on the specific lag and co-pollutants used. For example, in Cook County, for a 0-day lag, the PM_{10} coefficient for total mortality remained robust and statistically significant while coefficients for each of the gases were attenuated and became insignificant, whereas at a 1-day lag, the PM_{10} coefficient was attenuated and became insignificant, but coefficients for each of the gases were robust and remained statistically significant. In some other studies, reductions in PM effect estimates were reported with adjustment for some gaseous pollutants for some, but not all, endpoints studied (e.g., Kwon et al., 2001; Prescott et al., 1998). Other authors report that it is difficult to distinguish among effects of closely correlated pollutants (e.g., Linn et al., 2000, for CO, NO_2 and PM_{10}; Atkinson et al., 1999a, for SO_2, NO_2 and PM_{10}; Pope et al., 1999a, for CO and PM_{10}).

For many of the studies discussed above, PM and the gaseous co-pollutants are highly correlated, especially PM with CO, SO_2 and NO_2; and it is generally the case that where PM effect estimates were reduced in size with the inclusion of these co-pollutants, the pollutants were also highly correlated. Among the studies conducted in the United States, O_3 was positively correlated with the PM indices in Detroit (Ito 2003), Atlanta (Tolbert et al., 2000b) and Cook County, IL (Moolgavkar, 2003), where in some cases PM effects were reduced with the inclusion of O_3. In other locations, such as Santa Clara County, CA (Fairley, 2003) and Boston (Peters et al., 2000a),O_3 was not correlated with PM and PM effect estimates were not reported to change in multipollutant models with O_3. In contrast with many other U.S. areas, CO and NO_2 were not highly correlated with PM indices in Coachella Valley, CA (Ostro et al., 2003), and the PM effects estimates for there were reported to be robust to inclusion of gaseous pollutants. It should also be noted that, in a number of the studies where PM was highly correlated with the gaseous pollutants, the PM effect estimates were not affected by inclusion of the gaseous co-pollutants in the models.

Overall, then, a number of the recent studies have reported PM effect estimates that are robust to adjustment for gaseous co-pollutants and, in a number of studies, independent effects

of the gaseous pollutants were also found. There are also a number of studies showing generally independent effects of PM but, for certain health outcomes and co-pollutants, the PM effect estimate is reduced. For example, in analyses of mortality and hospital admissions data in Detroit, the authors concluded "...the coefficients of PM mass indices often remain significant in two-pollutant models, but can be reduced, especially by O_3; and gaseous pollutants also are associated with mortality and morbidity outcomes, but cause specificity of associations has not been consistent."(Lippmann et al. 2000, p. 33; reanalyzed in Ito, 2003). However, some other authors have concluded that PM effects were not robust to adjustment for gaseous co-pollutants. One notable example is the analyses of mortality and hospital admissions data in Cook and Los Angeles Counties, where the author concluded ". . . in Los Angeles (with the exception of COPD admissions with which NO_2 appeared to show the most robust association) it is clear that CO was the best single index of air pollution associations with health endpoints, far better than the mass concentration of either PM_{10} or $PM_{2.5}$. In Cook County the results were not so clear cut. However, any one of the gases was at least as good an index of air pollution effects on human health as PM_{10}" (Moolgavkar, 2003, p. 198).

In many of these studies, PM with and without added components of gases thusly appears to be a key putative agent. However, care must be exercised in interpreting such results, taking into account what is known about the toxicology and clinical studies of the gases. It is often clear that these gases, at concentrations present or given the nature of the effects, do not carry sufficient biologic plausibility to substantially affect the results seen. For example, SO_2 is mostly absorbed in upper airways under normal breathing conditions and, although it might affect airway neural reflexes to contribute to asthma exacerbation at typical U.S. ambient levels, it is not likely to exert sufficient effects on COPD or CVD to contribute to excess morbidity and mortality. Further, because of frequent lack of correlation, separating the effects of PM from O_3 seems justified on the basis of simply adjusting one for the other. The same may not be said for some of the other major gaseous pollutants. It is also the case that the most consistent findings from amidst the diversity of multipollutant evaluation results for different sites is that the PM signal most often comes through most clearly.

8.4.3.4 Bioaerosols as Possible Confounders or Effect Modifiers in PM Epidemiologic Studies

In addition to possible confounding or effect modification by gaseous co-pollutants, possible confounding or effect modification by bioaerosols needs to be considered in evaluating ambient PM epidemiologic findings. As discussed in Chapter 7, various airborne bioaerosols contain allergens that can contribute to upper (oronasal) respiratory tract irritation (hay fever-type allergic reactions) and/or to more serious lower respiratory tract effects (e.g., acute inflammation, bronchoconstriction, exacerbation of asthma attack frequency or intensity, etc.).

A number of epidemiology studies have reported significant associations between ambient air concentrations of fungal spores and asthma symptoms, hospital admissions, or medical visits for respiratory diseases (Neas et al., 1996; Delfino et al., 1996; Delfino et al., 1998a; Delfino et al., 2002; Ostro et al., 2001; Stieb et al., 2000; Lewis et al., 2000), although not all found statistically significant associations (e.g., Tolbert et al., 2000b). Significant associations between pollen count and respiratory health outcomes have also been reported (Moolgavkar et al., 2000; Stieb et al., 2000; Lewis et al., 2000), but a number of other studies that evaluated such effects did not find significant associations with pollen (Thurston et al., 1997; Delfino et al., 1998a; Delfino et al., 2002; Ostro et al., 2001; Tolbert et al., 2000b; Anderson et al.,1998). Where the studies have included tests for interaction or potential confounding between aeroallergens and nonbiological air pollutants for these health responses, all studies have indicated that the aeroallergen and air pollutant effects were independent, or the authors have concluded that effects were independent because the aeroallergens and pollutants were poorly correlated (Neas et al., 1996; Delfino et al., 1996; Delfino et al., 1997b; Delfino et al., 1998a; Delfino et al., 2002; Stieb et al., 2000; Moolgavkar et al., 2000; Anderson et al., 1998; Lewis et al., 2000).

It is important to emphasize, as discussed in Chapters 3 and 7, that ambient air levels of bioaerosol components (e.g., fungi, fungal spores, pollen, cytoplasmic fragments of pollen, endotoxin, or glucan components of bacteria cell walls, etc.) are all seasonally elevated during warmer, more humid months (e.g., April / May through August / September), but are very low during colder fall / winter months (October / November through March) in the U.S.

8.4.3.5 Adjustments for Meteorological Variables

As was noted earlier in Section 8.2.2, it was thought at the time of completion of the 1996 PM AQCD that issues related to model specifications used to control for weather effects in daily time-series analyses of ambient PM relationships to mortality/morbidity had largely been resolved. However, as also noted earlier, reanalyses of PM studies to address the GAM convergence criteria issue led to reexamination of the sensitivity of PM risk estimates to different model specifications and the consequent reemergence of model specification for control of weather effects as an important issue in interpreting PM epidemiologic analyses. The reanalyses results highlighted the sensitivity of modeling outcomes to kinds and numbers of weather-related variables included in base models and, also, the sensitivity of results to varying degrees of freedom allotted for smoothing of weather and temporal trends.

Putting the issue of controlling for weather effects into a historical perspective, the 1996 PM AQCD noted that various approaches had previously been used to evaluate potential contributions by weather to mortality or morbidity effects attributed in different studies to ambient PM exposures. It noted, as one example, one approach that simply qualitatively compared PM risk estimates derived from cities differing in typical climatic conditions and classified as "warm" or "cold" based on long-term mean temperatures — an approach that may be open to a number of questions, e.g., the fact that the "hot/cold" dichotomy does not adequately consider cities with moderate climates as part of a broader continuum representative of the actual range of weather conditions encountered in the United States (as is the case, say, for San Francisco versus New Orleans or Chicago) or the fact that long-term mean temperatures over several months are not likely an adequate control for more acute weather changes that are more likely to affect mortality counts on a daily basis. Other approaches included (a) stratifying mortality events in relation to one or another weather variable and discarding of the most extreme days (e.g., the highest X % of mean daily temperature days) from analyses of PM effects; (b) use of dummy variables that classify days as "hot" or "humid" or "hot/humid" days; or (c) use of rank-ordered temperatures, or mean temperature for groupings of days, etc. — none of which, it was noted in the PM AQCD, may provide adequate details to detect actual weather-mortality relationships.

The above approaches, to some extent, share certain features that attempt in common to adjust for the generally recognized nonlinearity of weather influences in mortality/morbidity, especially with regard to control for temperature effects. Results of various studies noted in the PM AQCD from the late 1980's and early 1990's provide illustrative examples of outcomes likely reflective of such nonlinearity of temperature-mortality associations. On the one hand, Ito et al. (1993) found mortality in London to be associated with BS and aerosol acidity levels and to a much lesser extent to be affected by weather (perhaps not surprising, given London's relatively moderate marine clime with relatively infrequent temperature extremes). On the other hand, several other investigators were noted in the 1996 PM AQCD as finding much more marked influences of weather in locations experiencing temperature extremes; and some reported findings indicative of synergistic effects of weather and ambient PM pollution and/or suggestive of weather exerting notably stronger effects on mortality than pollution. Ramlow and Kuller (1990), for example, found daily mortality to be more strongly related to prior day average temperatures than any pollution measure in Pittsburgh (Allegheny Co.) PA, and Wyzga and Lipfert (1996) reported on apparent synergistic relationship between weather and air pollution, in that days exceeding 85 °F appeared to contribute most to observed TSP-mortality relationships in Philadelphia, PA. Kunst et al. (1993) and Machenbach et al. (1993) found temperature extremes in summer and winter to be primarily determinants of mortality in two Netherlands studies, with the relationship between temperature and mortality being nonlinear and characterized by a U-shaped temperature curve with minimum mortality rates seen between 10 to 15 °C.

The 1996 PM AQCD went on to note further the advent of some relatively new approaches to statistical evaluation of potential weather influences in time-series analyses of ambient PM effects on mortality or morbidity. One approach, typified by Kalkstein (1991) and Kalkstein et al. (1994), it was noted, proposes that the meteorology of a given locale is defined by discrete, identifiable situations that represent frequency modes for combinations of weather elements. Meteorological delineation of synoptic weather patterns or categories that recognize the existence of such modes can be used to control for weather in statistical analyses. This view basically holds that the use of mean weather elements (e.g., mean daily temperature) do not

permit adequate evaluation of, or control for, daily weather extremes. Also, to the extent that consideration of weather in most PM/mortality studies focuses almost entirely on thermal (temperature) and less frequently on moisture (humidity) variables, then PM effect models may encounter potential weather control problems for some cities affected by certain meteorological phenomena (e.g., stormy situations associated with mid-latitude cyclones) that are not associated with thermal extremes and yet can be very important contributors to acute mortality (Kalkstein et al., 1994). These are rarely controlled for in PM/mortality studies, as they cannot be identified on the basis of temperature and humidity.

Another approach is one that views adjustment for weather-related variables as being needed to the extent that any empirical adjustment for such variables provides an adequate basis for removing potential confounding of excess mortality with PM or other air pollutants. The 1996 PM AQCD noted that one of the most completely empirical methods for adjusting daily time series data for covariates is by use of nonparametric functions, such as LOESS smoothers, generalized splines, or GAM, as demonstrated in Schwartz (1994b, 1995, 1997b) and Schwartz and Morris (1995). These may be empirically satisfactory and provide a better fit to data than synoptic categories, but at the loss of a basis for defining "offensive" weather episodes. Application of synoptic climatological procedures to control for weather, it was noted, has the potential to compensate for these difficulties and may add further insight by defining entire sets of meteorological conditions which can lead to increases in mortality.

Offensive air masses which lead to mortality totals significantly higher than the long-term baseline have been identified for a number of U.S. cities, as reported by Kalkstein and Tan (1995). In most cases "moist tropical" air masses were deemed offensive (especially in the East), but a very oppressive "dry tropical" air mass category was often associated with the greatest increases in mortality, especially in New York, St. Louis, Philadelphia, and in southwestern cities (Kalkstein and Tan, 1995). In some cases, daily mortality totals are over 50% above the baseline (World Health Organization, 1996). Such air mass analyses support the notion that acute mortality increases only after a meteorological threshold is exceeded. This threshold is not only temperature dependent; it represents an overall meteorological situation which is highly stressful. It is noteworthy that most cities demonstrate only one or two types of

offensive air masses which possess meteorological characteristics exceeding this threshold; and specific types of oppressive weather patterns associated with increased mortality can vary from city to city and must be defined individually for a given city for use in statistical analyses of PM effects.

Detailed analysis of synoptic weather pattern effects in a given city may yield additional information on specific factors that may need to be accounted for in analyzing PM mortality effects for that city. For example, the "moist tropical" type of air mass in Philadelphia, possessing the highest daily minimum and maximum temperatures, both brought mortality increases and was also associated with the greatest standard deviation in mortality of all air masses evaluated. That is, although many days within the offensive air mass were associated with high mortality totals, a number of days showed little mortality increase. The greatest daily mortality totals during moist tropical air mass incursions occurred as part of a lengthy string of consecutive days of the air mass, especially when minimum temperatures were particularly high. This type of information may be important when controlling for weather in PM-mortality analyses.

In a PM study where stressful weather days are removed from the data base, synoptic categorization provides an efficient means to remove such days. In studies where weather is stratified based on certain meteorological elements, synoptic categorization allows for a meteorologically realistic control and may be preferable to the use of arbitrary dummy variables when identifying meteorological conditions with an elevated mortality risk.

Evaluation of different weather and time trend model specifications for quantifying PM concentration-response relationships

The study by Pope and Kalkstein (1996), as discussed in the 1996 PM AQCD, provided detailed evaluation of the effects of several substantially different approaches to modeling PM concentration-response relationships and the influence of weather variables on ambient PM effects. The 1996 PM AQCD noted that the original analyses and reanalyses of the Utah Valley data by Samet et al. (1995) used quintiles of PM_{10} as the indicator. The reanalyses reported by Pope and Kalkstein (1996) as Models 1-8 used a linear model for 5-day moving average PM_{10} and eight different weather models: (1) no adjustment; (2) indicator variables for 20 seasons

(1985 to 1990); (3) indicators for 20 seasons and indicators for quintiles of temperature and relative humidity; (4) indicators for 20 seasons and indicators for 19 synoptic weather categories; (5) linear time trend and indicators for 19 synoptic categories; (6) LOESS smooth of time (span = 10 percent of days); (7) LOESS smooths of time (span = 10 percent of days), temperature (span = 50 percent of days), and relative humidity (span = 50 percent of days); and (8) LOESS smooth of time (10 percent of days) and indicator variables for 19 synoptic categories. The results (shown in Table 12-36 of the 1996 PM AQCD and reproduced here as Table 8-39) were relatively insensitive to the form of time trend and adjustment for weather variables, with RR for total mortality for 50 $\mu g/m^3$ increments in PM_{10} varying only from ~1.058 (Model 2) to 1.112 (Model 10), all of them being statistically significant. The pulmonary mortality models were somewhat more sensitive to the form of the covariate adjustments, with RR for 50 $\mu g/m^3$ ranging from 1.132 (Model 6) to 1.221 (Model 7); Model 2 showed only a marginally significant PM_{10} coefficient, the others being significant with one-tailed (Models 3 and 4) or two-tailed tests. The cardiovascular mortality models had RR ranging from 1.076 (Models 3 and 7) to 1.116 (Model 1), with Model 3 being one-tailed significant and all other models showing a significant PM_{10} effect on cardiovascular mortality. While the authors commented that other communities may show greater sensitivity to the statistical methods for adjusting for time trend and weather, the relative lack of sensitivity of the estimated PM_{10} effect over a very wide range of models is noteworthy.

Table 8-39 also shows subset models that correspond to Models 7 and 8. Cold season models called Models 9 and 11 by Pope and Kalkstein (1996, Table 4) consist of Models 7 and 8, respectively, limited to the months of October to March. Intra-seasonal differences were adjusted for by LOESS smoothers of time, and daily weather variation either by LOESS smoothers of temperature and relative humidity (Model 9) or by indicators for synoptic categories. Total mortality was highly significant in either case (1.070 for Model 9 and 1.059 for Model 11). Pulmonary mortality was higher (1.145 for Model 9 and 1.120 for Model 11) and marginally significant. Cardiovascular mortality had a RR = 1.062 in Model 9 (not significant) but RR = 1.075 (significant) in Model 11. The corresponding Models 10 and 12 for the warm season (April-September) showed higher RR effects for total and pulmonary mortality, but the

TABLE 8-39. EFFECTS OF DIFFERENT MODELS FOR WEATHER AND TIME TRENDS ON MORTALITY IN UTAH VALLEY STUDY

Model Identity*	Time Model	Weather Model	Relative Risk for PM_{10} 50 μg/m^3		
			Total Mortality	Pulmonary Mortality	Cardiovascular Mortality
Base I	—	—	1.076 (1.044, 1.109)	1.198 (1.035, 1.386)	1.094 (1.019, 1.174)
Base II	—	—	1.083 (1.030, 1.139)	1.215 (1.049, 1.408)	1.094 (1.020, 1.174)
1	None	None	1.074 (1.032, 1.118)	1.185 (1.056, 1.331)	1.116 (1.054, 1.181)
2	20 seasons	None	1.058 (1.002, 1.118)	1.133 (0.963, 1.333)	1.081 (1.000, 1.169)
3	20 seasons	Quintile	1.062 (1.003, 1.124)	1.150 (0.972, 1.361)	1.076 (0.992, 1.167)
4	20 seasons	Synoptic	1.068 (1.009, 1.130)	1.169 (0.988, 1.382)	1.090 (1.005, 1.183)
5	Linear	Synoptic	1.068 (1.020, 1.118)	1.183 (1.032, 1.356)	1.100 (1.030, 1.175)
6	LOESS	None	1.059 (1.017, 1.102)	1.131 (1.006, 1.273)	1.085 (1.024, 1.150)
7	LOESS	LOESS	1.077 (1.028, 1.129)	1.221 (1.063, 1.402)	1.076 (1.006, 1.152)
8	LOESS	Synoptic	1.068 (1.021, 1.117)	1.166 (1.018, 1.335)	1.099 (1.029, 1.173)
9	Cold season, LOESS	LOESS	1.070 (1.015, 1.129)	1.145 (0.981, 1.337)	1.062 (0.984, 1.146)
10	Warm season, LOESS	LOESS	1.112 (0.918, 1.346)	1.529 (0.813, 2.877)	1.053 (0.789, 1.404)
11	Cold Season, LOESS	Synoptic	1.059 (1.009, 1.111)	1.120 (0.971, 1.291)	1.075 (1.003, 1.153)
12	Warm season, LOESS	Synoptic	1.091 (0.947, 1.258)	1.394 (0.794, 2.577)	1.024 (0.780, 1.343)

*Models 1 through 5 were parametric models, and models 6 through 12 were nonparametric GAM models that have not been reanalyzed.

Source: Pope and Kalkstein (1996).

effects were not statistically significant. The lower statistical significance may reflect the halving of the sample size in these data sets, since the effect size estimates must be similar to those obtained by averaging the whole-data analyses across the corresponding seasons, with cold season = fall + winter approximately, and warm season = spring + summer approximately.

Pope and Kalkstein (1996) also showed four nonparametric smooth regression plots corresponding to Models 1, 6, 7, and 8, respectively. All of the models using a nonparametric regression for daily mortality on PM_{10} were approximately linear, showing some suggestion of nonlinear structure between roughly 60 and 100 $\mu g/m^3$ PM_{10}, but in no case indicating a threshold or consistent flattening of the concentration-response curve at any PM_{10} level. The authors noted that a chi-squared test comparing each nonparametric regression model for PM_{10} with the corresponding linear model showed no statistically significant deviation from linearity.

The 1996 PM AQCD also discussed another study, by Samet et al. (1996), that compared different methods for estimating modifying effects of different weather models on the relationship of TSP and SO_2 to total mortality in Philadelphia from 1973 to 1980. The models included the original Schwartz and Dockery (1992) weather specification, a nonparametric regression model, LOESS smoothing of temperature and dewpoint, and Kalkstein's Temporal Synoptic Index (TSI) or Spatial Synoptic Category (SSC) models. The first three methods allowed the weather model to be adjusted so as to provide an optimal prediction of mortality, whereas the latter two models were based completely on external criteria and the classification of days by SSC or TSI categories was not adjusted to improve prediction of mortality. The authors concluded that ". . . the association between air quality as measured by either TSP alone, SO_2 alone, or TSP and SO_2 together, cannot be explained by replacing the original Schwartz and Dockery weather model with either a nonparametric regression, LOESS, or by synoptic categories using either Kalkstein's TSI or SSC systems. In addition, there is little evidence in the Philadelphia total mortality data to support the hypothesis that the pollution effects are modified by the type of weather conditions as measured either by TSI or by strata created from the predicted weather-induced mortalities using the Dockery and Schwartz model or the LOESS model. . . . We did not find variation of the effect of pollution across categories of weather." Their results are not shown here.

The 1996 PM AQCD noted that additional studies systematically evaluating the differential effects of PM and other pollutants by weather category would be of interest. The Philadelphia study by Samet et al. (1996) used only TSP and SO_2, whereas the Utah Valley study by Pope and Kalkstein (1996) did not look at the effects of weather as a modifier with other pollutants as well as PM_{10}. Still, based on the above two major studies extensively evaluating a number of different approaches to adjust for weather effects (including evaluations using synoptic weather patterns), it was concluded in the 1996 AQCD that significant PM-mortality associations were robust and verifiable via a variety of model specifications controlling for weather.

With the identification of GAM-related statistical issues and in view of new insights gained from reanalyses addressing those issues (as discussed in Section 8.4.2), questions arise with regard to the potential resiliency of the findings reported and conclusions drawn based on the Pope and Kalkstein (1996) and Samet et al. (1996) studies. Given the lack of reanalyses addressing the GAM issues for these studies, it is neither clear as to the extent that use of GAM strict convergence criteria or alternative models using natural or penalized splines would confirm the basic results of the nonparametric GAM analyses in those studies nor as to the magnitude of reduction in PM effect size estimates that would likely occur. Still, based on likely analogy to reanalyses results for other GAM-related studies discussed in Section 8.4.2, it would not be unreasonable to assume that similar reanalyses for the nonparametric models used in these two new studies could generate PM effect estimates reduced by up to about 50% from the originally published one. Thus, for example, the Pope and Kalkstein (1996) original estimates for total mortality could be reduced from ~6 to 11% increase in excess deaths per 50 $\mu g/m^3$ PM_{10} to as low as ~3 to 5.5%, values that comport very well with the range of results obtained for most other PM_{10} total mortality studies. On the other hand, it is less possible at this time to project likely outcomes of sensitivity analyses that would evaluate effects of markedly varying degrees of smoothing or degrees of freedom used.

As noted in Section 8.4.2, based on the reanalyses results, the HEI (2003c) Special Panel Commentary concluded that none of the reanalyzed studies' original conclusions were changed in a meaningful way by use of stricter convergence criteria. However, the sensitivity of reanalyses outcomes to the choice of weather variables, to the degree of smoothing, and to the

numbers of degrees of freedom led the panel to note that neither the appropriate degree of control for time nor appropriate specification of effects of weather in these time series has been determined. And the Panel went on to recommend that the sensitivity of these studies to a wide range of alternative degrees of smoothing and alternative specification of weather variables in time-series models should continue to be evaluated.

Reanalyses conducted by Ito (2003) of PM_{10}- mortality/hospital admissions associations in Detroit are illustrative of the sensitivity of PM effect size estimates to alternative model specifications to control for temporal trends and potential weather effects. Sensitivity analyses provided by Ito (2003) varying the extent of smoothing for temporal trends and using several different specifications for weather variables (as well as varying degrees of freedom) provided results as shown in Figures 8-20 and 8-21 for PM_{10}-mortality and PM_{10}-pneumonia admissions during 1992-1994 in Detroit. One set of analyses in each figure shows the effect of varying the extent of smoothing for temporal trends, without inclusion of any adjustments for weather variables; whereas, the other sets of curves indicate the influence of several different weather model specifications on the magnitude of the PM_{10} effect estimate. In general, effect estimates for models controlling only for temporal trends were notably higher (up to 2- to 3-fold) than those derived from models adjusting for weather effects. However, most investigators, in fact, do now make some adjustment(s) for weather. Hence, of most crucial importance are the Ito (2003) results for the weather adjustment models shown in the two figures. Ignoring the unadjusted-for-weather line, the coefficients for various weather adjustment models for total mortality (Figure 8-20) tend to converge in a range from about a factor of ~2 to ~1.5 difference as the period of temporal smoothing is shortened. Decreasing the period length for temporal smoothing may, to some extent, be washing out the effects of weather (temperature and dewpoint). The effect of temporal smoothing on air pollution effects can be judged by the decrease in the coefficients as the temporal smoothing period decreases. Coefficients for pneumonia admissions (Figure 8-21) appear to be more sensitive to adjustments for temporal trends. Overall, both temporal smoothing and control for weather can decrease the size of the PM_{10} effect estimate.

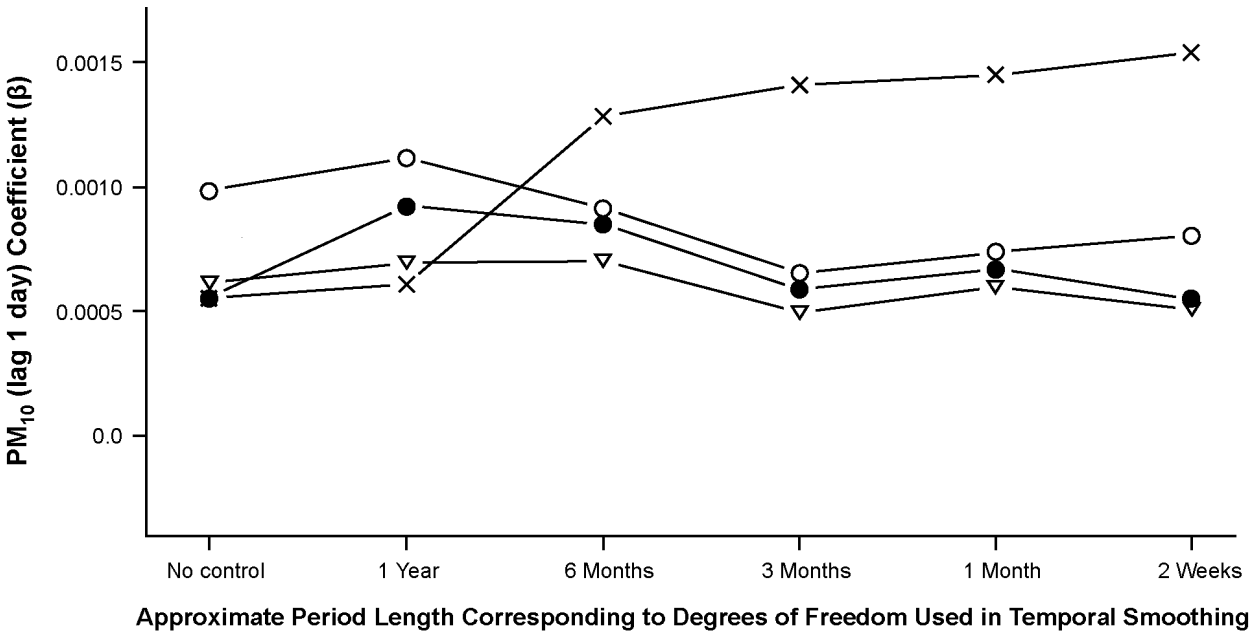

Figure 8-20. PM_{10} (lag 1 day) coefficient (β) for total mortality, for 1992-1994, as a function of alternative weather models and varying degrees of freedom for fitting temporal trends using natural splines. White circle: natural splines of same-day temperature and same-day dewpoint, both with *df* = 2; black circle: natural splines of same-day temperature (*df* = 2), the average of temperatures lagged 1 through 3 days (*df* = 2), and hot-and-humid day indicator; white triangle: natural splines of the same-day temperature (*df* = 6), the average of temperatures lagged 1 through 3 days (*df* = 6), same-day dewpoint (*df* = 3), and the average of dewpoints lagged 1 through 3 days (*df* = 3); × : no adjustment for weather.

Source: Ito (2003).

Most investigators would use periods of length 1 to 3 months for temporal smoothing. Using such periods, the agreement between the coefficients remained within about 50%, except that there is more variability between the periods of the temporal smoothing for hospital admissions. Ito, in a personal communication to EPA, indicated that the degree of temporal smoothing should depend on the size of the population. That is, for large cities or large multicity studies, more adjustment is likely warranted; but, for smaller cities, statistical power to detect the PM_{10} effect can be greatly reduced by over-adjustment for temporal effects. Considering the unadjusted-for-weather results, over-adjusting for temporal effects may be allowing this curve to

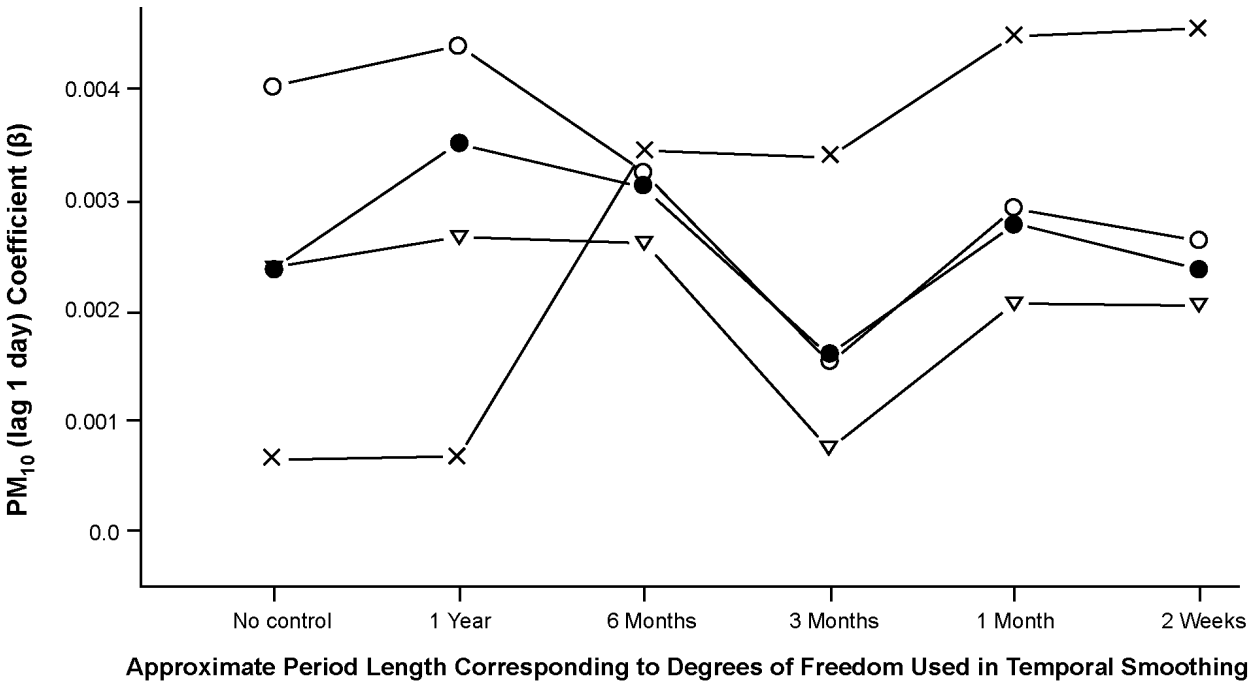

Figure 8-21. PM_{10} (lag 1 day) coefficient (β) for hospital admissions for pneumonia among the elderly, for 1992-1994, as a function of alternative weather models and varying degrees of freedom for fitting temporal trends using natural splines. White circle: natural splines of same-day temperature and same-day dewpoint, both with *df* = 2; black circle: natural splines of same-day temperature (*df* = 2), the average of temperatures lagged 1 through 3 days (*df* = 2); white triangle: natural splines of the same-day temperature (*df* = 6), the average of temperatures lagged 1 through 3 days (*df* = 6), same-day dewpoint (*df* = 3), and the average of dewpoints lagged 1 through 3 days (*df* = 3); × : no adjustment for weather.

Source: Ito (2003).

increase as more weather effects become negatively, rather than positively, correlated with PM_{10} values. This conclusion may apply only to Detroit. There, mortality/pneumonia are higher in winter and PM_{10} tends to be higher in summer due to summer sulfate in that region. So, adjusting for seasonal trends removes the opposing cycles and leaves the positive PM_{10}/mortality associations.

Some investigators (e.g., Schwartz) note that judgment on the part of the investigator is required to decide the appropriate amount of smoothing for weather and temporal effects and

that case-crossover analyses can likely be applied with less judgment considerations. However, case-crossover can be very sensitive to the choice of control periods (e.g., 7 or 14 days before and after the case period). So, there are also judgment considerations in applying that method as well. Still, future use of the case-crossover approach may add information to supplement outcomes from PM time series analyses.

Several studies published in recent years since the 1996 PM AQCD and not discussed elsewhere in this chapter provide interesting new information bearing on weather-related effects that should likely be of value in controlling for weather effects in future PM epidemiologic analyses. First, the study by Smoyer et al (2000a) of summer weather effects on mortality among the elderly ($\geq$ 64 yrs old) showed marked increases in mortality among the elderly over a 17-year period in five Southern Ontario metropolitan areas (Toronto, London, Windsor, Hamilton, Kitchner-Waterloo-Cambridge) on heat-stress days defined as those with an "apparent temperature" (heat index) above 32 °C. The study illustrates the likely need to consider combined effects of temperature and humidity/dewpoint rather than evaluating independent effects of such variables in controlling for weather effects. Also, relative vulnerability to heat-related weather effects may be increasing for U.S. populations with the aging of disproportionate numbers of individuals ("baby boomers") into older middle age groups. This may complicate future epidemiologic/statistical attempts at disentangling potential PM effects from those of weather.

Another paper by Smoyer et al. (2000b) evaluated the effects of "offensive weather events" and air pollution (TSP, O_3) in Birmingham, AL and Philadelphia, PA and found that in both cities offensive weather events had a higher impact on mortality than did high concentrations of TSP or O_3. The authors reported that the highest mortality levels occur when the hottest, but not necessarily the most polluted, air mass occurs over each of the two cities. Still, lesser increases in mortality were observed to be associated with TSP in Philadelphia during non-offensive weather situations, and neither TSP nor O_3 seemed to have any add-on effect to weather-related mortality. In contrast, potential interactive effects seem to be implied by the Birmingham results. That is, the authors noted that although Birmingham's high-mortality (offensive) air mass is not the most polluted, offensive air mass days with high pollutant concentrations still

exhibit higher mean mortality than offensive air mass days with low pollution concentrations. Also different from the Philadelphia results was the lack of associations in Birmingham between air pollution levels and mortality on non-offensive air mass days. These results appear to reinforce the need for city-specific evaluation of weather-related effects; and, they also hint at potential additive or synergistic effects of weather and air pollution, i.e., the joint occurrence of elevations of TSP and/or O_3 together with high heat-index conditions may increase mortality over levels than would have been associated with each factor alone.

Two other studies by Braga et al. (2001b, 2002) provide additional interesting results concerning the time course of weather-related deaths of possible importance for development of model specifications for control of weather effects in PM epidemiology studies. Braga et al. (2001b) modeled daily death counts in a Poisson regression, examining effects of temperature and humidity out to lags of 3 weeks and controlling for other covariables (i.e., season, day of week, barometric pressure) using nonparametric smoothing in GLM analyses for 12 U.S. cities that represented a wide range of typical climatic conditions and geographic regions (e.g., Northeast, Midwest, Northwest, South, etc.). Based on distributed lag modeling, the authors noted that both high and low temperatures were associated with increased total deaths in "cold" cities; and that the effects of cold temperatures persisted for days, whereas high-temperature effects were restricted to the day of death or to the immediately preceding day (likely reflecting harvesting by high temperatures, as also suggested by other patterns of results). In hot cities, neither hot nor cold temperatures per se had much effect on mortality; however, the effect of hot temperature varied with the range of summer temperature variations and the use of air conditioning. The authors noted that such dissimilarities between cities indicate that analyses of climate change (and presumably, other weather-related effects) should be taken into account when evaluating regional differences and temperature-associated harvesting.

The Braga et al. (2002) study used similar methods to evaluate weather-related effects on cause-specific (i.e., respiratory and cardiovascular) deaths in the same 12 U.S. cities. The effects and associated lag structures for both temperature and humidity were evaluated based on a distributed lag model. In cold cities, the authors noted that both low and high temperatures were associated with CVD deaths, with low-temperature effects persisting for days while high-

temperature effects were restricted to extreme temperatures on the day of death or the day before. For myocardial infarction (MI) deaths, hot-day effects were twice those of cold-day effects; but hot day effects were five times lower than cold days for all CVD causes. Harvesting effects on hot days were suggested by temporary deficits in numbers of deaths a few days later (not seen after days with cold temperature deaths). In hot cities, neither hot nor cold temperature days appeared to affect mortality counts for CVD or pneumonia deaths, but lagged effects were seen for MI or COPD deaths associated with high temperatures (lagged 4-6 and 3-4 days, respectively). For respiratory deaths, it was noted that wider variations in summer and winter temperatures were related to larger effects for hot and cold days, respectively. However, no clear patterns of results were discerned for humidity effects. Overall, these results suggest that individuals in cities (e.g., Houston, Atlanta, etc.) with generally warmer weather become adapted to such and cope better with high-temperature extremes. They also suggest potentially varying lags for different types of weather-related effects (hot versus cold) and for different cause-specific endpoints – which may be important to consider in model specifications for control of weather-related effects in future epidemiologic studies of ambient PM effects.

8.4.4 The Question of Lags

The effect of lag selection on resulting models for PM health effects is an important issue affecting overall interpretation of epidemiologic analyses. Some interesting and highly informative points related to lag selection can be discerned based on certain newly available individual study results and on several illustrative examples comparing lag-related results obtained by different investigators for analyses of PM effects in the same U.S. city.

Using simulated data with parameters similar to a Seattle $PM_{2.5}$ data series, Lumley and Sheppard (2000) showed that potential bias resulting from lag selection can be of similar size to the relative risk estimates from the measured data. The simulations included a data set where $PM_{2.5}$ was significantly associated with hospital admissions for asthma and another data set where there was no such association. The selection rule used was to choose the single-day lag (between 0 and 6 days) with the largest estimated relative risk. In the "positive control" model, where there was a known positive association, the bias associated with selecting the lag

with the largest effect size from a series of lags was negligible. However, in the analyses using simulated data where no association was present, selecting the lag with the largest effect size resulted in a positive bias. The mean bias found in this analysis of simulated data was about half the size of the effect estimate from a previous publication on associations between $PM_{2.5}$ and asthma hospital admissions (from Sheppard et al., 1999), and the authors reported that the relative risk from the previous study was at the 90th percentile of the bias distribution in this analysis. In comparisons to real data from Seattle for other years and from Portland, OR (with similar weather patterns to Seattle), similar bias issues became evident. Thus, if no association actually exists in the data, this analysis suggests that selecting the largest risk estimate from a series of lag periods can lead to potential positive bias toward finding an association.

In considering the results of models for a series of lag days, it is important to consider the pattern of results that is seen across the series of lag periods. If there is an apparent pattern of results across the different lags, (such as that seen in Figure 8-22 for results obtained by Peters et al., 2001b), then selecting the single-day lag with the largest effect from a series of positive associations is reasonable, although it is, in fact, likely to underestimate the overall effect size (since the largest single-lag day results do not fully capture the risk also distributed over adjacent or other days). The importance of considering the pattern of results is further illustrated by the study of Sheppard et al. (1999), in which the pollutant effects reported for asthma hospitalization at specific lag periods were larger than and consistent with estimates obtained for adjacent lags, thus lending support for selection of particular lag periods for reporting results. In contrast, analyses reported by Sheppard et al. (1999) for admissions for appendicitis yielded estimates from adjacent lags that changed abruptly and an overall unstable pattern was consistent with the pattern expected for a health endpoint not plausibly associated with air pollution.

In the NMMAPS analysis for mortality, a systematic approach across different data sets was used to investigate the question of lag selection. The Samet et al. (2000b) analysis, and the reanalysis by Dominici et al. (2002), for the 90 largest U.S. cities provide particularly useful information on this matter. Figure 8-23 depicts the Dominici et al. (2002) overall pooled results, showing the posterior distribution of PM_{10} effects on total mortality for the 90 cities for lag 0, 1, and 2 days. It can be seen that the effect size estimate for lag 1 day is about twice that for lag 0

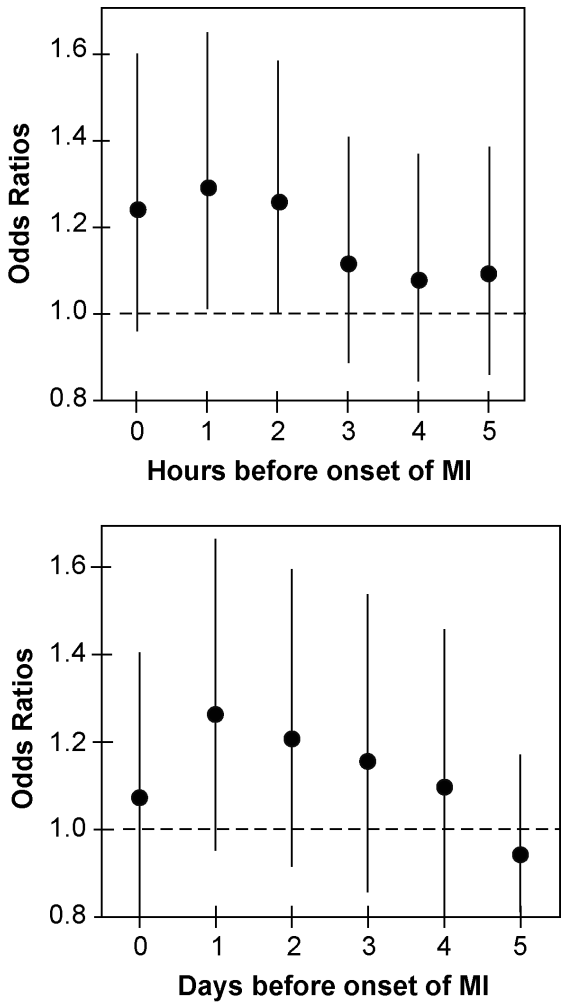

Figure 8-22. Odds ratios (and 95% confidence intervals) for associations between onset of myocardial infarction (MI) and 25 μg/m^3 increase in hourly (upper panel) or daily 24-h average (bottom panel) $PM_{2.5}$ concentrations. Based on univariate analyses of ambient $PM_{2.5}$ data measured in South Boston and interviews of patients with MI in greater Boston area during Jan. 1995 to May 1996.

Source: Peters et. al. (2001b).

or lag 2 days, although their distributions overlap. The pattern of lagged effects pooled for each of the seven regions (see Figure 8-5) in the 90 cities study also shows that the lag with the largest effect was at 1 day, except for Upper Midwest results where the estimated PM_{10} effect was about the same for lag 0 and 1 days.

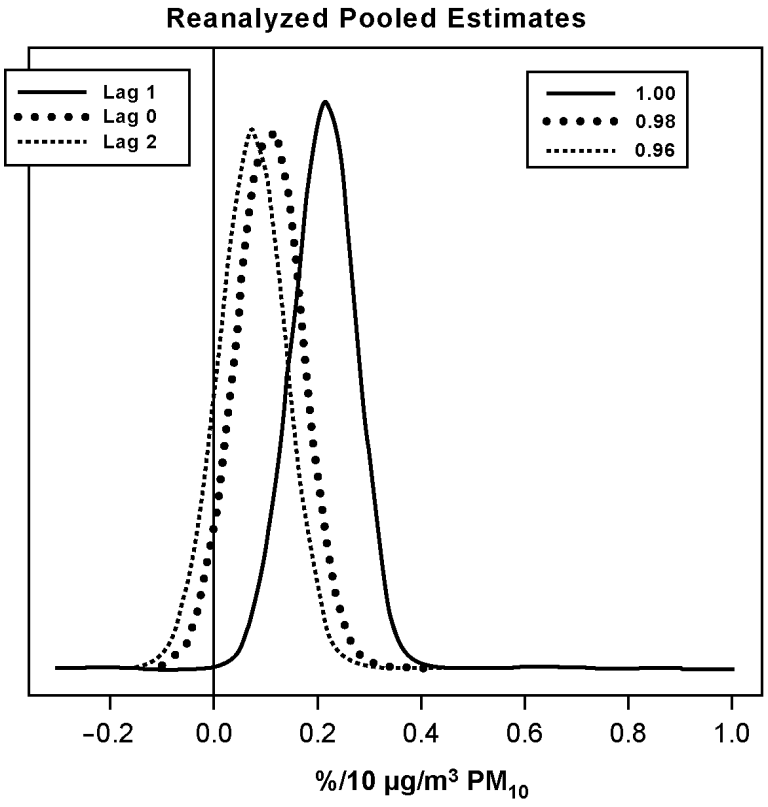

Figure 8-23. Marginal posterior distribution for effects of PM_{10} on all-cause mortality at lag 0, 1, and 2 for the 90 cities. The numbers in the upper right legend are posterior probabilities that overall effects are greater than 0.

Source: Dominici et al. (2002).

A review of current studies on short-term health effects of air pollution indicates that there are essentially three different approaches to deal with temporal structure: (1) assume all sites have the same lag (e.g., 1 day, for a given effect); (2) use the lag or moving average giving the largest or most significant effect and for each pollutant and endpoint; and (3) use a flexible distributed lag model, with parameters adjusted to each site. All three approaches apply to multicity studies, while the last two also apply to single-city studies. The NMMAPS mortality analyses used the first approach. This approach introduces a consistent response model across all locations. However, since the cardiovascular, respiratory, or other causes of acute mortality usually associated with PM are not at all specific, there is little a priori reason to believe that

they must have the same relation to current or previous PM exposures at different sites. The obvious advantage of the first approach in dealing with multicity data is its consistency in summarizing the point estimate. Conversely, a disadvantage to this approach is that effects may be underestimated in models using a single lag day. A major factor that makes it difficult to conduct a meta-analysis of existing PM health effects studies is the lack of consistency in how lag structures were modeled across the studies.

Figures 8-24 through 8-28 depict results obtained for PM-mortality and/or PM-morbidity associations as found and reported by different investigators for five U.S. cities. In most single-city air pollution health effects time-series studies, after the basic model (the best model with weather and seasonal cycles as covariates) was developed, several pollution lags (usually 0 to 3 or 4 days) were individually introduced and the most significant lag(s) were typically chosen for presentation of modeling results. Among the U.S. and Canadian mortality studies discussed in Section 8.2, a number of authors tested associations across a series of lag periods, as was reported in the NMMAPS multicity analysis. These studies reported stronger associations with shorter lags, with a pattern of results showing larger associations at the 0- and 1-day lag period that taper off with successive lag days for varying PM indicators (Moolgavkar, 2003; Ostro et al., 2000, reanalyzed Ostro et al., 2003; Tsai et al., 2000; Burnett et al., 2000, reanalyzed in Burnett and Goldberg, 2003; Mar et al., 2000, reanalyzed in Mar et al., 2003; Ito and Thurston, 1996). Several studies used only 0- and 1-day lags in the analyses for PM_{10}, $PM_{2.5}$ and $PM_{10-2.5}$ (for example, Schwartz et al., 1996a; Lipfert et al., 2000a; Klemm and Mason, 2000) and Chock et al. (2000) presented results for models in which 0- to 3- day lags for PM_{10} were included simultaneously, with stronger effects generally being seen with the 0-day lag period. However, some research groups selected longer moving average lag periods for PM_{10} as providing the best model fit (Pope et al., 1992, 5-day moving average; Styer et al., 1995, 3-day moving average). In selecting the lag periods to publish, these authors also discussed the pattern of effect size estimates across the different lag periods, analogous to what was described previously for Sheppard et al. (1999, reanalyzed in Sheppard et al., 2003).

Among the U.S. and Canadian studies on cardiovascular and respiratory morbidity, there is somewhat more variability in which lag periods have been selected for the best-fitting models

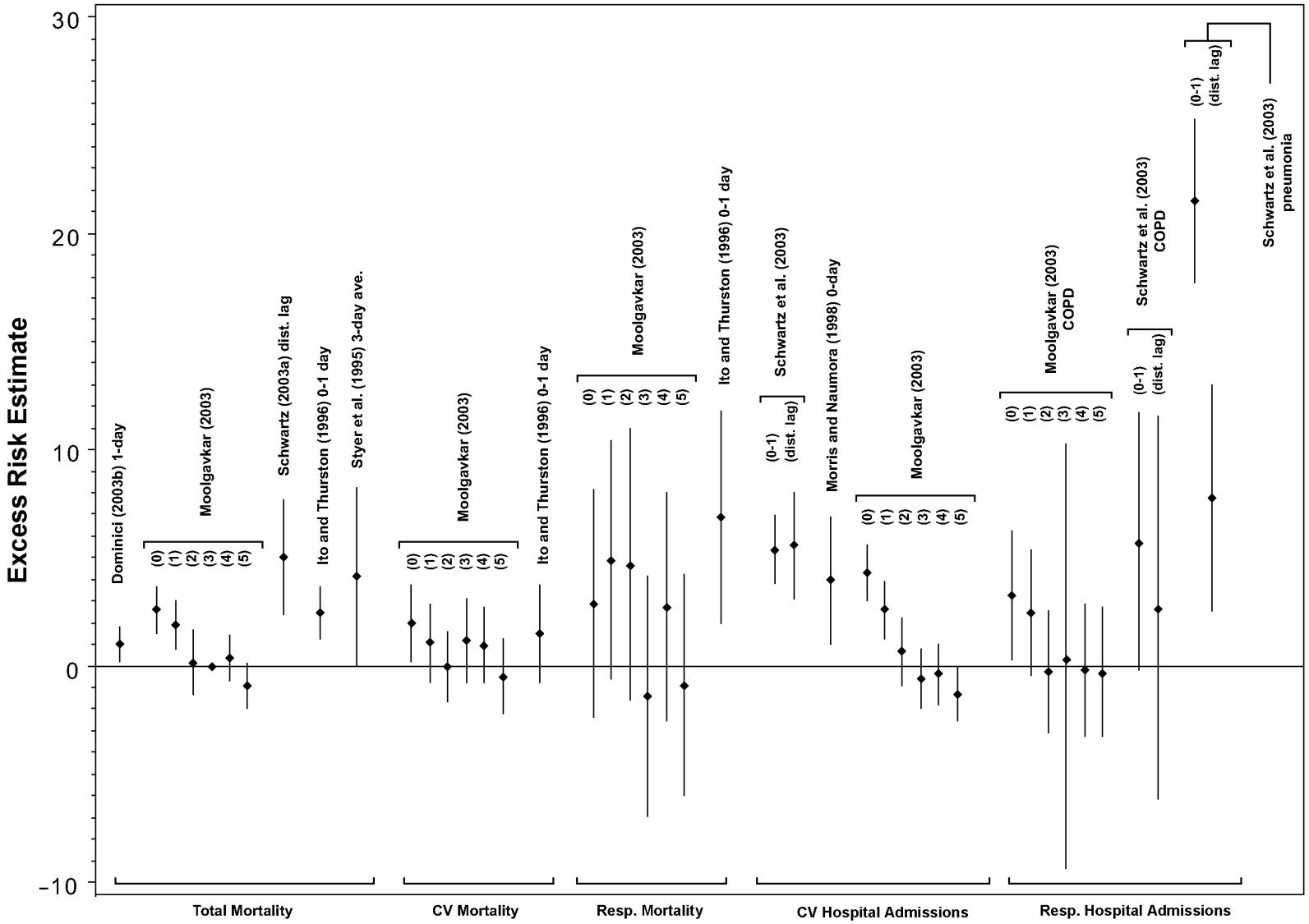

Figure 8-24. Excess risk estimates for associations between various health outcomes and PM_{10} (50 µg/m^3 increment) from different studies conducted in Cook County, IL. Results presented are for different PM_{10} lag periods from single-pollutant models in studies that either did not use GAM or were reanalyzed; GLM results presented are from reanalyses.

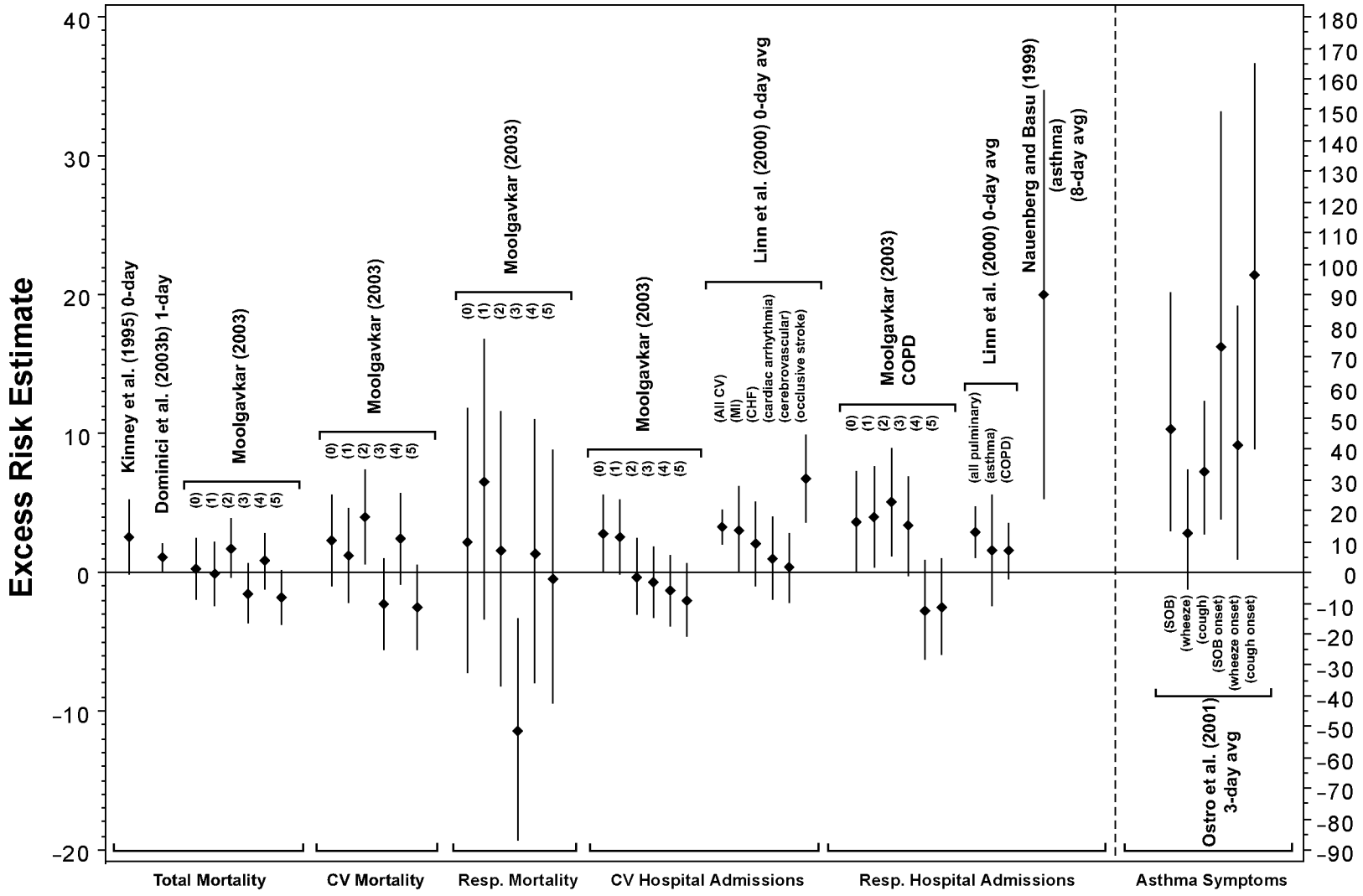

Figure 8-25. Excess risk estimates for associations between various health outcomes and PM_{10} (50 µg/m^3 increment) from studies conducted in Los Angeles County, CA. Results presented are for different PM_{10} lag periods from single-pollutant models in studies that either did not use GAM or were reanalyzed; GLM results presented are from reanalyses.

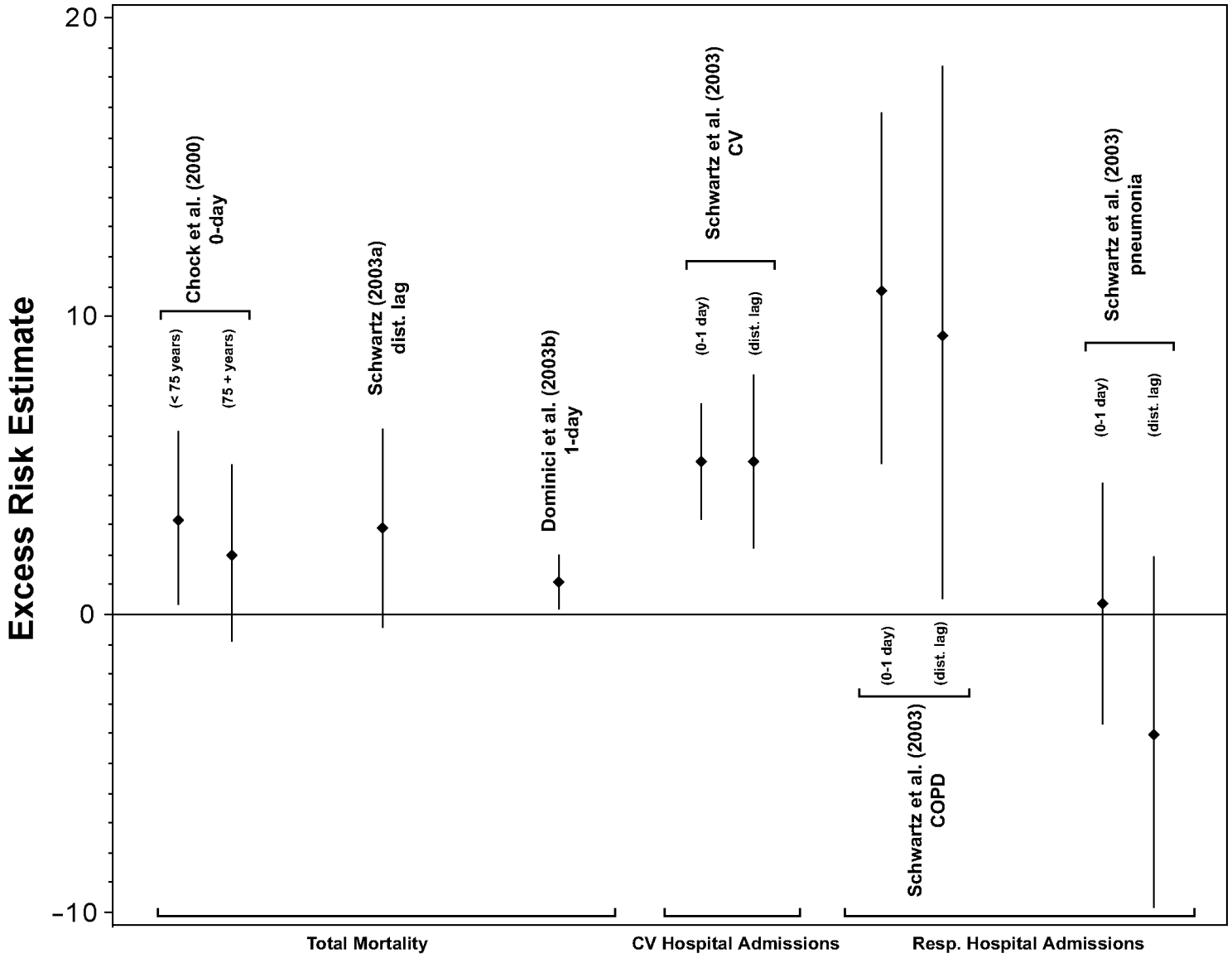

Figure 8-26. Excess risk estimates for associations between various health outcomes and PM_{10} (50 µg/m^3 increment) from studies conducted in Pittsburgh, PA. Results presented for different PM_{10} lag periods are from single-pollutant models in studies that either did not use GAM or were reanalyzed; GLM results presented are from reanalyses.

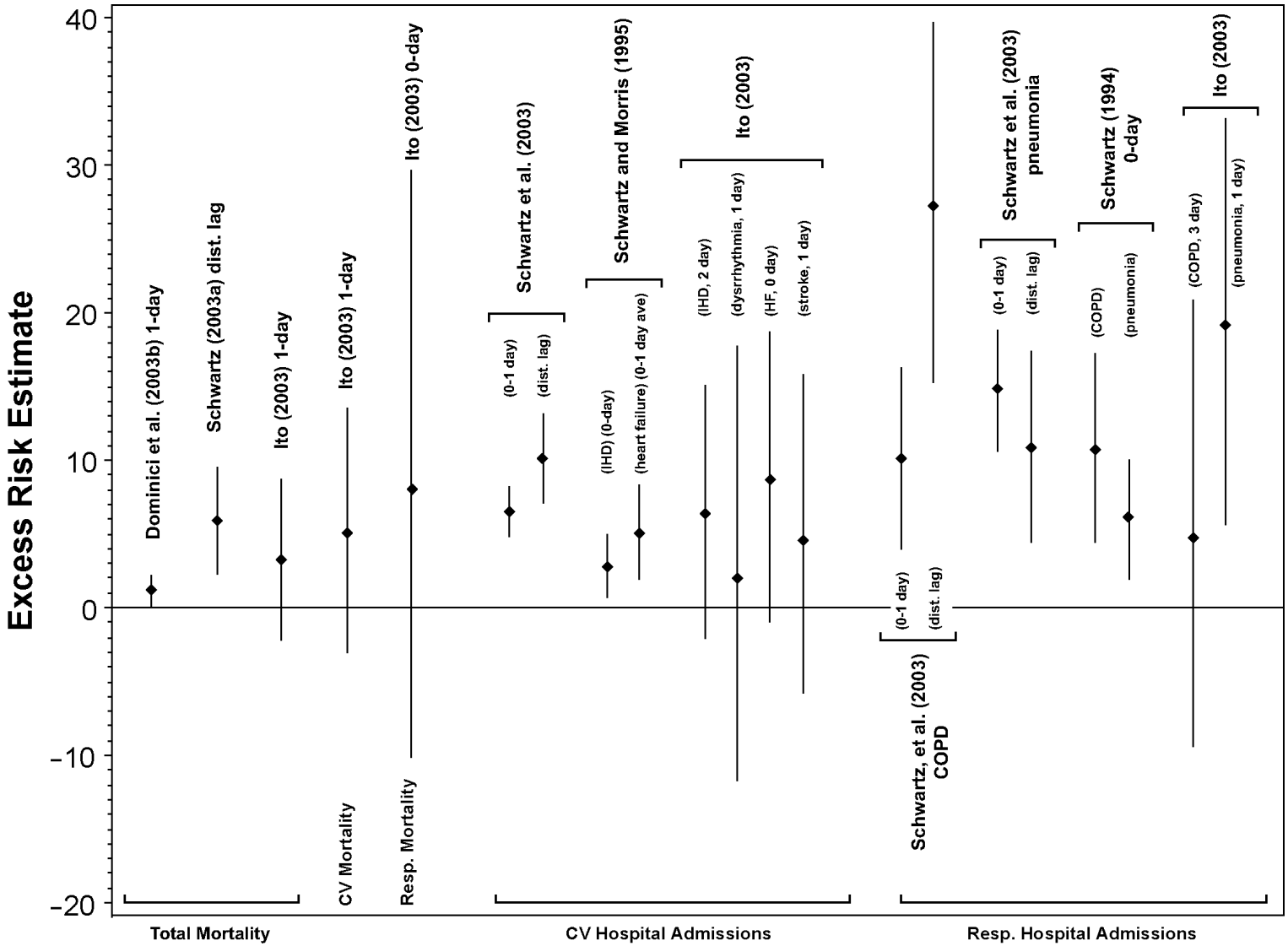

Figure 8-27. Excess risk estimates for associations between various health outcomes and PM_{10} (50 µg/m^3 increment) from studies conducted in Detroit, MI. Results presented are for different PM_{10} lag periods from single-pollutant models in studies that either did not use GAM or were reanalyzed; GLM results presented are from reanalyses.

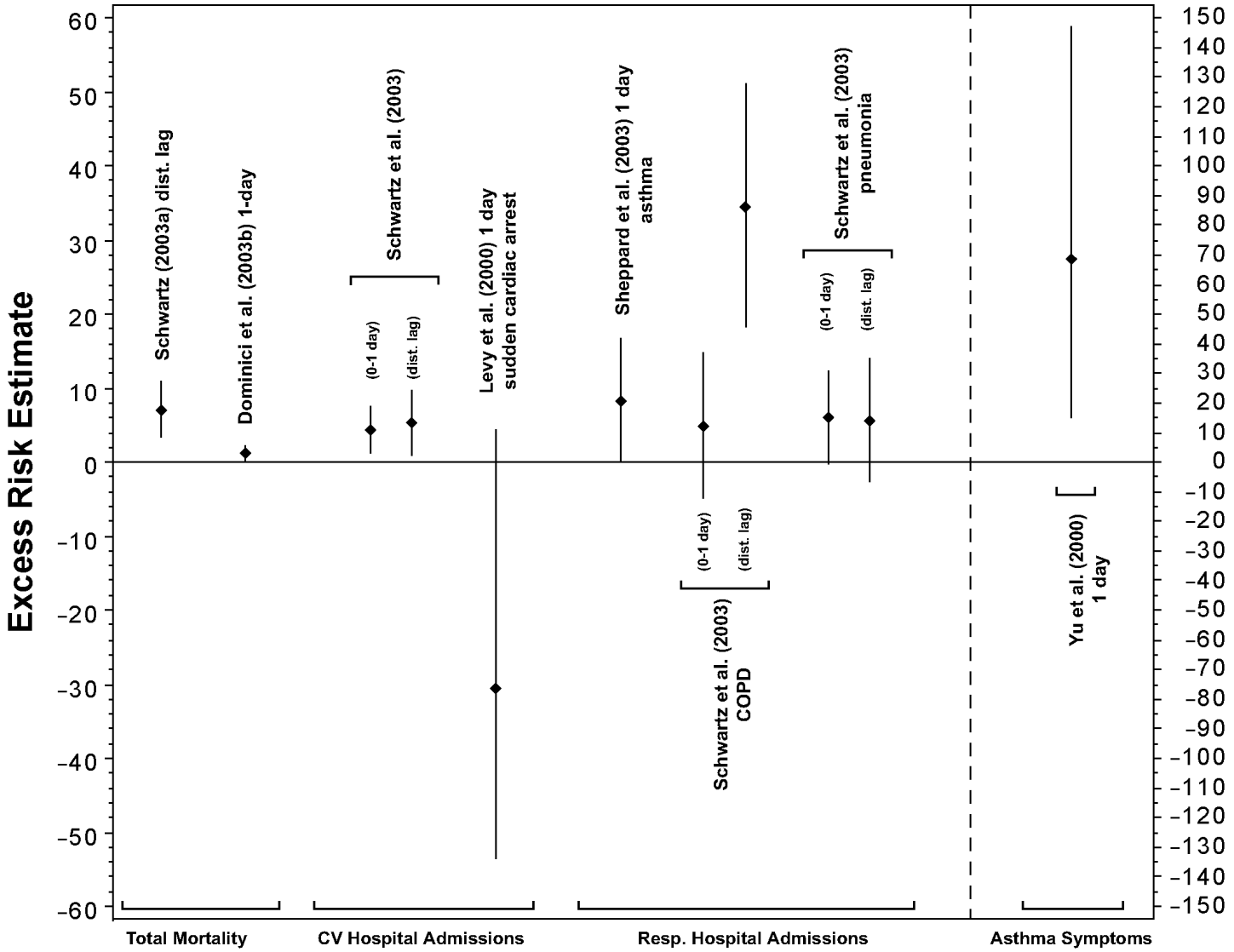

Figure 8-28. Excess risk estimates for associations between various health outcomes and PM_{10} (50 µg/m^3 increment) from studies conducted in Seattle or King County, WA. Results presented for different PM_{10} lag periods are from single-pollutant models in studies that either did not use GAM or were reanalyzed; GLM results presented are from reanalyses.

than shown for the mortality studies. In Section 8.3.2, it was found that the time-series studies of cardiovascular hospital admissions or emergency department visits suggest that PM effects are stronger at lag 0 with some carryover to lag 1; for cardiac physiology studies the results vary, with strongest associations for some effects seen with 1- to 2-h lag periods (e.g., Peters et al., 2001a). Sheppard et al. (1999, reanalyzed Sheppard et al., 2003), reported stronger associations with asthma hospitalization for 1-day lag periods for PM_{10}, $PM_{10-2.5}$ and $PM_{2.5}$; and Tolbert et al. (2000a) reported significant associations for asthma hospitalization in children with 1-day lagged PM_{10}. Lipsett et al. (1997) and Lin et al. (2002) presented results for asthma hospitalization or emergency department visits which indicate that longer moving average lag periods (out to 5- to 7-day moving averages) yield larger PM_{10} or $PM_{10-2.5}$ effect estimates and that the estimates are also fairly consistent across the different lag periods. In panel studies for respiratory symptoms, several research groups also reported larger effect sizes for longer moving average lag periods, including 2-, 3- and 4-day lags (e.g., Mortimer et al., 2002; Vedal et al.,1998; Ostro et al., 2001). Again, however, it is noted that authors generally report finding a pattern of PM-related effects; for example, Yu et al. (2000) reported a consistent pattern of PM results for asthma symptoms across 0-, 1- and 2-day lags and selected the 1-day lag for further investigation in multipollutant models.

It should also be noted that if one chooses the most significant single-lag day only, and if more than one lag day shows positive (significant or otherwise) associations with mortality, then reporting a RR for only one lag would also underestimate the pollution effects. Schwartz (2000b; reanalysis 2003b) investigated this issue, using the 10 U.S. cities data where daily PM_{10} values were available for 1986-1993. Daily total (nonaccidental) deaths of persons 65 years of age and older were analyzed. For each city, a GAM Poisson model (with stringent convergence criteria) and penalized splines adjusting for temperature, dewpoint, barometric pressure, day-of-week, season, and time were fitted. Effects of distributed lag were examined using two models: second-degree distributed lag model using lags 0 through 5 days; and unconstrained distributed lag model using lags 0 through 5 days. The inverse variance weighted averages of the ten cities' estimates were used to combine results. The results indicated that the effect size estimates for the quadratic distributed model and unconstrained distributed lag model using GAM were similar:

6.3% (CI: 4.9-7.8) per 50 μg/m^3 increase for the quadratic distributed lag model, and 5.8% (CI: 4.4-7.3) for the other model. These risk estimates are about twice as large as the two-day average (lag 0 and 1 day) estimate (3.4%; CI: 2.6-4.1) obtained in the reanalysis of the original 10 cities study (Schwartz, 2003b). There are indications that such distributed lag estimates are even larger when cause-specific of deaths are examined (see 10 U.S. cities study description in section 8.2.2.3).

The Mar et al. (2000, 2003) study of pollutant-mortality associations in Phoenix offers an interesting insight into lag structure. It is the only study to have everyday data (except for a few missing days) for PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, NO_2, CO, SO_2, and PM source category factors. Phoenix is also different from most cities studied in two important ways. As a high-temperature city, associations of mortality with high or low temperatures are minimal and hence more easily controlled for in data analysis. Correlations of $PM_{2.5}$ and $PM_{10-2.5}$ between four sites in Phoenix indicate high correlations for both $PM_{2.5}$ and $PM_{10-2.5}$ (Smith et al., 2000). In addition, the mortality data were limited in the Mar et al. (2000, 2003) analyses to ZIP code areas around the sampling site, further reducing the exposure error.

The pollution variables and the lag days for which the associations with cardiovascular mortality were statistically significant ($p < 0.05$, GLM with natural splines) are: PM_{10}, 0 and 1; $PM_{10-2.5}$, 0; $PM_{2.5}$, 1; CO, 1 and 4; NO_2, 1 and 4; SO_2, 4; regional sulfate, 0; motor vehicle and resuspended dust (MVRD), 1; vegetative burning, 3. It is reasonable that the $PM_{10-2.5}$ (lag 0) and the $PM_{2.5}$ (lag 1) would both contribute to a PM_{10} effect on lag days 0 and 1. Thus, to choose either a lag 0 or lag 1 for PM_{10} in Phoenix would underestimate the effects of PM_{10}, given that lag 0 would only capture the $PM_{10-2.5}$ effects and lag 1 would only capture the $PM_{2.5}$ effects. The Mar et al. source category analysis shows an association on lag day 1 for the MVRD factor. High loadings of CO and NO_2 on this source factor suggest that the lag 1 associations with CO and NO_2 are due to their high correlation with the MVRD factor. Because the correlation of sulfate with $PM_{10-2.5}$ was only 0.13, the association of the regional sulfate source factor on lag 0 may be considered to be independent of $PM_{10-2.5}$. There is also an association of the vegetative burning factor on lag 3. The effects of these two sources are not strong enough to show up as statistically significant as part of the $PM_{2.5}$ effects, although they may contribute to the positive risks on lag 0

and 3 and might well contribute to the risk determined in a distributed lag analysis. The associations on lag 4 are interesting, but as yet unexplained. The Mar et al. (2000, 2003) Phoenix results suggest that different pollutants are associated with cardiovascular mortality at different lags. It is also possible that different types of mortality may have different lags for different pollutants. Hence, the use of PM_{10} and total mortality would integrate across a variety of pollutant-type of mortality effects. Selection of any one lag day would neglect associations on other lag days. Thus, a distributed lag model should more correctly capture all associations. Few data sets exist with the every day data required for a distributed lag analysis. However, those that do and that have been analyzed for distributed lag (Schwartz, 2003b), show more excess risk associated with a distributed lag analysis than from any single day analyses.

An additional complication in assessing the shape of a distributed lag is that the apparent spread of the distributed lag may depend on the pattern of persistence of air pollution (i.e., episodes may persist for a few days), which may vary from city to city and from pollutant to pollutant. If this is the case, fixing the lag across cities or across pollutants may not be ideal, and may tend to obscure important nuances of lag structures that might provide important clues to possible different lags between PM exposures and different cause-specific effects.

One consideration for the evaluation of different lag periods is the availability of data. Where studies have used PM_{10} measured on an every-sixth-day sampling schedule, as is common in many U.S. cities, it is not possible to evaluate multiday lag models, such as moving average models and distributed lag models, that may be likely to have greater biological plausibility. It should also be noted that, with the every-sixth-day PM data, a different set of days of mortality series were evaluated at each lag. For example, an every-other-day sampling schedule was used in the Harvard Six City Study, for which the PM data on a given day has been used as though it were a 2-day moving average, alternately concurrent with mortality on half the days and lagging mortality by one day on the other days.

In summary, the NMMAPS 90 cities study indicated that, of the 0, 1, and 2 day PM_{10} lags examined, lag 1 day showed the strongest mortality associations. However, other lags are reported for various mortality and morbidity outcomes from other studies of one or another individual city.

8.4.5 Measurement Error: Concepts and Consequences

8.4.5.1 Theoretical Framework for Assessment of Measurement Error

Since the 1996 PM AQCD, much progress has been made in developing conceptual frameworks to evaluate potential measurement error effects on the estimation of PM health effects in time-series studies. Several new studies evaluate the extent of bias caused by measurement errors under scenarios that differ in extent of error variance and in covariance structure between co-pollutants.

Zidek et al. (1996) investigated, through simulation, the joint effects of multicolinearity and measurement error in Poisson regression model, with two covariates with varying extent of relative errors and correlation. Their error model was of classical error form ($W = X + U$, where W and X are surrogate and true measurements, respectively, and the error U is normally distributed). The results illustrated the transfer of effects from the "causal" variable to the confounder. However, in order for the confounder to have larger effect size than the true predictor, the correlation between the two covariates had to be very high ($r \geq 0.9$), with moderate error ($\sigma > 0.5$) for the true predictor and no error for the confounder in their scenarios. The transfer-of-causality effect was lessened when the confounder also became subject to error. Another interesting finding was the behavior of the standard errors of the coefficients: when the correlation between the covariates was high ($r = 0.9$) and both covariates had no error, the standard errors for both coefficients were inflated by a factor of 2; but this phenomenon disappeared when the confounder had error. Thus, multicolinearity influences the significance of the coefficient of the causal variable only when the confounder is accurately measured.

Marcus and Chapman (1998) also did a mathematical analysis of PM mortality effects in ordinary least square (OLS) model with the classical error model, under varying extent of error variance and correlation between two predictor variables. The error was analytical error (e.g., discrepancy between co-located monitors). Only positive regression coefficients were found to be attenuated; and null predictors (zero coefficient) or weak predictors only appeared stronger than true positive predictors under unusual conditions, i.e.: (1) true predictors must have very large positive or negative correlation (i.e., $r \geq 0.9$); (2) measurement error must be substantial (i.e., error variance $\approx$ signal variance); and (3) measurement errors must have high negative

correlation. They concluded that fine particle health effects are likely underestimated, but the bias due to analytical measurement error is not large.

Zeger et al. (2000) illustrated implications of the classical error model and the Berkson error model (i.e., X = W + U) in the context of time-series study design. Their simulation of the classical error model with two predictors, with various combinations of error variance and correlation between the predictors/error terms, showed results similar to those reported by Zidek et al. (1996). Most notably, for the transfer of the effects of one variable to another (i.e., error-induced confounding) to be large, the two predictors or their errors must to be highly correlated. Also, for the spurious association of a null predictor to be more significant than the true predictor, their measurement errors have to be extremely negatively correlated—a condition not yet seen in actual air pollution data sets.

Zeger et al. (2000) also laid out a comprehensive framework for evaluating effects of exposure measurement error on estimates of air pollution mortality relative risks in time-series studies. The error, i.e., the difference between personal exposure and an ambient pollutant concentration measured at a community monitoring site, was decomposed into three parts: (1) the error due to having aggregate rather than individual exposure; (2) the difference between the average personal exposure and the true ambient concentration level; and, (3) the difference between the true and measured ambient concentration level. By aggregating individual risks to obtain expected number of deaths, they found the first component of error (the aggregate rather than individual) to be a Berkson error and, therefore, not a significant contributor to bias in the estimated risk. The second error component is a classical error and can introduce bias if short-term associations exist between indoor source contributions and ambient concentration levels. Some analyses, however, both using experimental data (Mage et al., 1999; Wilson et al., 2000) and theoretical interpretations and models (Ott et al., 2000) indicate that there is no relationship between ambient concentrations and nonambient components of personal exposure to PM. Still, a bias could arise due to differences between personal exposures to ambient PM (indoors plus outdoors) and ambient concentrations. The third error component is the difference between the true and the measured ambient concentration. According to Zeger et al., the final term is largely

of the Berkson type if the average of the available monitors is an unbiased estimate of the true spatially averaged ambient level.

Using this framework, Zeger et al. (2000) then used PTEAM Riverside, CA data to estimate the second error component and its influence on estimated risks. The correlation coefficient between the error (the average population PM_{10} total exposure minus the ambient PM_{10} concentration) and the ambient PM_{10} concentration was estimated to be −0.63. Since this correlation is negative, the $\hat{\beta}_z$ (the estimated value of the pollution-mortality relative risk in the regression of mortality on z_t, the daily ambient concentration) will tend to underestimate the coefficient $\hat{\beta}_x$ that would be obtained in the regression of mortality on $\bar{x}_t$, the daily average total personal exposure, in a single-pollutant analysis. Zeger et al. (2000) then assessed the size of the bias that will result from this exposure misclassification, using daily ambient concentration, z_t. As shown in Equation 9 of Zeger et al. (2000), the daily average total personal exposure, $\bar{x}_t$, can be separated into a variable component, $\theta_1 z_t$, dependent on the daily ambient concentration, z_t, and a constant component, θ_o, independent of the ambient concentration:

$$\bar{x}_t = \theta_0 + \theta_1 Z_t + \varepsilon_t \qquad (8\text{-}5)$$

where ϵ_t is an error term.

If the nonambient component of the total personal exposure is independent of the ambient concentration, as appears to be the case, Equation 9 from Zeger et al. (2000) becomes the regression analysis equation familiar to exposure analysts (Dockery and Spengler, 1981; Ott et al., 2000; Wilson et al., 2000). In this case, θ_0 gives the average nonambient component of the total personal exposure and θ_1 gives the ratio of the ambient component of personal exposure to the ambient concentration. (The ambient component of personal exposure includes exposure to ambient PM while outdoors and, while indoors, exposure to ambient PM that has infiltrated indoors.) In this well-known approach to adjust for exposure measurement error, called regression calibration (Carroll et al., 1995), the estimate of β_X has the simple form $\hat{\beta}_x = \hat{\beta}_z / \hat{\theta}_1$. Thus, for the regression calibration, the value of β_X (based on the total personal exposure) does

not depend on the total personal exposure but is given by β_Z, based on the ambient concentration, times θ_1, the ratio of the ambient component of personal exposure to the ambient concentration. A regression analysis of the PTEAM data gave an estimate $\theta_1 = 0.60$.

Equation 9 from Zeger et al. (2000) was used with $\hat{\theta}_o = 59.95$ and $\theta_1 = 0.60$, estimated from the PTEAM data, to simulate values of daily average personal exposure, x^*_t, from the ambient concentrations, z_t, for PM_{10} in Riverside, CA, 1987-1994. They then compared the mean of the simulated $\hat{\beta}_x$ s, obtained by the series of log-linear regressions of mortality on the simulated x^*_t, with the normal approximation of the likelihood function for the coefficient $\hat{\beta}_z$ from the log-linear regression of mortality directly on z_t. The resulting $\hat{\beta}_z / \hat{\beta}_x = 0.59$ is very close to $\theta_1 = 0.60$. Dominici et al. (2000b) provide a more complete analysis of the bias in $\hat{\beta}_z$ as an estimate of β_x using the PTEAM Study and four other data sets and a more complete statistical model. Their findings were qualitatively similar in that $\hat{\beta}_x$ was close to $\hat{\beta}_z / \theta_1$. Thus, it appears that the bias is very close to θ_1, which depends not on the total personal exposure but only on the ratio of the ambient component of personal exposure to the ambient concentration.

Zeger et al. (2000), in the analyses described above, also suggested that the error due to the difference between the average personal exposure and the ambient level (the second error type described above) is likely the largest source of bias in estimated relative risk. This suggestion at least partly comes from the comparison of PTEAM data and site-to-site correlation (the third type of error described above) for PM_{10} and O_3 in 8 US cities. While PM_{10} and O_3 both showed relatively high site-to-site correlation ($\approx$0.6-0.9), a similar extent of site-to-site correlation for other pollutants is not necessarily expected. Ito et al. (2001) estimated site-to-site correlations (after adjusting for seasonal cycles) for PM_{10}, O_3, SO_2, NO_2, CO, temperature, dewpoint temperature, and relative humidity, using multiple stations' data from seven central and eastern states (IL, IN, MI, OH, PA, WV, WI), and found that, in a geographic scale of less 100 miles, these variables could be categorized into three groups in terms of the extent of correlation: weather variables ($r > 0.9$); O_3, PM_{10}, NO_2 (r: 0.6-0.8); CO and SO_2 ($r < 0.5$). These results suggest that the contribution from the third component of error, as described in Zeger et al. (2000), would vary among pollution and weather variables. Furthermore, the contribution from

the second component of error would also vary among pollutants; i.e., the ratio of ambient exposure to ambient concentration, called the attenuation coefficient, is expected to be different for each pollutant. Some ongoing studies are expected to shed light on this issue, but more information is needed on attenuation coefficients for a variety of pollutants.

With regard to the PM exposure, longitudinal studies (Wallace, 2000; Mage et al., 1999), show reasonably good correlation (r = 0.6 to 0.9) between ambient PM concentrations and average population PM exposure, lending support for the use of ambient data as a surrogate for personal exposure to ambient PM in time-series mortality or morbidity studies. Furthermore, fine particles are expected to show even better site-to-site correlation than PM_{10}. Wilson and Suh (1997) examined site-to-site correlation of PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ in Philadelphia and St. Louis, and found that site-to-site correlations were high ($r \approx 0.9$) for $PM_{2.5}$ but low for $PM_{10-2.5}$ ($r \approx 0.4$), indicating that fine particles have smaller errors in representing community-wide exposures. This finding supports Lipfert and Wyzga's (1997) speculation that the stronger mortality associations for fine than coarse particles found in the Schwartz et al. (1996a) study may be in part due to larger measurement error for coarse particles.

However, as Lipfert and Wyzga (1997) suggested, the issue is not whether the fine particle association with mortality is a "false positive", but rather, whether the weaker mortality association with coarse particles is a "false negative." Carrothers and Evans (2000) also investigated the joint effects of correlation and relative error, but they specifically addressed the issue of fine (FP) versus coarse particle (CP) effect, by assuming three levels of relative toxicity of fine versus coarse particles (β_{FP} / β_{CP} = 1, 3, and 10) and, then, evaluating the bias, ($B = \{E[\beta_{F'}]/ E[\beta_{C'}]\} / \{\beta_F / \beta_C\}$, as a function of FP-CP correlation and relative error associated with FP and CP. Their results indicate: (1) if the FP and CP have the same toxicity, there is no bias (i.e., B=1) as long as FP and CP are measured with equal precision; but, if, for example, FP is measured more precisely than CP, then FP will appear to be more toxic than CP (i.e., $B > 1$); but (2) when FP is more toxic than CP (i.e., β_{FP}/β_{CP} = 3 and 10), the equal precision of FP and CP results in downward bias of FP ($B < 1$), implying a relative overestimation of the less toxic CP. That is, to achieve non-bias, FP must be measured more precisely than CP, even more so as the correlation between FP and CP increases. In applying this model to real data from the

Harvard Six Cities Study, estimation of spatial variability for Boston was based on external data and a range of spatial variability for Knoxville (since no spatial data were available for this city). For Boston, where the estimated FP-CP correlation was low (r = 0.28), the estimated error was smaller for FP than for CP (0.85 versus 0.65, as correlation between true versus error-added series), and the observed FP to CP coefficient ratio was high (11), the calculated FP to CP coefficient ratio was even larger (26) - thus providing evidence against the hypothesis that FP is absorbing some of the CP coefficient. For Knoxville, where FP-CP correlation was moderate (0.54), the error for FP was smaller than for CP (0.9 versus 0.75), and the observed FP to CP coefficient ratio was 1.4, the calculated true FP to CP coefficient ratio was smaller (0.9) than the observed value. This indicates that the coefficient was overestimated for the better-measured FP, while the coefficient was underestimated for the poorer-measured CP. Since the amount (and the direction) of bias depended on several variables (i.e., correlation between FP and CP; the relative error for FP and CP; and, the underlying true ratio of the FP toxicity to CP toxicity), the authors concluded "...it is inadequate to state that differences in measurement error among fine and coarse particles will lead to false negative findings for coarse particles."

Fung and Krewski (1999) conducted a simulation study of measurement error adjustment methods for Poisson models, using scenarios like those used in the simulation studies that evaluated implications of joint effects of correlated covariates with measurement error. The measurement error adjustment methods used were the Regression Calibration (RCAL) method (Carroll et al., 1995) and the Simulation Extrapolation (SIMEX) method (Cook and Stefanski, 1994). Briefly, the RCAL algorithm consists of: (1) estimation of the regression of X on W (observed version of X, with error) and Z (covariate without error); (2) replacement of X by its estimate from (1) and conducting the standard analysis (i.e., regression); and (3) adjustment of the resulting standard error of coefficient to account for the calibration modeling. The SIMEX algorithm consists of: (1) addition of successively larger amount of error to the original data; (2) obtaining naive regression coefficients for each of the error added data sets; and (3) back extrapolation of the obtained coefficients to the error-free case using a quadratic or other function. Fung and Krewski examined the cases for: (1) $\beta_X = 0.25$; $\beta_Z = 0.25$; (2) $\beta_X = 0.0$; $\beta_Z = 0.25$; (3) $\beta_X = 0.25$; $\beta_Z = 0.0$., all with varying level of correlation (-0.8 to 0.8) with and

without classical additive error, and also considering Berkson type error. The behaviors of naive estimates were essentially similar to other simulation studies. In most cases with the classical error, RCAL performed better than SIMEX (which performed comparably when X-Z correlation was small), recovering underlying coefficients. In the presence of Berkson type error, however, even RCAL did not recover the underlying coefficients when X-Z correlation was large (> 0.5). This is the first study to examine the performance of available error adjustment methods that can be applied to time-series Poisson regression. The authors recommend RCAL over SIMEX, but did not discuss possible reasons why RCAL performed better than SIMEX in these scenarios; nor are the reasons clear from information given in the publication. Also, these error adjustment methods have not been used in real time-series health effects studies and require either replicate measurements or some knowledge on the nature of the error (i.e., distributional properties, correlation, etc.).

Another issue that measurement error may affect is the detection of threshold in time-series studies. Lipfert and Wyzga (1996) suggested that measurement error may obscure the true shape of the exposure-response curve, and that such error could have flattened the exposure-response curve to appear linear even when a threshold may exist. However, based on a simulation with realistic range of exposure error (due to site-to-site correlation), Cakmak et al. (1999) illustrated that the modern smoothing approach, LOESS, could adequately detect threshold levels (12.8 $\mu g/m^3$, 24.6 $\mu g/m^3$, and 34.4 $\mu g/m^3$) even with the presence of exposure error.

Other issues related to exposure error that have not been investigated include potential differential error among subpopulations. If the exposure errors are different between susceptible population groups (e.g., people with COPD) and the rest of the population, the estimation of bias may need to take such differences into account. Also, exposure errors may vary from season to season, due to seasonal differences in the use of indoor emission sources and air exchange rates due to air conditioning and heating. This may possibly explain reported season-specific effects of PM and other pollutants. Such season-specific contributions of errors from indoor and outdoor sources are also expected to be different from pollutant to pollutant.

In summary, studies that examined joint effects of correlation and error suggest that (a) PM effects are likely underestimated and (b) spurious PM effects (i.e., qualitative bias such as change

in the sign of coefficient) due to transferring of effects from other covariates require extreme conditions and are, therefore, unlikely. Also, one simulation study suggests that, under the likely range of error for PM, it is unlikely that a threshold is ignored by common smoothing methods. More data are needed to examine exposure errors for other co-pollutants, since their relative error contributions will influence their relative significance in relative risk estimates.

8.4.5.2 Measurement Error Issues Related to Divergence Between Monitors and to Monitoring Frequency

The measurement error framework posed in Dominici et al. (2000b) and Zeger et al. (2000) explicitly assumes that one of the error components has a Berkson error structure. As noted in (Zeger et al., 2000, p. 421): "This Berkson model is appropriate when z represents a measurable factor [e.g., measured PM or another pollutant] that is shared by a group of participants whose individual [true] exposures x might vary because of time-activity patterns. For example, z might be the spatially averaged ambient level of a pollutant without major indoor sources and x might be the personal exposures that, when averaged across people, match the ambient level." This assumption is likely accurate for sulfates, less so for fine particles and for PM_{10}, and almost certainly incorrect for gases such as CO and NO_2 that may vary substantially on an intra-urban spatial scale with widely distributed local sources.

The usual characterization of longitudinal or temporal pollutant correlation may not adequately reflect the spatial variation that is the more crucial aspect of association in evaluating possible Berkson errors. Temporal correlation coefficients, even across large distances (e.g., Ito et al., 2001) may be due to large-scale weather patterns affecting concentrations of many pollutants. Local concentrations for some pollutants with strong local sources and low regional dispersion (especially for CO and NO_2, and $PM_{10-2.5}$ to a lesser extent) may have somewhat smaller temporal correlations and much greater relative spatial variations than PM. Thus, persons in a large metropolitan area may have roughly similar levels of PM exposure x on any given day for which the ambient average PM concentration z is an adequate surrogate, whatever their space-time activity patterns, residence, or nonresidential microenvironments, whereas the same individuals may be exposed to systematically higher or lower concentrations of a co-pollutant than the spatial average of the co-pollutant. This violates the basic assumption of the Berkson

error model that within each stratum of the measured (spatially averaged) level z, the average value of the true concentration x is equal to z, i.e.,

$$E\{ x \mid z \} = z, \tag{8-6}$$

where $E\{.\}$ is the average or expected value over the population.

There are empirical reasons to believe that if the strata are chosen to be locations within a metropolitan area, some individuals far from local sources have consistently less exposure than the average ambient concentration (denoted p) for co-pollutants from local sources such as CO and NO_2, and $PM_{2.5}$, whose true exposure (denoted q) depends on the location of the person's residence or other micro-environment where most exposure occurs. For this group,

$$E\{ q \mid p \} < p, \tag{8-7}$$

while others in locations near the local source (such as a busy highway) have systematically higher exposure, so that

$$E\{q \mid p \} > p. \tag{8-8}$$

There is a growing body of evidence that adverse health effects are associated with proximity to a major road or highway (Wjst et al., 1993; Monn, 2001; Roemer and Van Wijnen, 2001). As shown below, there is good reason to believe that intra-city variation (even in $PM_{2.5}$) is substantial within some U.S. cities. If we assume for the sake of argument that concentrations of PM_{10} or $PM_{2.5}$ are relatively uniformly distributed, then associations of adverse health effects with proximity to a source cannot be readily attributed to a pollutant such as PM with a uniform spatial distribution. NO_2 is a pollutant often used to illustrate the spatial nonuniformity of the gaseous co-pollutants. Monn et al. (1997) compared the concentrations of NO_2 and PM_{10} as a function of curbside distance in a moderately busy urban street in Zurich and found that PM_{10}

levels decrease only slightly with increasing distance from the roadway, the decrease more likely being due to decreasing coarse than decreasing fine particle concentrations. The NO_2 levels showed a much stronger seasonal dependence, decreasing rapidly with increasing distance in the summer and showing little decrease with distance in the winter. However, the belief that $PM_{2.5}$ is spatially uniform should also not be accepted uncritically, as recent analyses for 27 U.S. cities shown in Chapter 3 and Appendix 3A of this document demonstrate.

The 90th percentile difference (P_{90}) between a pair of sites may provide a useful guide to the differences between monitor pairs (and by implication, personal exposure to fine particles) that might be reasonably expected within a metropolitan area. Table 8-40 shows statistics summarizing the spatial behavior of $PM_{2.5}$ concentrations, based on detailed analyses presented in Appendix 3A. The mean Pearson correlation coefficient for all site pairs considered in a given MSA, the average of the annual mean concentrations and the range of annual means at the sites considered, the average 90th percentile value (P90) of the absolute concentration difference and the average coefficient of determination (COD) are shown in Table 8-40 for MSAs satisfying data completeness criteria used for inclusion in Appendix 3A. Data in Table 8-40 show the ranges in the metrics (annual means) considered for all the MSAs included in the analyses. Typically, the range (i.e., the difference between the lowest and highest means for sites in an MSA) for annual mean concentrations is about one-quarter of the mean values. However, for about 10% of the time the average intersite difference in concentrations is greater than roughly one-half of the annual mean concentration, based on the P90 values. This result suggests that substantial concentration gradients exist on many days across some MSAs. The effects of outlying sites on the summary statistics were examined for the Atlanta, GA, Washington, DC, Seattle, WA and Los Angeles MSAs by removing them from the analyses. Their deletion either had no effect (as in Washington, DC) or a very large effect (as in Seattle, WA). In addition to outlying monitoring sites, located outside of the main urban air shed, monitoring sites within the urban core can also enhance the spatial variability in MSAs, as shown for Detroit, MI. As discussed in Chapter 3, there are a number of factors that contribute to spatial variability in ambient $PM_{2.5}$ concentrations in urban areas.

TABLE 8-40. SUMMARY STATISTICS SHOWING MEAN SITE-PAIR PEARSON CORRELATION COEFFICIENTS, ANNUAL MEAN $PM_{2.5}$ CONCENTRATIONS ($\mu g/m^3$), THE RANGE IN ANNUAL MEAN CONCENTRATIONS ($\mu g/m^3$), MEAN OF 90th PERCENTILE DIFFERENCES IN CONCENTRATIONS BETWEEN ALL SITE PAIRS ($\mu g/m^3$), AND COEFFICIENTS OF DIVERGENCE (COD) FOR MSAs MEETING SELECTION CRITERIA GIVEN IN APPENDIX 3A. VALUE IN ( ) REFERS TO NUMBER OF SITES.

	Mean Correlation	Annual Mean Concentration ($\mu g/m^3$)	Range in Annual Means ($\mu g/m^3$)	Mean P_{90} ($\mu g/m^3$)	Mean COD
Eastern U.S.					
Philadelphia, PA-NJ (5)	0.89	15.3	2.3	5.1	0.12
Washington, DC (6)	0.84	14.6	3.4	7.1	0.17
Washington, DC* (5)	0.85	14.6	3.4	6.1	0.17
Norfolk, VA (5)	0.96	13.5	0.7	3.6	0.08
Columbia, SC (4)	0.92	15.6	1.8	4.3	0.09
Atlanta, GA (7)	0.71	20.2	4.5	10.3	0.18
Atlanta, GA* (6)	0.78	20.6	3.5	8.5	0.15
Birmingham, AL (5)	0.83	20.3	5.3	11.5	0.18
Tampa, FL (4)	0.74	12.4	1.6	4.3	0.12
Central U.S.					
Cleveland, OH (8)	0.9	17.1	6.2	8.8	0.17
Pittsburgh, PA (11)	0.81	17.9	8.2	11.8	0.16
Steubenville, OH-WV (5)	0.86	17.7	2.4	8.1	0.18
Detroit, MI (10)	0.89	16.7	6.4	9	0.17
Detroit, MI ** (9)	0.92	15.9	4.7	8.2	0.16
Grand Rapids, MI (4)	0.96	12.7	1.2	4.6	0.13
Milwaukee, WI (8)	0.9	13.7	1.3	4	0.12
Chicago, IL (11)	0.89	17.6	6.1	7.4	0.14
Gary, IN (4)	0.75	15.8	3.6	7.7	0.18
Louisville, KY (5)	0.9	17.1	2.7	5.1	0.12
St. Louis, MO-IL (11)	0.83	17.4	5.6	8.8	0.15
Baton Rouge, LA (3)	0.95	14.3	0.4	2.7	0.08
Kansas City, KS-MO (6)	0.91	12.6	2.4	4.2	0.13
Dallas, TX (7)	0.94	12.6	2.2	4.1	0.11
Western U.S.					
Boise, ID (4)	0.88	9.5	1.6	6.4	0.17
Salt Lake City, UT (6)	0.91	11.3	5.0	7.9	0.21
Seattle, WA (5)	0.62	8.9	6.1	10.8	0.3
Seattle, WA* (4)	0.85	10.4	3.0	6.1	0.17
Portland, OR (4)	0.83	7.7	2.8	5.3	0.19
Los Angeles, CA*** (5)	0.61	17.9	13.9	21.4	0.28
Los Angeles, CA (6)	0.77	21	5.4	12.2	0.18
Riverside, CA (5)	0.89	27.5	5.0	12.3	0.17
San Diego, CA (4)	0.79	15.8	2.4	8.7	0.17

* outlying site removed.
** interior site removed.
*** Results from analysis including site in Lancaster, CA (included in L.A. MSA, but located across mountains to east of downtown LA)..

The data shown in Table 8-40 can be used to rank different MSAs according to the relative degree of spatial homogeneity that concentrations exhibit in them. In Table 8-41, MSAs are first ranked according to the mean Pearson correlation coefficient (r) for site pairs considered in the MSA, and then they are ranked according to the average P90 for concentration differences. It appears that, in general, the western MSAs are not as homogeneous as many in the East, but there are a number of MSAs in the East where $PM_{2.5}$ levels are as heterogeneous as in the West. It can be seen that there are often substantial differences in rankings according to which of the two parameters, r or P90, is used. This result suggests that concentration gradients can exist in MSAs whose monitoring sites are highly correlated and that use of correlation coefficients alone is not enough to characterize spatial variability. Because of incomplete data capture for some individual monitors on a given day in a particular MSA, when large concentration gradients exist across that MSA, day-to-day differences in calculated area-wide 24-h average PM levels may not accurately reflect the day-to-day changes that would be obtained by the full set of monitors.

The above results provide clear evidence that fine particle concentrations may be less homogenous in at least some MSAs than has been previously assumed. As noted in Chapter 3, these differences may not be strictly related to the distance between monitors, especially where topography and sources of primary PM play a role. In many eastern sites, however, particle distribution may be more substantially governed by regional rather than by local sources. Considerable heterogeneity much more often exists across monitoring sites in a given MSA or county for PM_{10} values and/or for coarse fraction ($PM_{10-2.5}$) concentrations typically estimated by differencing between PM_{10} and $PM_{2.5}$ readings on a given day in a given MSA. When the differencing is done between daily averages for PM_{10} and $PM_{2.5}$ values derived from sets of non-collocated operative monitors in an MSA that may vary from day to day, the resulting estimates of $PM_{10-2.5}$ can be subject to considerable error, even leading to such anomalies as negative values for MSA-wide 24-h average coarse-fraction ($PM_{10-2.5}$) levels on some days. Estimates of MSA- or county-wide averages for coarse-fraction thoracic particles derived by first subtracting $PM_{2.5}$ from PM_{10} readings from collocated samplers (or the same dichotomous sampler with PM_{10} and $PM_{2.5}$ cutpoints) and then averaging of those values across the MSA or county should yield more credible estimates of MSA-or county-wide $PM_{10-2.5}$ concentrations.

TABLE 8-41. SUMMARY OF RELATIVE HOMOGENEITY/HETEROGENEITY CHARACTERISTICS FOR MSAs GIVEN IN TABLE 8-40. RANKINGS ARE MADE ACCORDING TO THE MEAN PEARSON CORRELATION COEFFICIENT (left side) AND 90th PERCENTILE DIFFERENCE IN $PM_{2.5}$ CONCENTRATIONS (right side).

	r		P_{90}	
Spatial Variability[1]	**East**	**West**	**East**	**West**
Relatively Homogenous	Norfolk, VA		Baton Rouge, LA	
	Grand Rapids, MI		Norfolk, VA	
	Baton Rouge, LA		Milwaukee, WI	
	Dallas, TX		Dallas, TX	
	Detroit, MI**		Kansas City, KS-MO	
	Columbia, SC		Columbia, SC	
	Kansas City, KS-MO	Salt Lake City, UT	Tampa, FL	
	Cleveland, OH		Grand Rapids, MI	
	Milwaukee, WI		Louisville, KY	
	Louisville, KY		Philadelphia, PA	Portland, OR
Intermediate	Chicago, IL	Riverside, CA	Washington, DC*	Seattle, WA*
	Detroit, MI	Boise, ID	Washington, DC	Boise, ID
	Philadelphia, PA		Chicago, IL	
	Steubenville, OH		Gary, IN	Salt Lake City, UT
	Washington, DC*	Seattle, WA*	Steubenville, OH	
	Washington, DC		Detroit, MI**	
	St. Louis, MO	Portland, OR	Atlanta, GA*	
	Birmingham, AL		St. Louis, MO	San Diego, CA
	Pittsburgh, PA	San Diego, CA	Cleveland, OH	
Heterogeneous	Atlanta, GA*		Detroit, MI	
	Gary, IN	Los Angeles, CA*	Atlanta, GA	Seattle, WA
	Tampa, FL		Birmingham, AL	Los Angeles, CA*
Very Heterogeneous	Atlanta, GA		Pittsburgh, PA	Riverside, CA
		Seattle, WA		Los Angeles, CA***
		Los Angeles, CA***		

* outlying site removed. ** interior site removed. *** Results from analysis including site in Lancaster, CA.

Homogeneous: $r \geq .90$; $P90 \leq 5.0$. Intermediate: $r = .80 - .89$; $P90 = 5.1 - 10.0$
Heterogeneous: $r = .90 - .79$; $P90 = 10.1 - 20.0$; Very Heterogeneous: $r \leq .69$; $P90 \geq 20.0$

Some studies have examined potential implications of variations in addressing the role of spatial siting of monitors and/or the influence of frequency of data collection on the estimating of PM effects. Ito et al. (1995) evaluated the influence of the use of different monitors with varying monitoring schedules on associations between total mortality with PM_{10} in Cook Co., IL and Los Angeles Co., CA. The authors used data from six PM_{10} monitors in Cook Co., with one monitor operating on a daily basis and the remaining monitors operating on a 1-in-6 day schedule, and four sites in Los Angeles Co., all of which operated on a 1-in-6 day schedule. The monitoring sites were located in urban and suburban settings, according to the State's objectives. Three of the LA sites were located in residential areas and one was located in an area zoned for commercial use. One of the Cook Co. sites was classified as residential, two as commercial, and three as industrial. One of the Cook Co. sites was intended to monitor population exposure, three to monitor maximum concentrations, and two to monitor both maximum concentrations and population exposure. There was considerable variation among the distribution of PM_{10} concentrations in both cities, especially at the upper ends of the distributions. The authors tested for correlation between individual site pairs, located from 4 to 26 miles apart. The sites were all temporally well correlated in Cook Co., with correlation coefficients of 0.63 to 0.83 for the site pairs. Site pairs using three of the Los Angeles Co. sites also had high correlation coefficients ranging from 0.7 to 0.9, but site pairs that included the fourth monitor had correlation coefficients ranging from 0.36 to 0.47.

For illustrative epidemiological analyses, Ito et al (1995) then used a sinusoidal model to account for temporal components. Two methods were used for averaging PM_{10} data across monitors: (1) averaging data from all sites, as available; and (2) averaging data from all sites after first filling in missing data with regression analyses using data from other available monitors. The authors tested associations between mortality and PM_{10} measurements averaged across all sites by each of these methods and at each individual monitor for LA Co. and Cook Co. Similar results were obtained for both counties, in that (after detrending) the strongest correlations between PM_{10} and mortality were found for same-day (lag 0) data in each county and O_3 also showed positive associations for up to 2 days lagged with mortality in each county.

Because more sites were available in Cook Co., additional regression analyses were run to examine the sensitivity of using data from alternative PM_{10} sites and/or alternate every 6-day

samples from one PM_{10} site. In those analyses, the data from the monitor running every day in Cook Co. were divided into six data sets to study the influence of the 1-in-6 day monitoring schedule on the PM_{10}-mortality associations observed, and such associations were also evaluated with a 1-in-6 day subset from the two average data sets. The results of these analyses are summarized in Figure 8-29. Similar associations can be seen using the two methods of averaging PM_{10} data. Site 2 is the monitor that operated on a daily basis. The PM_{10}-mortality association using data from this site is very similar in magnitude to that for the average across all sites ("avg A"), showing the influence of this site's data on the daily average. Using the PM_{10} average with data filled in for the remaining sites ("avg B"), the PM_{10}-mortality association is slightly larger but is not significantly different from the association using the first averaging method. For analyses using 1-in-6 day subsets of the averaged PM_{10} data ("avg A_6" and "avg B_6"), the associations are slightly larger (but confidence intervals much wider) than associations using average data for all study days.

In contrast, there is considerable variation in the associations reported for modeling based on data from one or another individual monitor, i.e., for sites 1 through 6. In addition, the PM_{10}-mortality associations shown for the six 1-in-6 day subsets of data from site 2 vary widely as well. The risk estimate sizes derived from the different 1-in-6 day data from site 2 vary in a range similar to that shown for the individual PM_{10} monitoring sites. The authors observed that it is not clear whether this sensitivity is due to exposure errors in assigning the PM_{10} values at individual sites to the area population, or to exposure errors related to an individual monitor (possibly from local sources), or to both.

To the extent that the use of less-than-every-day monitoring data is a source of uncertainty for time-series analyses, it is important to note that many (but not all) U.S. and Canadian time-series epidemiological studies have used every-day monitoring for PM, with the availability of daily monitoring data often being described as an important study site selection criterion. However, a few studies have used data from monitors operating less frequently. One of the more notable examples is the NMMAPS 90 U.S. cities mortality analyses (Samet et al., 2000b; Dominici et al., 2003b), where every-day PM_{10} monitoring data were available for just a few of the cities (e.g., Pittsburgh, Chicago, St. Paul, Seattle), but PM_{10} data were collected on varying

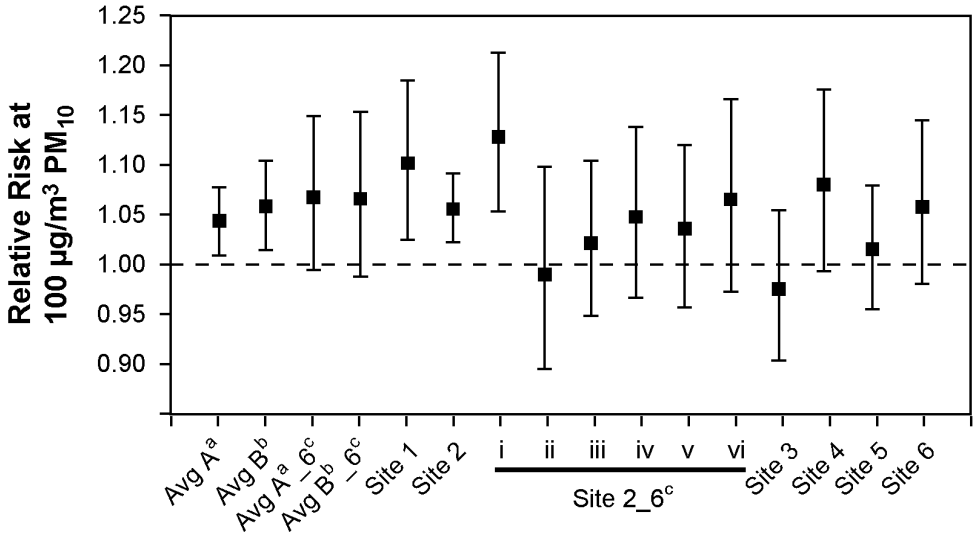

Figure 8-29. Relative risk estimates and 95% confidence intervals for total mortality per 100 µg/m^3 increase in PM_{10}, adjusting for ozone, temperature, seasonal cycles, day of week, and linear trend for 1985-1990 in Cook County, IL. Key: a = average of data from any available sites; b = average of data from all sites after filling missing data for each site; c = subsample for 1-in-6 day monitor frequency, with i through vi representing each 6th day subsample from site 2.

Source: Ito et al. (1995).

schedules (mainly 1-in-6 days) for most of the cities. However, the 14 U.S. cities selected for use in the NMMAPS morbidity analyses all had every-day monitoring for PM_{10}. Some other studies used data from monitors that operated on varying schedules, including the Harvard Six Cities Study (Schwartz et al., 1996a; reanalyzed Schwartz, 2003a), which used dichot impactor data collected daily during some periods or at least 1-in-2 days for the full monitoring period. As for another multicity study, PM data collected on a 1-in-6 day monitoring schedule were used in the Canadian eight cities study (Burnett et al., 2000; Burnett and Goldberg, 2003). The single-city analyses for San Jose (Fairley 1999; reanalyzed Fairley, 2003), Los Angeles (Moolgavkar, 2000; reanalyzed Moolgavkar, 2003a,b,c; Kinney et al., 1995) and Toronto (Lin et al., 2002) also used 1-in-6 day PM monitoring data; whereas the single-city city studies in Detroit (Lippmann et al.,

2000, reanalyzed Ito, 2003) and Santa Clara County, LA (Lipsett et al., 1997) used PM data derived from varying sampling schedules.

Lipfert et al. (2000a) examined relationships between the areas in which mortality occurred among residents and the locations of monitoring sites or averages over monitoring sites for several particle size components and particle metrics. The mortality data were located for Philadelphia, PA, for three additional suburban Philadelphia counties, and for Camden, NJ and other New Jersey counties in the Philadelphia – Camden MSA. A single site was used to obtain data for fine and coarse particles from Harvard School of Public Health monitors. Additional PA and NJ thoracic particle data were available for 2 to 4 stations and results were averaged for at least two stations reporting data. The authors concluded that mortality in any part of the region may be associated with air pollution concentrations or average concentrations in any other part of the region, whether particles or gases. The authors suggest two interpretations: (a) the associations of mortality with pollution were random (from carrying out multiple significance tests) and not causal, or (b) both particles and gaseous pollutants have a broad regional distribution. They also noted that interpretation (b) may lead to large uncertainties in identifying which pollutant exposures for the population are primarily responsible for the observed effects. These data could be studied further to evaluate smaller-scale spatial relationships among health effects and gases.

Lippmann et al. (2000) evaluated the effects of monitor siting choice using 14 TSP monitoring stations in Detroit, MI, and nearby Windsor, ON, Canada. The stations operated from 1981-1987 with almost complete data. When a standard log-linear link Poisson regression model for mortality was fitted to TSP data for each of the 14 sites, the relative risk estimates were similar for within-site increments of 5th to 95th percentiles, generally highest and positive at lag day 1 but not statistically significant at $p < 0.05$, except for site "w" (site 12, south of the urban center of Wayne County) and nearly significant at sites "f" (west of the city of Detroit), "g" (south of the city) and "v" (suburban site in northwestern Wayne County, MI, generally "upwind" of the urban center). However, as the authors noted, all of the reported relative risks were for site-specific increments, which varied by a factor of about 2.5 across the Wayne County-Windsor area. When converted to a common increment of 100 $\mu g/m^3$ TSP, the largest excess risks were found when data used in the model were from site "f" (4.5%), "v" (4.2%), or "w" (3.8%), which

also showed the most significant effects among the 14 monitors. As the authors noted, " . . . the distributional increments [used] to calculate relative risk tend to standardize the scale of relative risks. This actually makes sense in that if there is a concentration gradient of TSP within a city, and if the various TSP concentrations fluctuate together, then using a site with a low mean TSP for time-series analysis would result in a larger coefficient. This result does warn against extrapolating the effects from one city to an other using a raw regression coefficient [excess relative risk]."

Other recent studies also point out other aspects of intra-urban spatial variation in PM concentrations. Kinney et al. (2000) noted that, in a study of personal and ambient $PM_{2.5}$ and diesel exhaust particle (DEP) exposure in a dense urban area of New York City, $PM_{2.5}$ levels showed only a moderate site-to-site variation (37 to 47 $\mu g/m^3$) due, probably, to broader regional sources of $PM_{2.5}$, but elemental carbon (EC) concentrations showed a four-fold range of site-to-site variations, reflecting greater local variation in EC as a marker for DEP than for $PM_{2.5}$ in general.

Several PM health studies for Seattle (King County), WA (e.g., Levy et al., 2001, for out-of-hospital primary cardiac arrests) found few statistically significant relationships, partly attributed by the authors to Seattle having a topographically diverse terrain with local "hot spots" of residential wood burning, especially in winter. Sheppard et al. (2001) explored reasons for these findings, focusing on adjustments for location by use of a "topographic index" that included "downstream" normal flow of wood smoke from higher elevations and trapping of wood smoke in topographic bowls or basins even at higher elevations. They also adjusted for weather using a "stagnation index" (average number of hours per day with wind speed $\leq$ 25th percentile of wind speeds) and temperature, as well as interaction terms for stagnation on hilltop sites and temperature at suburban wood smoke-exposed valley sites. Adjustments for exposure measurement error based on methods developed in Sheppard and Damian (2000) and Sheppard et al. (2001) had little effect on effect size estimates for the case-crossover study (Levy et al., 2001), but may be useful in other studies where localized pollutant exposures are believed to be important.

Daniels et al. (2001) evaluated relative sources of variability or heterogeneity in 1996 PM_{10} monitoring in the Pittsburgh, PA area, a data-rich area having 25 monitors in a ~40 by 80 km

rectangle. The authors found no isotropic spatial dependence after accounting for other sources of variability, but indications of (a) heterogeneity in variability of small-scale processes over time and space and (b) heterogeneity in the mean values and covariate effects across sites. Important covariates included temperature, precipitation, wind speed and direction. The authors concluded that significant unmeasured processes might be in operation.

8.4.5.3 Measurement Error and the Assessment of Confounding by Co-Pollutants in Multipollutant Models

The Zeger et al. (2000) discussion may be interpreted as addressing the extent to which the apparent lack of a $PM_{10-2.5}$ effect in models with both fine and coarse particles demonstrates a "false negative" due to larger measurement error of coarse particle concentrations. However, a more important question may involve the relative attenuation of estimated effects of $PM_{2.5}$ and gaseous co-pollutants, especially those such as CO that are known to be highly correlated with $PM_{2.5}$. Tables 1 and 2 in Zeger et al. (2000) may be particularly relevant here. The evidence discussed in this chapter supports the hypothesis that PM has adverse health effects, but leaves open the question as to the extent the gaseous co-pollutants may contribute to the observed effects as well when their exposure is measured much less accurately than that of the PM metric. If both the PM metric and the co-pollutant have effects, Table 1 of Zeger et al. (2000) shows that the co-pollutant effect size estimate may be greatly attenuated and the PM effect size estimate much less so, depending on the magnitude of correlation between the true PM and gaseous pollutant exposures and the correlation between their measurement errors. One would expect that $PM_{2.5}$, CO, and NO_2 would often have a high positive correlation and their "exposure measurement errors" would also be positively correlated if PM and the gaseous pollutants were positively correlated due to common activity patterns, weather, and source emissions. In view of the substantially greater spatial heterogeneity of traffic-generated ambient pollutants such as CO and NO_2 and the relative (though not absolute) regional spatial uniformity of ambient $PM_{2.5}$ in some cities (but not others), it then seems reasonably likely that effect size estimates in multipollutant models are attenuated downward to a greater extent for gaseous co-pollutants than for PM metrics in some cities. This may explain part of the heterogeneity of findings for multipollutant models in different cities. Low effect size estimates for the gaseous co-pollutants

in a multipollutant model should be interpreted cautiously. The representativeness of the monitoring sites for population exposure of both the particle metrics and gaseous pollutants should be evaluated as part of the interpretation of the analysis. Indices such as the maximum 90th percentile of the absolute difference in concentrations between pairs of sites and the median cross-correlation across sites may be useful for characterizing spatial heterogeneity of gaseous co-pollutants as well as for particles.

8.4.6 Role of Particulate Matter Components

In the 1996 PM AQCD, extensive epidemiologic evidence substantiated very well positive associations between ambient PM_{10} concentrations and various health indicators, e.g., mortality, hospital admissions, respiratory symptoms, pulmonary function decrements, etc. Some studies were also then available which mortality and morbidity associations with various fine particle indicators (e.g., $PM_{2.5}$, sulfate, H^+, etc.). One mortality study, the Harvard Six Cities analysis by Schwartz et al. (1996a), evaluated relative contributions of the fine ($PM_{2.5}$) versus the coarse ($PM_{10-2.5}$) fraction of PM_{10}, and found, overall, that $PM_{2.5}$ appeared to be associated more strongly with mortality effects than $PM_{10-2.5}$. A few studies seemed to be indicative of possible coarse particle effects, e.g., increased asthma risks associated with quite high PM_{10} concentrations in a few locations where coarse particles strongly dominated the ambient PM_{10} mix.

8.4.6.1 Thoracic Particle (PM_{10}) Mortality/Morbidity Effects

Many new studies have reported associations between mortality and PM_{10}, as discussed in Section 8.2.2.2. Several new PM epidemiology studies which conducted time-series analyses in multiple cities were noted to be of particular interest, in that they provide evidence of effects across various geographic locations (using standardized methodologies) and more precise pooled effect size estimates with narrow confidence bounds, reflecting the typically much stronger power of such multicity studies over individual-city analyses to estimate a mean effect. Based on pooled analyses across multiple cities, using GAM stringent convergence criteria, the percent total (nonaccidental) excess deaths per 50 $\mu g/m^3$ PM_{10} (24-h) increment were estimated in different

multicity analyses to be: (a) 1.4% in the 90 largest U.S. cities; (b) 3.4% in 10 large U.S. cities; (c) 3.6% in the 8 largest Canadian cities; and (d) 3.0% in European cities.

As discussed in Section 8.3.1, a substantial body of new results has emerged since the 1996 PM AQCD that evaluates PM_{10} effects on cardiovascular-related hospital admissions and visits. Especially notable new evidence has been provided by multicity studies (Samet et al., 2000a,b; Zanobetti and Schwartz, 2003b) that yield pooled estimates of PM-CVD effects across numerous U.S. cities and regions. This study found not only significant PM associations, but also associations with other gaseous pollutants as well, thus hinting at likely independent effects of certain gases (O_3, CO, NO_2, SO_2) and/or interactive effects with PM. These and other individual-city studies generally appear to confirm likely excess risk of CVD-related hospital admission for U.S. cities in the range of 2 to 9% per 50 $\mu g/m^3$ PM_{10}, especially among the elderly ($\geq$ 65 years old).

In addition, a number of new studies for respiratory-related hospital admissions and medical visits have reported results that are generally consistent with and supportive of the findings presented in the 1996 PM AQCD. As summarized in Section 8.3.3, the excess risk estimates fall most consistently in the range of 5 to 20% per 50 $\mu g/m^3$ PM_{10}, with those for asthma visits and hospital admissions generally somewhat higher than for COPD and pneumonia hospital admissions.

8.4.6.2 Fine and Coarse Fraction Particle Effects on Mortality

The 1996 PM AQCD included results from a small number of studies in which air quality measurements of fine and coarse fraction thoracic particles were used. Some more recent additional studies are now available that have evaluated associations between various health outcomes and fine and coarse-fraction particles, the key findings of which are discussed below.

Short-term exposure studies

PM-mortality effect estimates from studies in which both $PM_{2.5}$ and $PM_{10-2.5}$ were measured are shown in Figure 8-5 (Section 8.2.2.5; p. 8-58). Among the more important newly available results are those derived from reanalyses of two major U.S. and Canadian multicity studies that investigated associations between $PM_{2.5}$ and $PM_{10-2.5}$ and total nonaccidental mortality. These

include (1) the Schwartz (2003a), the Klemm and Mason (2000) and Klemm and Mason (2003) reanalyses of the Harvard Six Cities data, all confirming the basic original findings by Schwartz et al. (1996a); and (2) the Burnett et al. (2000) study of the eight largest Canadian cities and Burnett and Goldberg (2003) reanalysis of that study. These studies found roughly comparable, statistically significant excess risk estimates of ~2% increased total mortality risk per 25 $\mu g/m^3$ $PM_{2.5}$. In the Harvard Six cities reanalyses, as reported for the original study, $PM_{10-2.5}$ was not significantly associated with total mortality across the six cities, though a significant association was reported for one of the cities (Steubenville, OH). Burnett and colleagues reported an association of ~2% increased total mortality risk per 25 $\mu g/m^3$ $PM_{10-2.5}$, although it was noted that this association was more sensitive than that with $PM_{2.5}$ in the reanalyses.

Effect estimates of about the same size for $PM_{2.5}$ and $PM_{10-2.5}$ were reported for single-city analyses conducted in Philadelphia (Lipfert et al., 2000a), Pittsburgh (Chock et al., 2000), and Detroit (Ito, 2003), as well as in some areas outside the U.S. such as Santiago, Chile (Cifuentes et al., 2000). Several U.S. and Canadian studies reported larger effect estimates for $PM_{2.5}$ than for $PM_{10-2.5}$. Of these, Fairley (2003) reported significant associations for $PM_{2.5}$ only for Santa Clara Co., CA; and in the preliminary analyses by Klemm and Mason (2000), associations with both $PM_{2.5}$ and $PM_{10-2.5}$ in Atlanta, GA did not achieve statistical significance. In two western areas, Coachella Valley, CA (Ostro et al., 2003) and Phoenix, AZ (Clyde et al., 2000), associations between mortality and $PM_{10-2.5}$ were reported to be greater than those for $PM_{2.5}$. In all studies, positive associations were reported; however, most associations with $PM_{2.5}$ were statistically significant while statistically significant associations with $PM_{10-2.5}$ were reported for just a few locations.

In addition, a number of new studies reported associations between both $PM_{2.5}$ and $PM_{10-2.5}$ with mortality from cardiovascular or respiratory causes. For cardiovascular mortality, Mar et al. (2003) reported significant associations with both $PM_{2.5}$ and $PM_{10-2.5}$, although the confidence intervals for associations with $PM_{2.5}$ were very broad. Also, for both cardiovascular and respiratory mortality, effect estimates of about the same size for $PM_{2.5}$ and $PM_{10-2.5}$ were reported in single-city analyses conducted for Philadelphia (Lipfert et al., 2000a), Santa Clara Co. (Fairley, 2003) and Detroit (Ito, 2003). For both $PM_{2.5}$ and $PM_{10-2.5}$, the associations were all positive and

many were statistically significant for cardiovascular mortality, but for respiratory mortality the confidence intervals were broader and the associations generally did not reach statistical significance.

While the associations reported for coarse fraction particles are often not statistically significant, the findings may well reflect actual associations between mortality and $PM_{10-2.5}$, at least in some locations. This may most consistently be the case in arid areas, e.g., in the Phoenix area (e.g., Mar et al., 2000, 2003) and in Santiago, Chile (Cifuentes et al., 2000). Elevations in coarse fraction particle mortality risks have also been reported for Steubenville, OH, an eastern U.S. urban area in the Harvard Six City Study (Schwartz et al., 1996a, Schwartz 2003a; Klemm et al., 2000; Klemm and Mason, 2003). These results may reflect contamination of later-resuspended coarse particles by metals in fine particles emitted from smelters (Phoenix) or steel mills (Steubenville) that was earlier deposited on nearby soils.

Three new papers discussed below provide particularly interesting new information on relationships between short-term fine and coarse particle exposures and total elderly mortality (age 65 and older), using TEOM data from the same EPA ORD/NERL monitoring site in Phoenix, AZ to index PM exposures. Each study , most notably, used quite different models but each found statistically significant relationships between total mortality and coarse PM (specifically $PM_{10-2.5}$) and some associations with $PM^{2.5}$.

Smith et al. (2000), using a three-day running average as the exposure metric, performed linear regression of the square root of daily mortality on the long-term trend, meteorological and air pollution variables. Analyses were done with mortality data obtained for the city of Phoenix, and for a larger regional area. Two mortality variables were used: (a) total (nonaccidental) deaths for the city of Phoenix regressed against central EPA site $PM_{2.5}$ data (assuming $PM_{2.5}$ levels to be homogeneous in that area) and (b) total mortality for a larger, regional area within 50 miles around Phoenix regressed against central EPA site $PM_{10-2.5}$ concentrations (assuming such levels to be homogeneous in areas around Phoenix). Using linear analysis, associations between mortality and $PM_{10-2.5}$ were statistically significant for both regions, whereas associations with $PM_{2.5}$ were not. When the possibility of a nonlinear response was taken into account, no evidence was found for a nonlinear concentration-response relationship for $PM_{10-2.5}$, but for $PM_{2.5}$ there was evidence suggesting a threshold for effects at 20 to 25 $\mu g/m^3$. There was no evidence

of confounding between fine and coarse fraction PM, suggesting that the two are "essentially separate pollutants having distinct effects". Smith et al. (2000) also observed a seasonal effect for $PM_{10-2.5}$, the effect being statistically significant only during spring and summer. Based on a principal component analysis of elemental concentrations, crustal elements are highest in spring and summer and anthropogenic elements lowest, but Smith et al. (2000) observed that the implication that crustal, rather than anthropogenic elements, were responsible for the observed relationship with mortality was counterintuitive.

Clyde et al. (2000) used a more conventional model, a Poisson regression of log-transformed mortality data with linear pollution variables; and also employed Bayesian model averaging to consider a wide variety of variations in the basic model. They conducted analyses that related mortality for three regions (the Phoenix metropolitan area; a small subset of zip codes to give a region with presumably uniform $PM_{2.5}$ concentrations; and a still smaller zip code-based region surrounding the monitoring site that was considered to have uniform PM_{10} concentrations) to the air pollution data from the central EPA site. Lag periods of 0, 1, 2, or 3 days were considered. Stronger associations were reported with $PM_{10-2.5}$ than $PM_{2.5}$; the association between total mortality and $PM_{2.5}$ was found only in the uniform $PM_{2.5}$ concentration region.

Mar et al. (2000, 2003) used conventional Poisson regression methods, but limited their mortality analyses to residents living in zip code locations near the EPA monitoring site (an area in Phoenix termed "uniform PM_{10} in Clyde et al., 2000). Mar et al. reported modeling data for lag days 0 to 4. Positive associations with cardiovascular mortality were reported for both $PM_{2.5}$ and $PM_{10-2.5}$; associations were significant at a 0-day lag for $PM_{10-2.5}$ and at a 1-day lag for $PM_{2.5}$. A significant association was also reported with a regional sulfate factor derived from source apportionment. The low correlation coefficient between sulfur in $PM_{2.5}$ (measured by XRF) with $PM_{10-2.5}$ (0.13) suggested separate and distinct effects for regional fine particle sulfate and $PM_{10-2.5}$.

In summary, the effects estimates from the newly reported studies are generally consistent with those derived from the earlier 1996 PM AQCD assessment, which reported risk estimates for excess total (nonaccidental) deaths associated with short-term (e.g.., 24-hour) PM exposures as generally falling within the range of 1 to 8% increased per 50 $\mu g/m^3$ PM_{10} and 2 to 6% per 25 $\mu g/m^3$ $PM_{2.5}$; the few earlier studies with $PM_{10-2.5}$ data provided little evidence for associations with mortality. Many new single-city studies have reported positive associations (many

statistically significant at $p<0.05$) between $PM_{2.5}$ and mortality, with effect estimates from U.S. and Canadian studies typically ranging from 1.5 to 6.5% increase per 25 $\mu g/m^3$ $PM_{2.5}$ for total mortality. Excess total mortality risks reported to be associated with short-term exposure to $PM_{10-2.5}$ generally fall in the range of 0.2 to 6.0% increase per 25 $\mu g/m^3$ $PM_{10-2.5}$, though many of the results are not statistically significant. Cause-specific estimates appear to mainly fall in the range of 3.0 to 7.0% increase per 25 $\mu g/m^3$ $PM_{2.5}$ for cardiovascular or combined cardiorespiratory mortality and 2.0 to 7.0% increase per 25 $\mu g/m^3$ $PM_{2.5}$ for respiratory mortality in U.S. cities. Effect size estimates for $PM_{10-2.5}$ generally fall in the range of 3.0 to 8.0% for cardiovascular mortality and 3.0 to 16.0% for respiratory mortality per 25 $\mu g/m^3$ $PM_{10-2.5}$.

Long-term exposure / mortality risk studies

Evidence for relationships between long-term exposures to fine and coarse fraction particles and mortality risk is available from extensive analyses using the Six Cities and ACS cohorts (original analyses, reanalyses and "extended" analyses with additional cohort follow-up) and from analyses using the AHSMOG and VA study cohorts. As discussed in Section 8.2.3, emphasis is placed on the results of the Six Cities and ACS prospective cohort studies, based on several factors – the larger study population in the ACS study, the larger air quality data set in the Six Cities study, the more generally representative study populations used in the Six Cities and ACS studies, and the fact that these studies have undergone extensive reanalyses. These prospective cohort studies have reported statistically significant risk estimates for total mortality in the range of 14 to 28% per 10 $\mu g/m^3$ $PM_{2.5}$ (annual average) but no significant associations with $PM_{10-2.5}$. While placing emphasis on the results of the Six Cities and ACS studies, it is noted that larger associations with $PM_{2.5}$ than with $PM_{10-2.5}$ were reported for males in the AHSMOG cohort, though none of the associations reached statistical significance and the effect estimates for $PM_{2.5}$ were in the same range as reported for the ACS and Six Cities cohorts. In the VA study, the results were more inconsistent from the analyses of differing subsets of data.

Significant associations have also been reported between $PM_{2.5}$ and cardiorespiratory and lung cancer mortality in the Six Cities and ACS cohort studies, with effect estimate sizes ranging from about 6 to 23% per 10 $\mu g/m^3$ $PM_{2.5}$ for cardiorespiratory mortality and from 8 to 21% per 10 $\mu g/m^3$ $PM_{2.5}$ for lung cancer mortality. Again, no statistically significant associations have

been reported between long-term exposure to coarse fraction particles and cause-specific mortality.

Significant associations for total and cardiopulmonary mortality were also reported with sulfates, an indicator of fine particles. In the reanalyses of the ACS study, Krewski and colleagues (2000) reported that the associations between total mortality and $PM_{2.5}$ or sulfates were unchanged in models including variables on other risk factors such as personal health or demographic factors. These associations were also robust to the inclusion of gaseous co-pollutants in the models, with the exception of SO_2. However, SO_2 emissions are linked with the formation of sulfates and secondarily-formed fine particles, so it can be difficult to disentangle their effects.

Past cross-sectional studies have generally found the fine particle component, as indicated either by $PM_{2.5}$ or sulfates, to be the PM constituent most consistently associated with mortality. While relative measurement errors of various PM indicators must be further evaluated as a possible source of bias in these estimate comparisons, the new evidence from prospective cohort studies indicates that the fine mass components of PM are more strongly associated with mortality effects of chronic PM exposure than are coarse fraction indicators.

8.4.6.3 Source-Oriented Analyses of PM and Mortality

Other recent studies on the relation of mortality to particle composition and source (Laden et al., 2000; Mar et al., 2000; Tsai et al., 2000) suggest that particles from certain sources may have much higher potential for adverse health effects than others, as shown by source-oriented evaluations involving factor analyses. For example, Laden et al. (2000) conducted factor analyses of the elemental composition of $PM_{2.5}$ for Harvard Six Cities study data for 1979 to 1988. For all six cities combined, the excess risk for daily mortality was estimated to be 9.3% (CI: 4.0, 14.9) per 25 $\mu g/m^3$ $PM_{2.5}$ (average of 0 and 1 day lags) increment in a mobile source factor; 2.0% (CI: −0.3, 4.4) for a coal source factor, and −5.1% (CI: −13.9, 4.6) for a crustal factor. There was large variation among the cities and suggestion of an association (not statistically significant) with a fuel oil factor identified by V or Mn.

Mar et al. (2000) applied factor analysis to evaluate mortality in relation to 1995 to 1997 fine PM elemental components and gaseous pollutants (CO, NO_2, SO_2) in an area of Phoenix, AZ

close to the air pollution monitors. The $PM_{2.5}$ constituents included sulfur, Zn, Pb, soil-corrected potassium, organic and elemental carbon, and a soil component estimated from oxides of Al, Si, and Fe. Based on models fitted using one pollutant at a time, statistically significant associations were found between total mortality and PM_{10}, CO (lags 0 and 1), NO_2 (lags 0, 1, 3, 4), S (negative), and soil (negative). Statistically significant associations were also found between cardiovascular mortality and CO (lags 0 to 4), NO_2 (lags 1 and 4), SO_2 (lags 3 and 4), $PM_{2.5}$ (lags 1, 3, 4), PM_{10} (lag 0), $PM_{10-2.5}$ (lag 0), and elemental, organic, or total carbon. Cardiovascular mortality was significantly related to a vegetative burning factor (high loadings on organic carbon and soil-corrected potassium), motor vehicle exhaust/resuspended road dust factor (with high loadings on Mn, Fe, Zn, Pb, OC, EC, CO, and NO_2), and a regional sulfate factor (with a high loading on S). However, total mortality was negatively associated with a soil factor (high loadings on Al, Fe, Si) and a local SO_2 source factor, but was positively associated with the regional sulfate factor.

Tsai et al. (2000) analyzed daily time-series of total and cardiorespiratory deaths, using short periods of 1981-1983 data for Newark, Elizabeth, and Camden, NJ. In addition to inhalable particle mass (PM_{15}) and fine particle mass ($PM_{2.5}$), the study evaluated data for metals (Pb, Mn, Fe, Cd, V, Ni, Zn, Cu) and for three fractions of extractable organic matter. Factor analyses were carried out using the metals, CO, and sulfates. The most significant sources or factors identified as predictors of daily mortality were oil burning (targets V, Ni), Zn and Cd processing, and sulfates. Other factors (dust, motor vehicles targeted by Pb and CO, industrial Cu or Fe processing) were not significant predictors. In Newark, oil burning sources and sulfates were positive predictors, and Zn/Cd a negative predictor for total mortality. In Camden oil burning and motor vehicle emissions predicted total mortality, but copper showed a marginal negative association. Oil burning, motor vehicle emissions, and sulfates were predictors of cardiorespiratory mortality in Camden. In Elizabeth, resuspended dust indexed by Fe and Mn showed marginal negative associations with mortality, as did industrial sources traced by Cu.

The set of results from the above factor analyses studies do not yet allow one to identify with great certainty a clear set of specific high-risk chemical components of PM. Nevertheless, some commonalities across the studies seem to highlight the likely importance of mobile source

and other fuel combustion emissions (and apparent lesser importance of crustal particles) as contributing to increased total or cardiorespiratory mortality.

8.4.6.4 Fine and Coarse Fraction Particle Effects on Morbidity

Short-term exposure / morbidity studies

A body of new studies published since the 1996 PM AQCD provides further evidence examining ambient PM association with increased human morbidity. At the time of the 1996 PM AQCD, fine particle morbidity studies were mostly limited to Schwartz et al. (1994) , Neas et al. (1994, 1995); Koenig et al. (1993); Dockery et al. (1996); and Raizenne et al. (1996); and discussion of coarse particles morbidity effects was also limited to only a few studies (Gordian et al., 1996; Hefflin et al., 1994). Since the 1996 PM AQCD, several new studies have been published in which newly available size-fractionated PM data allowed investigation of the effects of both fine ($PM_{2.5}$) and coarse fraction ($PM_{10-2.5}$) particles. PM_{10}, fine (FP) and coarse fraction (CP) particle results are noted below for studies by morbidity outcome areas, as follows: cardiovascular disease (CVD) hospital admissions (HA's); respiratory medical visits and hospital admissions; and respiratory symptoms and pulmonary function changes.

Several new U.S. and Canadian studies evaluated fine-mode PM effects on cardiovascular outcomes. Lippmann et al. (2000) and Ito (2003) report a positive but not a significant association with $PM_{2.5}$; and Moolgavkar (2003) reported $PM_{2.5}$ to be significantly associated with CVD HA for lag 0 and 1 in Los Angeles. Burnett et al. (1997a) reported that fine particles were significantly associated with CVD HA in a single pollutant model, but not when gases were included in multipollutant models for the 8 largest Canadian city data. Stieb et al. (2000) reported both PM_{10} and $PM_{2.5}$ to be associated with CVD emergency department (ED) visits in single pollutant, but not multipollutant models. Similarly, Morgan et al. (1998) reported that $PM_{2.5}$ measured by nephelometry was associated with CVD HA for all ages and 65+ years, but not in the multipollutant model. Tolbert et al. (2000a) reported that coarse particles were significantly associated with dysrhythmias, whereas $PM_{2.5}$ was not. Other studies (e.g., Liao et al., 1999; Creason et al., 2001; Pope et al., 1999b,c) reported associations between increases in $PM_{2.5}$ and several measures of decreased heart rate variability, but Gold et al. (2000) reported a negative association of $PM_{2.5}$ with heart rate and decreased variability in r-MSSD (one heart rate

variability measure). A study by Peters and colleagues (2001a) reported significant temporal associations between acute (2-h or 24-h) measures of $PM_{2.5}$ and myocardial infarction. Overall, these new studies collectively appear to implicate fine particles, as well as possibly some gaseous co-pollutants, in cardiovascular morbidity, but the relative contributions of fine particles acting alone or in combination with gases such as O_3, CO, NO_2 or SO_2 remain to be more clearly delineated and quantified. The most difficult issue relates to interpretation of reduced PM effect size and /or statistical significance when co-pollutants derived from the same source(s) as PM are included in multipollutant models.

Section 8.3.1 also discussed U.S. and Canadian studies that present analyses of coarse fraction particles (CP) relationships to CVD outcomes. Lippmann et al. (2000) and Ito (2003) found significant positive associations of $PM_{10-2.5}$ with ischemic heart disease hospital admissions in Detroit (RR = 1.08, CI: 1.04, 1.16). Tolbert et al. (2000a) reported significant positive associations of heart dysrhythmias with CP ($p = 0.04$) as well as for elemental carbon ($p = 0.004$), but these preliminary results must be interpreted with caution until more complete analyses are carried out and reported. Burnett et al. (1997b) noted that CP was the most robust of the particle metrics examined to inclusion of gaseous covariates for cardiovascular hospitalization, but concluded that particle mass and chemistry could not be identified as an independent risk factor for exacerbation of cardiorespiratory disease in this study. Based on another Canadian study, Burnett et al. (1999), reported statistically significant associations for CP in univariate models but not in multipollutant models; but the use of estimated rather than measured PM exposures indices limits the interpretation of the PM results reported.

The collective evidence reviewed above, in general, appears to suggest excess risks for CVD-related hospital admissions of ~1 to 10% per 25 $\mu g/m^3$ per $PM_{2.5}$ or $PM_{10-2.5}$ 24-h increment.

Section 8.3.2 also discussed new studies of effects of short-term PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ exposure on the incidence of respiratory hospital admissions and medical visits. Several new U.S. and Canadian studies have yielded particularly interesting results that are also suggestive of roles of both fine and coarse particles in respiratory-related hospital admissions. In an analysis of Detroit data, Lippmann et al. (2000) and Ito (2003) found comparable effect size estimates for $PM_{2.5}$ and $PM_{10-2.5}$. That is, the excess risk for pneumonia hospital admissions (in no co-pollutant model) was 18.6% (CI: 5.6, 33.1) per 50 $\mu g/m^3$ PM_{10}, 10% (CI: 1.5, 19.5) per

25 μg/m^3 $PM_{2.5}$ and 11.2% (CI: −0.02, 23.6) per 25 μg/m^3 $PM_{10-2.5}$. Because $PM_{2.5}$ and $PM_{10-2.5}$ were not highly correlated, the observed association between coarse particles and health outcomes were possibly not confounded by smaller particles. Despite the greater measurement error associated with $PM_{10-2.5}$ than with either $PM_{2.5}$ and PM_{10}, this indicator of the coarse particles within the thoracic fraction was associated with some of the outcome measures. The interesting result is that $PM_{10-2.5}$ appeared to be a separate factor from other PM metrics. Burnett et al. (1997b) also reported PM (PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$) associations with respiratory hospital admissions in 10 Canadian cities, even with O_3 in the model. Notably, the $PM_{10-2.5}$ association was significant (RR = 1.13 for 25 μg/m^3; CI: 1.05, 1.20); and inclusion of ozone still yielded a significant coarse mass RR = 1.11 (CI: 1.04, 1.19). Moolgavkar (2000a, 2003) reported that, in Los Angeles, both PM_{10} and $PM_{2.5}$ yielded both positive and negative associations at different lags for single pollutant models but not in two pollutant models. Delfino et al. (1997a) reported that both $PM_{2.5}$ and PM_{10} are positively associated with ED visits for respiratory disease. Morgan et al. (1998) reported that $PM_{2.5}$ estimated from nephelometry yielded a $PM_{2.5}$ association with COPD hospital admissions for 1-h max PM that was more positive than 24-h average $PM_{2.5}$.

A new study examines PM associations with asthma-related hospital admissions. Sheppard et al. (1999) and Sheppard (2003) studied relationships between PM metrics that included $PM_{10-2.5}$ and non-elderly adult hospital admissions for asthma in the greater Seattle area and reported significant relative risks for PM_{10}, $PM_{2.5}$ and $PM_{10-2.5}$ (lagged 1 day). For $PM_{10-2.5}$, the relative risk was 1.05 (CI: 1.0, 1.14) and for PM2.5, the relative risk 1.07 (1.02, 1.11).

Thus, although PM_{10} mass has most often been implicated as the PM pollution index affecting respiratory hospital admissions, the overall collection of new studies reviewed in Section 8.3.2 appears to suggest relative roles for PM_{10} and for both fine and coarse thoracic PM mass fractions, such as $PM_{2.5}$ and $PM_{10-2.5}$.

Section 8.3.3 assessed relationships between PM exposure on lung function and respiratory symptoms. While most data examined PM_{10} effects, several studies also examined fine and coarse fraction particle effects.

Several new asthma studies report associations with ambient PM measures. The peak flow analyses results for asthmatics tend to show small decrements for both PM_{10} and $PM_{2.5}$. Several studies included $PM_{2.5}$ and PM_{10} independently in their analyses of peak flow. Of these,

Pekkanen et al. (1997) and Romieu et al. (1996) found comparable results for $PM_{2.5}$ and PM_{10} and the study of Peters et al. (1997c) found slightly larger effects for $PM_{2.5}$. Of studies that included both PM_{10} and $PM_{2.5}$ in their analyses of respiratory symptoms, the studies of Peters et al. (1997c) and found similar effects for the two PM measures. Only the Romieu et al. (1996) study found slightly larger effects for $PM_{2.5}$. While the PM associations with adverse health effects among asthmatics and others are well documented, the type/source(s) of those particles most associated with adverse health effects among asthmatics are not known at this time. Indeed, the makeup of PM varies greatly from place to place and over time, depending upon factors such as the sources that contribute to the pollution and the prevailing atmospheric conditions, affecting particle formation, coagulation, transformation, and transport.

For nonasthmatics, several studies evaluated $PM_{2.5}$ effects. Naeher et al. (1999) reported similar AM PEF decrements for both $PM_{2.5}$ and PM_{10}. Neas et al. (1996) reported a nonsignificant negative association for PEF and $PM_{2.1}$, and Neas et al. (1999) also reported negative but nonsignificant PEF results. Schwartz and Neas (2000) reported a significant PEF association with $PM_{2.5}$, and Tiittanen et al. (1999) also reported negative but nonsignificant association between PEF and $PM_{2.5}$. Gold et al. (1999) reported significant PEF associations with $PM_{2.5}$. Schwartz and Neas (2000) reported significant $PM_{2.5}$ effects relative to lower respiratory symptoms. Tiittanen et al. (1999) showed significant effects for cough and $PM_{2.5}$ for a 4-day average.

Nonasthmatics were evaluated in fewer studies for coarse fraction particle effects. Schwartz and Neas (2000) report that cough was the only response in which coarse fraction particles appeared to provide an independent contribution to explaining the increased incidence. The correlation between CP and $PM_{2.5}$ was moderate (0.41). Coarse fraction particles had little association with evening peak flow. Tiittanen et al. (1999) also reported a significant effect of $PM_{10-2.5}$ for cough. Thus, cough may be an appropriate outcome related to coarse fraction particle effects. However, the limited data base suggests that further study is appropriate. The report by Zhang, et al. (2000) of an association between coarse fraction particles and the indicator "runny nose" is noted also.

The above new studies offer much more information than was available in 1996. Effects were noted for several morbidity endpoints: cardiovascular hospital admissions, respiratory

hospital admissions and cough. The data from these relatively limited studies are still insufficient to allow strong conclusions at this time as to which size-related ambient PM components may be most strongly related to one or another morbidity endpoints. Very preliminarily, however, fine particles appear to be more strongly implicated in cardiovascular outcomes than are coarse fraction particles, whereas both seem to impact respiratory endpoints.

Long-term exposure / morbidity studies

Evidence available in the 1996 PM AQCD included cross-sectional studies using data from a cohort of children in 24 U.S. and Canadian cities (Dockery et al., 1996; Raizenne et al., 1996). Positive associations were reported with incidence of respiratory illness or symptoms (Dockery et al., 1996), and negative associations with lung function measurements (Raizenne et al., 1996) for changes in $PM_{2.1}$, though the associations were stronger and more likely to reach statistical significance with measurements of aerosol acidity. Results were not presented for coarse fraction particles.

The best evidence for effects associated with chronic exposure to fine or coarse-fraction particles are found in the newer studies that combine the features of cross-sectional and cohort studies. These include several reports from the Southern California children's cohort study (McConnell et al., 1999; Gauderman et al., 2000, 2002). McConnell et al. (1999) present results of cross-sectional analyses using pulmonary function measured upon initiation of the children's cohort, where positive but not statistically significant associations were reported with some measures of increased respiratory illness in children with asthma; no associations were reported for children without asthma. Gauderman et al. (2000, 2002) analyzed lung function growth using spirometry measurements made in 4th and 7th grades for two separate cohorts, each having been recruited as 4th grade children. Gauderman et al. (2000) reported results for both $PM_{2.5}$ and $PM_{10\text{-}2.5}$, noting that decreased lung function growth was associated with 10 $\mu g/m^3$ changes for both indices (some but not all associations reached statistical significance). Gauderman et al. (2002) also later reported decreased lung function growth with $PM_{2.5}$ (though the associations were not statistically significant) but did not report results using $PM_{10\text{-}2.5}$ data.

The recent studies suggest that long-term exposure to fine particles is associated with development of chronic respiratory disease and reduced lung function growth; little evidence is

available on potential effects of exposure to coarse fraction particles. These findings build upon the information available in the 1996 PM AQCD. As was true then, there are fewer studies of long-term exposure effects than short-term exposures, but the evidence indicates fine particle exposures may result in chronic respiratory effects.

Long-term PM exposure and lung cancer

Of particular interest with regard to PM-related cause-specific mortality is growing evidence linking long-term PM exposure with increased risk of lung cancer mortality. Historical evidence includes studies of lung cancer trends, studies of occupational groups, comparisons of urban and rural populations, and case-control and cohort studies using diverse exposure metrics (Cohen and Pope, 1995). Numerous past ecological and case-control studies of PM and lung cancer incidence and mortality have generally indicated positive associations with living in areas having higher PM exposures despite possible problems with respect to potential exposure and other risk factor measurement errors. Table 8-42 provides a partial listing of such studies beyond those discussed below.

Prospective cohort studies offer a potentially more powerful approach to evaluation of apparent associations between PM exposures and development of lung cancer. The 1996 PM AQCD (U.S. Environmental Protection Agency, 1996a) summarized three of these more elaborate studies that carefully evaluated PM air pollution exposure effects on lung cancer using the prospective cohort design. In the AHSMOG Study, Abbey et al. (1991) followed a cohort of Seventh Day Adventists, whose extremely low prevalence of smoking and uniform, relatively healthy dietary patterns reduce the potential for confounding by these factors. Excess lung cancer incidence was observed in females in relation to both particle (TSP) and O_3 exposure after 6 years follow-up time. Dockery et al. (1993) reported the results of a 14- to 16-year prospective follow-up of 8,111 adults living in six U.S. cities that evaluated associations between air pollution and mortality. After controlling for individual differences in age, sex, cigarette smoking, BMI, education, and occupational exposure, Dockery et al. (1993) found an elevated but nonsignificant risk for lung cancer mortality (RR = 1.37; CI: 0.81, 2.31) for a difference in $PM_{2.5}$ pollution equal to that of the most polluted versus the least polluted city. Pope et al. (1995) similarly analyzed

TABLE 8-42. SUMMARY OF PAST ECOLOGIC AND CASE-CONTROL EPIDEMIOLOGIC STUDIES OF OUTDOOR AIR AND LUNG CANCER

Study Type	Authors	Locale	Exposure Classification	Rate Ratio (95% CI)
Ecologic	Henderson et al., 1975	Los Angeles, CA	High PAH Areas	1.3 @ 96-116 ug/m^3 TSP (CI: N/A)
	Buffler et al., 1988	Houston, TX	TSP by Census Tract	1.9 @ 16 ug/m^3 TSP (CI: N/A)
	Archer, 1990	Utah	TSP by county	1.6 @ 85 ug/m^3 TSP (CI: N/A)
Case-Control	Pike et al., 1979	Los Angeles	BAP Geo. Areas	1.3 @ 96-116 ug/m^3 TSP
	Vena, 1982	Buffalo, NY	TSP Geo. Areas	1.7 @ 80-200 ug/m^3 TSP (CI: 1.0-2.9)
	Jedrychowski, et al., 1990	Cracow, Poland	TSP and SO_2 Geo. Areas	1.1 @ TSP > 150 ug/m^3 (CI: N/A)
	Katsouyanni, et al., 1990	Athens, Greece	Soot Concentration Geo. Areas	1.1 @ soot up to 400 ug/m^3 (CI: N/A)
	Barbone et al., 1995	Trieste, Italy	High Particle Deposition Areas	1.4 @ > 0.3 g/m^2/day (CI: 1.1-1.8)
	Nyberg et al., 2000	Stockholm, Sweden	High NO_2 Areas	1.3 (CI: 0.9-1.9)

Source: Derived from Cohen (2000).

$PM_{2.5}$ and sulfate (SO_4^{2-}) air pollution as predictors of mortality in a prospective study of 7-year survival data (1982 to 1989) for about 550,000 adult volunteers obtained by the American Cancer Society (ACS).

Both the ACS and Harvard studies have been subjected to much scrutiny, including an extensive independent audit and reanalysis of the original data (Krewski et al., 2000) that confirmed the originally published results. The ACS study controlled for individual differences in age, sex, race, cigarette smoking, pipe and cigar smoking, exposure to passive cigarette smoke, occupational exposure, education, BMI, and alcohol use. In the original ACS study, lung cancer mortality was significantly associated with particulate air pollution when SO_4^{2+} was used as the index, but not when $PM_{2.5}$ mass was used as the index for a smaller subset of the study population that resided in metropolitan areas where $PM_{2.5}$ data were available from the Inhalable Particle (IP)

Network. Thus, while these prospective cohort studies have also indicated that long-term PM exposure is associated with an increased cancer risk, the effect estimates were generally not statistically significant, quite possibly due to inadequate statistical power by these studies at that time (e.g., due to inadequate population size and/or follow-up time for long-latency cancers).

A recent follow-up analysis of the major ACS study by Pope et al. (2002) responds to a number of criticisms previously noted for the earlier ACS analysis (Pope et al., 1995) in the 1996 PM AQCD (U.S. Environmental Protection Agency, 1996a). Most notably, the new study examined other pollutants, had better occupational indices and diet information, and also addressed possible spatial autocorrelations due to regional location. The recent extension of the ACS study included ~500,000 adult men and women drawn from ACS-CPS-II enrollment and follow-up during 1982 to 1998. This new analysis of the ACS cohort substantially expands the prior analysis, including: (1) more than doubling of the follow-up time to 16 years (and more than tripling of the number of deaths in the analysis); (2) substantially expanded exposure data, including gaseous co-pollutant data and new $PM_{2.5}$ data collected in 1999 to 2001; (3) improved control of occupational exposures; (4) incorporation of dietary variables that account for total fat consumption, as well as that of vegetables, citrus and high-fiber grains; and (5) utilization of recent advances in statistical modeling, including incorporation of random effects and nonparametric spatial smoothing components in the Cox proportional hazards model.

In the extended ACS analysis, long-term exposure to air pollution, and especially to $PM_{2.5}$, was found to be associated with increased annual risk of mortality. With the longer 16-year follow-up period and improved $PM_{2.5}$ exposure metrics, this study detected for the first time, a statistically significant association between living in a city with higher $PM_{2.5}$ and increased risk of dying of lung cancer. Each 10 ug/m^3 increment in annual average fine PM was associated with a 13% (CI: 4-23%) increase in lung cancer mortality. Coarse particles and gaseous pollutants were generally not significantly associated with excess lung cancer mortality. SO_4^{2-} was significantly associated with mortality and lung cancer deaths in this extended data set, yielding RR's consistent with (i.e., not significantly different from) the SO_4^{2-} RR's reported in the previously published 7-year follow-up (Pope et al, 1995). However, while $PM_{2.5}$ was specific to the causes most biologically plausible to be influenced by air pollution in this analysis (i.e., cardiopulmonary

and cancer), SO_4^{2-} was significantly associated with every mortality category in this new analysis, including that for "all-other causes". This suggests that the $PM_{2.5}$ associations found are more biologically plausible than the less specific SO_4^{2-} associations found. The $PM_{2.5}$ cancer mortality risk appears greatest for nonsmokers and among those with lower socioeconomic status (as indicated by lower educational attainment).

The AHSMOG investigators have re-examined the association between long-term PM exposure and increased risk of both lung cancer incidence and lung cancer mortality in nonsmokers using longer-term follow-up of this cohort and improved analytical approaches. Beeson et al. (1998) considered this cohort of some 6,338 nonsmoking, non-Hispanic, white Californian adults, ages 27 to 95 years, that was followed from 1977 to 1992 for newly diagnosed cancers. Among the AHSMOG cohort, incident lung cancer in males was positively and significantly associated with IQR increases for mean concentrations of PM_{10} (RR = 5.21; CI: 1.94, 13.99). For females in the cohort, incident lung cancer was positively and significantly associated with increases in SO_2 (RR = 2.14; CI: 1.36,3.37) and frequency of PM_{10} levels above 50 $\mu g/m^3$ (RR = 1.21; CI: 0.55, 2.66) and 60 ug/m^3 (RR = 1.25; CI: 0.57, 2.71). Thus, increased risks of incident lung cancer were deemed by the authors to be associated with elevated long-term ambient concentrations of PM_{10} and SO_2 in both genders. The higher PM_{10} effect estimate for cancer in males appeared to be partially due to gender differences in long-term air pollution exposures. Abbey et al. (1999) also related long-term ambient concentrations of PM_{10}, SO_4^{2-}, SO_2, O_3, and NO_2 to 1977-1992 mortality in the AHSMOG cohort. After adjusting for a wide array of potentially confounding factors, including occupational and indoor sources of air pollutants, PM_{10} showed a strong association with lung cancer deaths in males (PM_{10} IQR RR = 2.38; CI: 1.42, 3.97). In this cohort, males spent more time outdoors than females, thus having higher estimated air pollution exposures than the cohort females. Ozone showed an even stronger association with lung cancer mortality for males, and SO_2 showed strong associations with lung cancer mortality for both sexes. The authors reported that other pollutants showed weak or no association with mortality. Therefore, increases in both lung cancer incidence and lung cancer mortality in the extended follow-up analysis of the AHSMOG study were found to be

most consistently associated with elevated long-term ambient concentrations of PM_{10}, O_3, and SO_2, especially among males.

Overall, these new cohort studies confirm and strengthen the published older ecological and case-control evidence indicating that living in an area that has experienced higher PM exposures can cause a significant increase in the RR of lung cancer incidence and associated mortality. In particular, the new ACS cohort analysis more clearly indicates that living in a city with higher $PM_{2.5}$ levels is associated with an elevated risk of lung cancer amounting to an increase of some 10 to 15% above the lung cancer mortality risk in a cleaner city.

With regard to specific ambient fine particle constituents that may significantly contribute to the observed ambient PM-related increases in lung cancer incidence and mortality, PM components of gasoline and diesel engine exhaust represent one class of hypothesized likely important contributors. Such mobile source PM typically comprises a noticeable fraction of ambient fine particles in many urban areas, having been estimated to comprise from ~5 to 30% of ambient $PM_{2.5}$ in some U.S. urban areas (see Chapter 3). These mobile sources are reasonable candidates as contributors to ambient PM-lung cancer risks, given their being sources of known cancer-causing agents (e.g., PAHs), as are other coal-combustion and/or woodburning emission sources (at least during some seasons).

8.4.7 Concentration-Response Relationships for Ambient PM

In the 1996 PM AQCD, the limitations of identifying possible "thresholds" in the concentration-response relationships in observational studies were discussed, including difficulties related to the low data density in the lower PM concentration range, the small number of quantile indicators often used, and the possible influence of measurement error. Also, a threshold for a population, as opposed to a threshold for an individual, has some conceptual issues that should be noted. For example, since individual thresholds vary from person to person due to individual differences in genetic level susceptibility and preexisting disease conditions (and even can vary from one time to another for a given person), it is extremely difficult mathematically to demonstrate convincingly that a clear threshold exists in the population studies. This is especially true if the most sensitive members of a population are unusually sensitive even down to very low

concentrations. The person-to-person difference in the relationship between personal exposure and the concentration observed at a monitor may also add to the variability in observed exposure-response relationships, possibly obscuring otherwise more evident thresholds. Since one cannot directly measure but can only compute or estimate a population threshold, it would be difficult to interpret an observed population threshold biologically, without pertinent collateral dosimetric/toxicologic information. Despite these issues, several PM-related epidemiologic studies have attempted to address the question of threshold.

Cakmak et al. (1999) investigated methods to detect and estimate threshold levels in time-series studies. Based on the realistic range of error observed from actual Toronto pollution data (average site-to-site correlation: 0.90 for O_3; 0.76 for CoH; 0.69 for TSP; 0.59 for SO_2; 0.58 for NO_2; and 0.44 for CO), pollution levels were generated with multiplicative error for six levels of exposure error (1.0, 0.9, 0.8, 0.72, 0.6, 0.4, site-to-site correlation). Mortality series were generated with three PM_{10} threshold levels (12.8 $\mu g/m^3$, 24.6 $\mu g/m^3$, and 34.4 $\mu g/m^3$). LOESS with a 60% span was used to observe the exposure-response curves for these 18 combinations of exposure-response relationships with error. A parameter threshold model was also fit using nonlinear least squares. Both mortality and PM_{10} data were prefiltered for the influence of seasonal cycles using LOESS smooth function. The threshold regression models were then fit to the prefiltered data. Graphical presentations indicate that LOESS adequately detects threshold under no error, but the thresholds were "smoothed out" under the extreme error scenario. Use of a parametric threshold model was adequate to give "nearly unbiased" estimates of threshold concentrations even under the conditions of extreme measurement error, but the uncertainty in the threshold estimates increased with the degree of error. They concluded, "if threshold exists, it is highly likely that standard statistical analysis can detect it."

Daniels et al. (2000; reanalysis by Dominici et al., 2003a) tested for presence of a threshold using data for the largest 20 U.S. cities during 1987 to 1994. In their original analyses, the authors compared three log-linear GAM regression models: (1) using a linear PM_{10} term; (2) using a natural cubic spline of PM_{10} with knots at 30 and 60 $\mu g/m^3$ (corresponding approximately to 25 and 75 percentile of the distribution); and, (3) using a threshold model with a grid search in the range between 5 and 200 $\mu g/m^3$ with 5 $\mu g/m^3$ increment. The covariates

included in these models are similar to those previously used by the same research group (Kelsall et al., 1997; Samet et al., 2000a,b), including the smoothing function of time, temperature and dewpoint, and day-of-week indicators. The 2003 reanalysis evaluated total, cardiorespiratory, and "other" mortality series by means of covariate adjustments made using natural splines in GLM models. These models were fit for each city separately and, for model (1) and (2), the combined estimates across cities were then obtained by using inverse variance weighting if there was no heterogeneity across cities or by using a two-level hierarchical model if there was heterogeneity. The best fits among the models, within each city and over all cities, were also determined using Akaike's Information Criterion (AIC).

As seen in Figure 8-30, the results using the natural spline model showed that, for total and cardiorespiratory mortality, the exposure-response spline curves for mean lag were roughly linear, but less so for current and previous day PM_{10}, making it difficult to discern any evident threshold. However, the curves for mortality from other causes, most clearly increased once PM_{10} concentrations exceeded 50 $\mu g/m^3$. The posterior probabilities for a threshold for PM_{10} effects on total and cause-specific mortality groupings are shown in Figure 8-31 (CVDRESP = cardiorespiratory causes). There appears to be a reasonably likely possibility of a threshold existing for daily total or CVDRESP mortality at PM_{10} levels of ~15-20 $\mu g/m^3$ or below; but the likelihood of a threshold occurring above ~25 $\mu g/m^3$ seems to be essentially zero, based on the latter analyses. The hypothesis of linearity was examined more formally by comparing AIC values across models, with the results indicating that the linear model was preferred over the spline and the threshold models. Thus, these findings do not rule out the possibility that linear models without a threshold may be appropriate for estimating the effects of PM_{10} on the types of mortality of main interest. The available information simply does not allow for a clear choice of "threshold" or "no threshold" over the other.

Smith et al. (1999) analyzed the slope of the PM_{10}-mortality relationship in Birmingham, AL and in Cook County, IL. Temperature was modeled using piece-wise linear term with a change point. PM_{10} data were modeled at lag 0 through 3 and 3-day averages at these lags. In addition to the linear model, the existence of a threshold was also investigated by using B-splines and a parametric threshold model with the profile log likelihood evaluated at changing

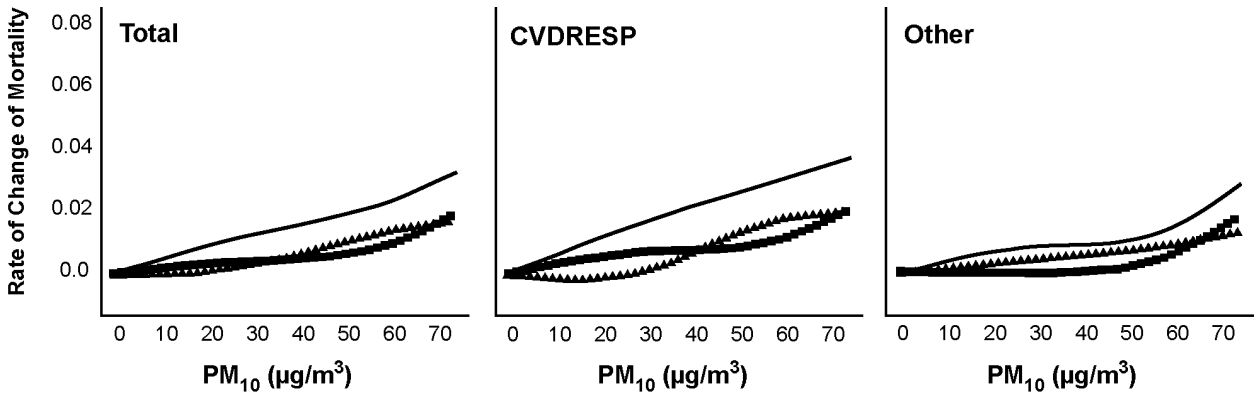

Figure 8-30. Concentration-response curves for PM_{10} mortality relationships in 20 largest U.S. cities (1987-1994), for total (Total) mortality, cardiovascular and respiratory (CVDRESP) mortality, and other-causes (Other) mortality. The concentration-response curves for the mean lag, current day, and previous day PM_{10} are denoted by solid lines, squared points, and triangle points, respectively.

Source: Dominici et al. (2003a).

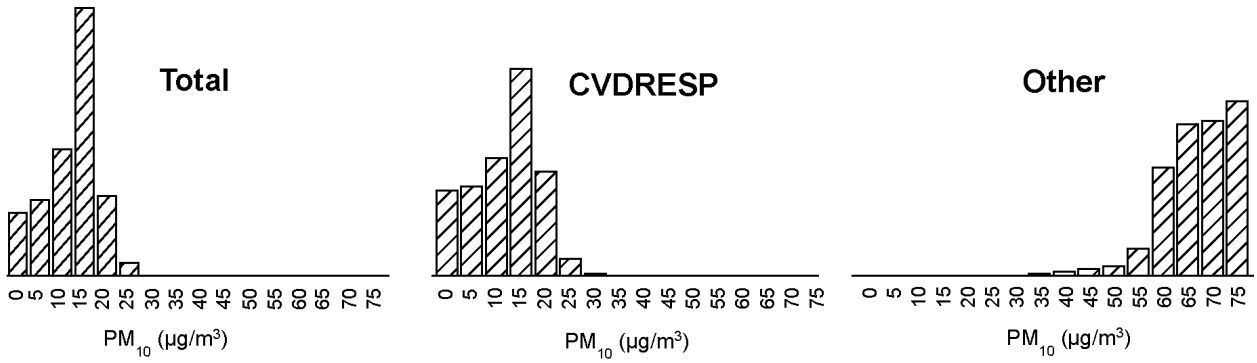

Figure 8-31. Posterior probabilities of thresholds for each cause-specific mortality and for mean PM_{10}, 20 largest U.S. cities, 1987-1994. Total = total nonaccidental mortality; CVDRESP = cardiovascular mortality and respiratory mortality; Other = mortality from other causes.

Source: Dominici et al. (2003a).

threshold points. B-splines results suggest that an increasing effect above 80 μg/m^3 for Birmingham, and above 100 μg/m^3 for Chicago. The threshold model through examination of log likelihood across the range of threshold levels also suggested similar change points, but not to an extent that statistically significant distinctions were demonstrated.

The Smith et al. (2000) study of associations between daily total mortality and $PM_{2.5}$ and $PM_{10-2.5}$ in Phoenix, AZ (during 1995-1997) also investigated the possibility of a threshold. In the linear model, the authors found that mortality was significantly associated with $PM_{10-2.5}$, but not with $PM_{2.5}$. In modeling possible thresholds, they applied: (1) a piecewise linear model in which several possible thresholds were specified; and (2) a B-spline (spline with cubic polynomials) model with 4 knots. Using the piecewise model, there was no indication that there was a threshold for $PM_{10-2.5}$. However, for $PM_{2.5}$, the piecewise model resulted in suggestive evidence for a threshold, around 20 to 25 μg/m^3. The B-spline results also showed no evidence of threshold for $PM_{10-2.5}$, but for $PM_{2.5}$, a nonlinear curve showed a change in the slope around 20 μg/m^3. A further Bayesian analysis for threshold selection suggested a clear peak in the posterior density of $PM_{2.5}$ effects around 22 μg/m^3. These results make it difficult to evaluate the relative roles of different PM components (in this case, $PM_{2.5}$ versus $PM_{10-2.5}$). However, the concentration-response curve for $PM_{2.5}$ presented in this publication suggests more of a U- or V-shaped relationship than the usual "hockey stick" relationship. Such a relationship is, unlike the temperature-mortality relationship, difficult to interpret biologically. Because the sample size of this data (3 years) is relatively small, further investigation of this issue using similar methods but a larger data set is warranted. Other studies evaluate nonlinear relationships using a multicity meta-smoothing approach based on non- or semi-parametric smoothers rather than on linear parametric models.

In summary, the results from large multicity studies suggest that there is no strong evidence of a clear threshold for PM mortality effect; nor is there clear evidence against possible thresholds for PM-related effects. Some single-city studies do provide some suggestive hints for possible thresholds, but not in a statistically clear manner. More data need to be examined with alternative approaches in order to better resolve the issue.

8.4.8 The Question of Heterogeneity of Particulate Matter Effects Estimates

Approximately 35 then-available acute PM exposure community epidemiologic studies were assessed in the 1996 PM AQCD as collectively demonstrating increased risks of mortality being associated with short-term (24-h) PM exposures indexed by various ambient PM measurement indices (e.g., PM_{10}, $PM_{2.5}$, BS, CoH, sulfates, etc.) in many different cities in the United States and internationally. Much homogeneity appeared to exist across various geographic locations, with many studies suggesting, for example, increased relative risk (RR) estimates for total nonaccidental mortality mainly on the order of 1.025 to 1.05 (or 2.5 to 5.0% excess deaths) per 50 $\mu g/m^3$ increase in 24-h PM_{10}, with statistically significant results extending more broadly in the range of 1.5 to 8.0%. The elderly $\geq$ 65 years old and those with preexisting cardiopulmonary conditions had somewhat higher excess risks. One study, the Harvard Six City Study, also provided estimates of increased RR for total mortality falling in the range of 1.02 to 1.056 (2.0 to 5.6% excess deaths) per 25 $\mu g/m^3$ 24-h $PM_{2.5}$ increment.

8.4.8.1 Evaluation of Heterogeneity in Time-Series Studies

More than 80 new time-series PM-mortality studies assessed earlier in this chapter provide extensive additional evidence which, qualitatively, largely substantiates significant ambient PM-mortality relationships, based on 24-h exposures indexed by a wide variety of PM metrics in many different cities of the United States, in Canada, in Mexico, and elsewhere (in South America, Europe, Asia, etc.). The newly available effect size estimates from such studies are reasonably consistent with the ranges derived from the earlier studies reviewed in the 1996 PM AQCD. For example, newly estimated PM_{10} effects generally fall in the range of 1.0 to 8.0% excess deaths per 50 $\mu g/m^3$ PM_{10} increment in 24-h concentration; and new $PM_{2.5}$ excess death estimates for short-term exposures generally fall in the range of 2 to 8% per 25 $\mu g/m^3$ increment in 24-h $PM_{2.5}$ concentration.

However, in contrast to the past appearance of considerable homogeneity among risk estimates, somewhat greater spatial heterogeneity appears to exist across newly reported study results, both with regard to PM-mortality and morbidity effects associations. The newly apparent heterogeneity of findings across locations is perhaps most notable in relation to reports based on

multiple-city studies in which investigators used the same analytical strategies and models adjusted for the same or similar co-pollutants and meteorological conditions, raising the possibility of different findings reflecting real location-specific differences in exposure-response relationships rather than potential differences in models used, pollutants included in the models, etc. Some examples of newly reported and well-conducted multiple-city studies include: the NMMAPS analyses of mortality and morbidity in 90 and 20 U.S. cities (Samet et al., 2000a,b; Dominici et al., 2000a); the Schwartz (2000b,c) analyses of 10 U.S. cities; the study of eight largest Canadian cities (Burnett et al., 2000); the study of hospital admissions in eight U.S. counties (Schwartz, 1999); and the APHEA studies of mortality and morbidity in several European cities (Katsouyanni et al., 1997; Zmirou et al., 1998).

The large NMMAPS studies of mortality and morbidity in U.S. cities provide important information about potential U.S. within- and between-region heterogeneity. HEI (2003a), after examining the NMMAPS GAM reanalyses by Dominici et al. (2002), concluded that while formal tests of PM effects across cities did not indicate evidence of heterogeneity because of the individual-city effects standard error being generally large, the power to assess the presence of heterogeneity was low and, as such, the possibility of heterogeneity still exists.

Some insight into the possible extent of heterogeneity can be gained by close examination of data from the NMMAPS study (Samet et al., 2000b). Data for excess risk and 95% confidence intervals were plotted by EPA against the total number of effective observations, measured by the number of days of PM_{10} data times the mean number of daily deaths in the community. This provides a useful measure of the weight that might be assigned to the results, since the uncertainty of the RR estimate based on a Poisson mean is roughly inversely proportional to this product. That is, the expected pattern should typically show less spread of estimated excess risk with increasing death-days of data. A more refined weight index would also include the spread in the distribution of PM concentrations. The results for NMMAPS, including the GAM reanalyses results, conform to some extent to the expected pattern. That is, with increasingly more mortality-days observations, the 95% confidence intervals generally became narrower. However, the results for relationships between effect size estimates and precision estimates for different regions vary considerably. In the Northeast, for example, there is some degree of consistency of

effect size for larger study-size cities, even with moderately wide confidence intervals for those with log mortality-days > 8 to 9, and all clearly exceed the overall nationwide grand mean. On the other hand, the smaller study-size Northeast cities (with much wider confidence intervals at log mortality-days < 8) show much greater variability of effect size estimates and less precision. As for the estimates derived for cities in other U.S. regions, there is even less consistency between magnitude of effect size and precision of the estimates, suggesting that other factors may account for differences in direction and/or size of the risk estimates.

Burnett and Goldberg (2003) also investigated heterogeneity in effects across eight Canadian cities, and concluded that there was not sufficient evidence to conclude that the PM association with mortality varies across the eight cities. In the initial analyses using GAM, a positive estimate of heterogeneity was reported, but in reanalyses using GLM with natural splines, negative estimates were reported. The authors stated that this reflected reduced variation in effect size estimates across cities along with increased within-city estimation error in the reanalysis results. In addition, as discussed in Section 8.2.2.3.3, in the initial analyses using data from the APHEA cohort, some apparent heterogeneity was found between results for western and eastern European cities; however, in reanalyses of these results, the distinctions between the western and eastern cities were less clear. Variables that may potentially influence heterogeneity of effects were further investigated in the APHEA2 analyses for 29 European cities, with mean NO_2 concentration in the cities (indicator of traffic-related pollution), warmer climate and low overall mortality rate being associated with increased PM-mortality associations.

Further closer reexamination of results for different areas in the U.S. or elsewhere may reveal interesting new insights into what factors may account for apparent differences among the cities within a given region or across regions. Some potential factors include differences in PM sources or composition, differences in population exposures across cities, and differences in potentially susceptible groups (e.g., % of population $\geq$ 65 yr old). The NMMAPS investigators reported no substantial differences in PM_{10}-mortality associations based on $PM_{2.5}$ / PM_{10} ratios or socioeconomic indicators for the various cities; however, no statistically significant evidence of heterogeneity was reported for that study. As stated previously, European investigators discussed several factors that may have influenced heterogeneity in PM-mortality associations across 29 European cities. These included variations in presence of an indicator of traffic-related

pollution, warmer climate (postulated to be related to better estimation of exposures since people were more likely to open windows) and low mortality rate (which the authors suggested was due to the larger number of potentially susceptible people in cities with lower mortality rates). These findings are consistent with those reported by Janssen et al. (2002, reanalyzed in Zanobetti and Schwartz (2003a), where PM_{10}-hospitalization associations were greater in areas with less use of central air conditioning and with greater contributions of PM_{10} emissions from vehicle emissions and oil combustion.

8.4.8.2 Comparison of Spatial Relationships in the NMMAPS and Cohort Reanalyses Studies

Both the NMMAPS and HEI Cohort Reanalyses studies had a sufficiently large number of U.S. cities to allow considerable resolution of regional PM effects within the "lower 48" states, but an attempt was made to take this approach to a much more detailed level in the Cohort Reanalysis studies than in NMMAPS. There were: 88 cities with PM_{10} effect size estimates in NMMAPS; 50 cities with $PM_{2.5}$ and 151 cities with sulfates in the original Pope et al. (1995) ACS analyses and in the HEI reanalyses using the original data; and 63 cities with $PM_{2..5}$ data and 144 cities with sulfate data in the additional analyses done by the HEI Cohort Reanalysis team. The relatively large number of data points utilized in the HEI reanalyses effort and additional analyses allowed estimation of surfaces for elevated long-term concentrations of $PM_{2.5}$, sulfates, and SO_2 with resolution on a scale of a few tens to hundreds of kilometers.

The patterns for $PM_{2.5}$ and sulfates are similar, but not identical. In particular, the modeled $PM_{2.5}$ surface (Krewski et al., 2000; Figure 18) had peak levels around Chicago-Gary, in the eastern Kentucky-Cleveland region, and around Birmingham AL, with elevated but lower $PM_{2.5}$ almost everywhere east of the Mississippi, as well as southern California. This is similar to the modeled sulfate surface (Krewski et al., 2000; Figure 16), with the absence of a peak in Birmingham and an emerging sulfate peak in Atlanta. The only area with markedly elevated SO_2 concentrations was the Cleveland - Pittsburgh region. Secondary sulfates in particles derived from local SO_2 appeared more likely to be important in the industrial midwest, south from the Chicago - Gary region into Ohio, northeastern Kentucky, West Virginia, and southwest Pennsylvania, possibly related to combustion of high-sulfur fuels.

The overlay of mortality with air pollution patterns is also of much interest. The spatial overlay of long-term $PM_{2.5}$ and mortality (Krewski et al., 2000; Figure 21) was highest from southern Ohio to northeastern Kentucky/West Virginia, but also included a significant association over most of the industrial midwest. This was reflected, in diminished form, by the sulfates and SO_2 maps (Krewski et al., 2000; Figures 19 and 20), where there appeared to be a somewhat tighter focus of elevated risk in the upper Ohio River Valley area. This suggests that, while SO_2 was an important precursor of sulfates in this region, there may also have been some other (non-sulfur) contributors to associations between $PM_{2.5}$ and long-term mortality, encompassing a wide area of the North Central Midwest and noncoastal Mid-Atlantic region.

The apparent differences in PM_{10} and/or $PM_{2.5}$ effect sizes across different regions should not be attributed merely to possible variations in measurement error or other statistical artifact(s). Some of these differences may reflect: real regional differences in particle composition or co-pollutant mix; differences in relative human exposures to ambient particles or other gaseous pollutants; sociodemographic differences (e.g., percent of infants or elderly in regional population); or other important, as of yet unidentified PM effect modifiers.

8.4.9 Age-Related Differences in PM Effect Estimates

Numerous epidemiological studies have reported health responses to PM and other pollutants for one or another specific age group. For example, in the U.S., data on hospital admissions for older people (aged 65 years and older) are available through a national data system maintained by the Health Care Financing Administration; and, thus, many U.S. hospital admissions studies have focused on health responses in this age group. Other studies, such as panel studies for asthma symptoms, have evaluated groups of schoolchildren. In general, such studies have indicated that both the elderly and children are likely susceptible subpopulations for PM-related effects (see Sections 8.3.1.4 and 8.3.2.5).

Though less commonly done, possible age-related differences in ambient PM health effects have been evaluated in certain recently published epidemiological studies that assessed health responses to air pollution by means of stratified analyses for different age groups within the population studied. For example, a number of studies have assessed relationships between PM

and total mortality across all ages, then evaluated possible differences in risk for the subset of older adults (50+ or 65+ years); and some of these have reported slightly larger effect estimates for the older age group (e.g., Schwartz et al., 1996a; Styer et al., 1995; Borja-Aburto et al., 1998), whereas others have found associations that are similar in magnitude or even slightly smaller for the older age group (e.g., Ostro et al., 1999a, 1995; Castillejos et al., 2000). Also, Chock et al. (2000) reported associations between PM and total mortality that were not substantially different for age groups of 0 to 74 and 75+ years.

In other studies of hospital admissions or medical visits for asthma or respiratory disease, some studies have reported larger effect estimates for children than for adults (e.g., Anderson et al., 1998; Medina et al., 1997), whereas others have reported effect estimates of generally similar size across young and adult age groups (e.g., Atkinson et al., 1999b; Hajat et al., 1999; Wong et al., 1999a) and some studies of respiratory hospital admissions have shown larger effect sizes for adults (e.g., Prescott et al., 1998). For hospital admissions or medical visits for cardiovascular diseases, most studies (but not all -- e.g., Atkinson et al., 1999a), have reported somewhat larger effect estimate sizes for older adults (65+ years) than adults in younger age categories (e.g., Le Tertre et al., 2003; Wong et al., 1999a; Prescott et al., 1998; Morgan et al., 1998).

The above rather small group of studies does not show striking differences in effect estimates from analyses across age group strata, but they do tend to support previous findings that, depending on the specific type of effect under study, older adults and children may be more susceptible to certain PM- related effects. More specifically, older adults (aged 65+ years) appear to be most clearly at somewhat higher risk for PM exacerbation of cardiovascular-related disease effects and , perhaps, tend to experience higher PM-related total (nonaccidental) mortality risk, as well. On the other hand, more limited evidence points toward children possibly being at somewhat higher risk for respiratory-related (especially asthma) PM effects than adults.

8.4.10 Implications of Airborne Particle Mortality Effects

The public health burden of mortality associated with exposure to ambient PM depends not only on the increased risk of death, but also on the amount of life shortening that is attributable to

those deaths. The 1996 PM AQCD concluded that confident quantitive determination of years of life lost to ambient PM exposure was not yet possible and life shortening may range from days to years (U.S. Environmental Protection Agency, 1996a). Now, some newly available analyses provide further interesting insights with regard to potential life-shortening associated with ambient PM exposures.

8.4.10.1 Short-Term Exposure and Mortality Displacement

A few studies have investigated the question of "harvesting," a phenomenon in which a deficit in mortality occurs following days with (pollution-caused) elevated mortality, due to depletion of the susceptible population pool. This issue is very important in interpreting the public health implication of the reported short-term PM mortality effects. The 1996 PM AQCD discussed suggestive evidence observed by Spix et al. (1993) during a period when air pollution levels were relatively high. Recent studies, however, generally used data from areas with lower, non-episodic pollution levels.

Schwartz (2000c; reanalysis 2003a) separated time-series air pollution, weather, and mortality data from Boston, MA, into three components: (1) seasonal and longer fluctuations; (2) "intermediate" fluctuations; (3) "short-term" fluctuations. By varying the cut-off between the intermediate and short term, evidence of harvesting was sought. The idea is, for example, if the extent of harvesting were a matter of a few days, associations between weekly average values of mortality and air pollution (controlling for seasonal cycles) would not be seen. Schwartz's reanalysis using natural splines reported reductions in COPD mortality $PM_{2.5}$ risk estimates for longer time scale, suggesting that most of the COPD mortality was only displaced by a few weeks. However, for pneumonia, ischemic heart disease, and all cause mortality, the effect size increased, as longer time scales were included. For example, the percent increase in nonaccidental deaths associated with a 25 $\mu g/m^3$ increase in $PM_{2.5}$ increased from 5.8% (CI: 4.5, 7.3) for the15-day window to 9.7% (CI: 8.2, 11.2) for the 60-day window. Note, however, that the 60-day time scale window is in the range of influenza epidemics. Some caution is therefore needed in interpreting risk estimates in this range.

Zanobetti et al. (2000b) used what they termed "generalized additive distributed lag models" (penalized splines using an algorithm that did not require back-fitting were used for all

the smoothing terms) to help quantify mortality displacement in Milan, Italy, 1980 to 1989. Nonaccidental total deaths were regressed on smooth functions of TSP distributed over the same day and the previous 45 days using penalized splines for the smooth terms and seasonal cycles, temperature, humidity, day-of-week, holidays, and influenza epidemics. The mortality displacement was modeled as the initial positive increase, negative rebound (due to depletion), followed by another positive coefficients period, and the sum of the three phases were considered as the total cumulative effect. TSP was positively associated with mortality up to 13 days, followed by nearly zero coefficients between 14 and 20 days, and then followed by smaller but positive coefficients up to the 45 th day (maximum examined). The sum of these coefficients was over three times larger than that for the single-day estimate.

Zanobetti et al. (2000a; reanalysis by Zanobetti and Schwartz, 2003b) also applied the same concept described above (up to 41 lag days) to 10 cities from APHEA2 to estimate distributed lag PM_{10} mortality risks. They applied the covariate adjustment in a GAM model used in APHEA2 (Katsouyanni et al., 2001) and in reanalysis (Zanobetti and Schwartz, 2003b), they also used penalized splines in addition to the GAM model with stringent convergence criteria. The resulting city specific coefficients were pooled in the second-stage model, taking into account heterogeneity across cities. The estimated shape of the distributed lag pooled across 10 cities showed a similar pattern to that from Milan data described above, with the second "hump" of smaller but positive coefficients between approximately 20 to 35 days. The results indicated that, compared to PM_{10} risk estimates obtained for the average of lag 0 and 1 days, the distributed lag estimates up to 40 days were about twice larger in both GAM and penalized splines models. For example, the combined distributed lag estimates for the 10 cities using penalized splines was 5.6% (CI: 1.5, 9.8), as compared to 2.9% (CI: 1.4, 4.4). It should be noted, however, that the results for individual cities varied. For example, the estimates for average of lag 0 and 1 days and the distributed lag model were comparable in Tel Aviv, whereas it was nearly seven times bigger for distributed lag model in Lodz. Thus, while these results do support the lack of mortality displacement up to 40-45 day period, the pattern of lagged associations may vary from city to city.

Two new studies conducted very different analyses, beginning with the assumption that harvesting is occurring. Both research groups used models to estimate the size of the frail

populations. In one study, as part of their analysis of PM_{10}-mortality association in Birmingham, AL and Cook County, IL, Smith et al. (1999) used a latent variable structure fitted through Bayesian techniques using Monte Carlo sampling. The resulting posterior mean for the size of the frail population in Chicago was 765 (posterior s.d. = 189). The mean numbers of days lost per person as a result of 10 $\mu g/m^3$ increase in PM_{10} was estimated to be 0.079 day (posterior s.d. = 0.032). In the other study, Murray and Nelson (2000) used Kalman filtering to estimate a hazard function of TSP in a state space model in the Philadelphia mortality data during 1973 to 1990. The model framework, which assumes an harvesting effect, allows estimation of at-risk population and the effect of changes in air quality on the life expectancy of the at-risk population. Combinations of TSP, linear temperature, squared temperature, and interaction of TSP and temperature were considered in six models. The size of at-risk (or frail) population estimated was about 500 people. Life expectancy was estimated to be reduced by about 2.5 days with TSP exposure for the roughly 500 at-risk frail individuals in Philadelphia suggesting that the hazard causing agent makes a difference of only 2.5 days in the at-risk frail population. In both cases, the estimated size of the frail population is very small with short life expectancy. In these cases, based on the assumption that harvesting is occurring and only small frail populations are at risk, life shortening due to PM exposures is estimated to be on the order of just a few days.

Zeger et al. (1999) first illustrated, through simulation, the implication of harvesting for PM regression coefficients (i.e., mortality relative risk) as observed in a frequency domain. Three levels of harvesting (3 days, 30 days, and 300 days) were simulated. As expected, the shorter the harvesting, the larger the PM coefficient in the higher frequency range. However, in the analysis (and reanalysis by Dominici et al., 2003a) of real data from Philadelphia, regression coefficients increased toward the lower frequency range, suggesting that the extent of harvesting, if it exists, is not in the short-term range. Zeger suggested that "harvesting-resistant" regression coefficients could be obtained by excluding coefficients in the very high frequency range (to eliminate short-term harvesting) and in the very low frequency range (to eliminate seasonal confounding). Since the observed frequency domain coefficients in the very high frequency range were smaller than those in the mid frequency range, eliminating the "short-term harvesting" effects would only increase the average of those coefficients in the rest of the frequency range.

Frequency domain analyses are rarely performed in air pollution health effects studies, except perhaps for spectral analysis (variance decomposition by frequency) to identify seasonal cycles. Examinations of the correlation by frequency (*coherence*) and the regression coefficients by frequency (*gain*) may be useful in evaluating the potential frequency-dependent relationships among multiple time series. A few past examples in air pollution health effects studies include: (1) Shumway et al.'s (1983) analysis of London mortality analysis, in which they observed that significant coherence occurred beyond two week periodicity (they interpreted this as "pollution has to persist to affect mortality"); (2) Shumway et al.'s (1988) analysis of Los Angeles mortality data, in which they also found larger coherence in the lower frequency; (3) Ito's (1990) analysis of London mortality data in which he observed relatively constant gain (regression coefficient) for pollutants across the frequency range, except the annual cycle. These results also suggest that associations and effect size, at least, are not concentrated in the very high frequency range.

Dominici et al. (2003c) also explored associations between air pollution and mortality using data from the four cities included in NMMAPS that had every-day PM_{10} measurements, Chicago, Minneapolis, Pittsburgh, and Seattle. The authors first used discrete Fourier transformation to decompose the air pollution time series into distinct component series: < 3.5, 3.5-6, 7-13, 14-29, 30-59, and ≥ 60 days. They then calculated associations without decomposition and with each of the timescale components, with the expectation that under a short-term mortality displacement scenario, mortality would be mainly associated with air pollution at the short timescales. For both individual cities and the four cities overall, a pattern was found of larger effects at the longer timescales and smaller effects at the shorter timescales. For a 1-day lag, the 4-city overall relative risk of 0.22% increase in cardiovascular and respiratory mortality per 10 $\mu g/m^3$ PM_{10} (CI: -0.02, 0.46) was comparable to that found in the 90-city analyses (Dominici et al., 2003b). At the ≥ 60 day timescale, the authors report relative risks of 1.35% (CI: 0.52, 2.17) per 10 $\mu g/m^3$ PM_{10} for total mortality, and 1.87% (CI: 0.75, 2.99) per 10 $\mu g/m^3$ PM_{10} for cardiovascular and respiratory mortality. The authors also investigated the sensitivity of their findings to alternative lag period choice (optimal lags from 0-6 days selected), adjustment for long-term trends and seasonality (ranging from 3.5 to 14 degrees of freedom per year for time), and alternative assumptions of heterogeneity in effects between cities. For all, the authors report that the overall pattern of results remains similar, though the confidence intervals widened considerably with greater

heterogeneity. The authors conclude that the results are inconsistent with the short-term mortality displacement hypothesis.

In a commentary on the previous analyses, Smith (2003) conducted further analyses using the software developed by Dominici et al. (2003b) and TSP data from Philadelphia. Results are presented for models including alternative timescales for meteorological factors in the analyses, with a consistent pattern of results showing larger effect estimates with longer timescales. Smith (2003) also used the frequency decomposition software with a simulated data set that had an assumed association between TSP and mortality (1% increase per 10 $\mu g/m^3$ TSP). From these results, the author concluded that it was more difficult to determine time-scale dependency in response, particularly for the results of the simulated harvesting model, where the effect estimate appears to be consistent in size across all time scales but the longest ($\geq$ 60 days). In addition, the author conducted a simpler analysis using multi-day averaged TSP concentrations, up to a 30-day average, with the results of different models indicating a peak in the time-dependent TSP effect at ~15 days but with different patterns for longer time scales. The author concluded that interpretation of results from these models remained as difficult as ever. In response, Dominici et al. (2003b) agreed that careful interpretation of air pollution-mortality models and consideration of assumptions is needed. The authors discuss further their results of analyses using data from the four NMMAPS cities, observing that their "harvesting-resistent" effect estimates are larger than the "harvesting-prone" estimates, and that these results are consistent with air pollution effects on all people, not simply the very frail.

Schwartz (2000c), Zanobetti et al. (2000b), Zanobetti et al., (2000a); reanalysis by Zanobetti and Schwartz, (2003b) and Zeger et al.'s analysis (1999); reanalysis by Dominici et al. (2003a, 2003b) all suggest that the extent of harvesting, if any, is not a matter of only a few days. Other past studies that used frequency domain analyses are also at least qualitatively in agreement with the evidence against the short-term only harvesting. Since long wave cycles (> 6 months) need to be controlled in time-series analyses to avoid seasonal confounding, the extent of harvesting beyond 6 months periodicity is not possible in time-series study design. Also, influenza epidemics can possibly confound the PM-mortality associations in the 1 to 3 month periodicity ranges. Therefore, interpreting PM risk estimates in these "intermediate" time scale also requires caution.

In contrast to this group of studies, Smith et al. (1999) and Murray and Nelson (2000) suggest that the frail population is very small and its life expectancy short, such that PM or any external stress cannot have more than a few days of life-shortening impacts on this specific subpopulation. This may, in part, reflect the limitation of the model itself when applied only to a small frail subpopulation. Thus, there appears to be consistency in results within the similar models but not across different types of models. Clearly, more research is needed in this area both in terms of development of a conceptual framework that can be tested with real data, and applications of these models to more data sets. However, at least in the models that extend the common time-series modeling, there appears to be no strong evidence to suggest that PM is shortening life by only a few days.

8.4.10.2 Life-Shortening Estimates Based on Prospective Cohort Study Results

Brunekreef (1997) reviewed available evidence for long-term PM exposure effects on mortality and, using life table methods, derived a rough preliminary estimate of the reduction in life expectancy implied by those effect estimates. Based on the results of Dockery et al. (1993) and Pope et al. (1995), a relative risk of 1.1 per 10 $\mu g/m^3$ exposure over 15 years was assumed for the effect of PM air pollution on men 25 to 75 years old. A 1992 life table for men in the Netherlands was developed for 10 successive five-year categories that make up the 25 to 75 year old age range. Life expectancy of a 25 year old was then calculated for this base case and compared with the calculated life expectancy for the PM-exposed case, in which the death rates were increased in each age group by a factor of 1.1. A difference of 1.11 years was estimated between the "exposed" and "clean air" cohorts' overall life expectancy at age 25. Looked at another way, this implies that the expected lifespan for persons who actually died from air pollution would be reduced by more than 10 years, because they represent a small percentage of the entire cohort population. A similar calculation by present EPA authors, based on the 1969-71 life table for U.S. white males, yielded a larger estimated reduction of 1.31 years for the entire U.S. population's life expectancy at age 25. Thus, these calculations imply that relatively small differences in long-term exposure to ambient PM may have substantial effects on life expectancy. However, these "back of the envelope" calculations have not been verified by others and can only be viewed as providing very rough "ballpark" estimates of potential life-shortening effects of PM.

They depend heavily on the specific PM risk estimates used and, for example, would likely have to be adjusted downward to reflect the newer (presumably more credible) lower RR estimates derived from the Pope et al. (2002) ACS extension study.

8.4.10.3 Potential Effects of Infant Mortality on Life-Shortening Estimates

Deaths among children would logically have the greatest influence on a population's overall life expectancy, but the Brunekreef (1997) life table calculations did not consider any possible long-term air pollution exposure effects on the population aged < 25 years. Thus, any premature mortality that may occur among children due to PM exposure would logically be likely to increase significantly any overall population life shortening over and above that estimated by Brunekreef (1997) for long-term PM exposure of adults aged ≥ 25 years. However, as discussed earlier, only a few older cross-sectional studies and a few more recent studies provide very limited evidence bearing on the extent to which infants may be among subpopulations affected by long-term PM exposure. Thus, much more definitive future research is needed before infant mortality can be considered in generating estimates of potential PM-related life shortening in the U.S. population.

8.5 SUMMARY OF KEY FINDINGS AND CONCLUSIONS DERIVED FROM PARTICULATE MATTER EPIDEMIOLOGY STUDIES

Important types of additions to the epidemiologic database beyond that assessed in the 1996 PM AQCD, as evaluated above in this chapter, include:

- Several new multicity studies of mortality and morbidity effects which provide more precise estimates of PM effect sizes than most smaller-scale individual city studies;

- A large number of new studies of various health endpoints using mass-based indicators of thoracic particles (e.g., PM_{10}); fine-fraction particles (e.g., $PM_{2.5}$ and/or components such as sulfates, nitrates, H^+, and ultrafine particles [$PM_{1.0}$ and smaller]); and, to a lesser extent, coarse-fraction particles (e.g., $PM_{10-2.5}$ and components such as crustal particles).

- Many new studies that reflect consideration of ambient PM as a component of complex air pollution mixtures and which evaluate the sensitivity of estimated PM effects to the inclusion of gaseous co-pollutants (e.g., O_3, CO, NO_2, SO_2) and/or various different PM indicators / components in analytical models;

- New and reanalyzed studies that provide insight into the sensitivity of PM effects to the use of alternative statistical models and model specifications for addressing weather and other temporal variables;

- New studies providing insight into various key issues such as alternative lag structures (e.g., single-day and distributed lags), concentration-response relationships, spatial heterogeneity of PM effects, measurement error effects (e.g., differential error across various PM components and/or gaseous co-pollutants);

- Initial studies using new approaches to evaluate the effects of combinations of air pollutant or mixtures including PM components, based on empirical combinations (e.g., factor analysis or source profiles);

- New evidence from "found experiments," or so-called "intervention studies" that evaluate associations between reduced air pollution levels and improvements in health endpoints;

- Numerous new studies of cardiovascular endpoints, with particular emphasis on assessment of cardiovascular risk factors as well as symptoms;

- Additional new studies on asthma and other respiratory conditions potentially exacerbated by ambient PM exposure;

- New and extended studies of long-term PM exposure effects, notably including analyses of lung cancer associations with long-term exposures to ambient PM;

- New studies of infants and children as a potentially susceptible population; and

- New studies providing insights into the public health impacts of ambient PM associations with mortality, as well as with other health indices (e.g., physician visits).

Evaluation of the new epidemiologic studies, in conjunction with previously existing ones involves consideration of several salient aspects of the evidence so as to reach conclusions as to the likely causal significance of observed associations between ambient PM indicators and various health endpoints. As discussed in Section 8.1.4, these aspects include what can be

generally characterized as the strength and consistency of the epidemiologic evidence, as well as broader aspects of plausibility and coherence that reflect an integration of the epidemiologic evidence with information derived from other types of studies (e.g., exposure, dosimetry, toxicology, etc.). Evaluation of the evidence involves an objective appraisal of these salient aspects, recognizing that they do not lend themselves to the application of simple formulas for reaching conclusions with a known degree of certainty, but rather involve an exercise in reaching scientific judgments, taking into account the broad range of views held by the scientific experts engaged in this review. Conclusions derived from such an appraisal of the epidemiologic evidence are presented below, with a broader, more integrative synthesis of all relevant information being presented in Chapter 9.

(1) Thoracic Particles. An extensive body of epidemiology evidence, confirming earlier-reported associations between short- and long-term exposures (inferred from stationary air monitor measures) to ambient thoracic particles (typically indexed by PM_{10}) and mortality/morbidity effects, supports the general conclusion that ambient thoracic particles, acting alone and/or in combination with gaseous co-pollutants, are likely causally related to various human health endpoints.

The strength of the evidence across such endpoints includes especially strong evidence for PM_{10} associations with total (nonaccidental) mortality. A large majority of relevant mortality studies show positive PM_{10} effect estimates, with most all (especially the relatively more precise) estimates being statistically significant. In particular, several multicity studies in the U.S., Canada, and Europe provide strong support for this conclusion, reporting statistically significant associations with total mortality effect estimates ranging from ~1.0 to 3.5% (per 50 $\mu g/m^3$ 24-h PM_{10} increment). These estimates are generally within (but toward the lower end of) the range of PM_{10} estimates previously reported in the 1996 PM AQCD. It is notable that the effect estimates from the largest of the multicity studies (for the 90 largest U.S. cities) have also been shown to be robust to the inclusion of gaseous co-pollutants, and the significance of the effect estimates has been shown to be robust to the use of alternative statistical models. The multicity estimates as well as total mortality risk estimates from many individual-city studies, generally falling in the range of ~1.0 to 8.0% per 50 $\mu g/m^3$ 24-h PM_{10} increment, also comport well with results of numerous new studies reporting increased cause-specific cardiovascular- and

respiratory-related mortality (most statistically significant) and/or cardiovascular and respiratory-related (most statistically significant) morbidity effects.

(2) Fine-fraction particles. A growing body of epidemiologic evidence both (a) confirms associations between short- and long-term ambient exposures (inferred from stationary air monitor measures) to fine-fraction particles (generally indexed by $PM_{2.5}$) and various mortality or morbidity endpoint effects and (b) supports the general conclusion that $PM_{2.5}$ (or one or more $PM_{2.5}$ components), acting alone and/or in combination with gaseous co-pollutants, are likely causally related to observed ambient fine particle-associated health effects.

The strength of the evidence varies across such endpoints, with relatively stronger evidence of associations with cardiovascular than respiratory endpoints. As seen in the PM_{10} studies, a large majority of studies of fine-fraction particles show positive effects estimates, with most all of the relatively more precise estimates being statistically significant. In addition, mortality associations with long-term exposures to $PM_{2.5}$, in conjunction with evidence of associations with short-term exposures, provide strong evidence in support of a casual inference. This conclusion is also supported by studies showing associations with ultrafine particles and other fine-particle components (e.g., sulfates), and by studies showing associations with air pollution factors linked to key sources of fine-fraction particles (e.g., motor vehicles, other oil and/or coal combustion sources, etc).

(3) Coarse-fraction particles. A much more limited body of evidence is suggestive of associations between short-term (but not long-term) exposures (inferred from stationary air monitor measures) to ambient coarse-fraction thoracic particles (generally indexed by $PM_{10-2.5}$) and various mortality and morbidity effects observed at times in some locations. This suggests that $PM_{10-2.5}$, or some constituent component(s) of $PM_{10-2.5}$, may contribute under some circumstances to increased human health risks.

The strength of the evidence varies across endpoints, with somewhat stronger evidence for coarse-fraction particle associations with morbidity (especially respiratory) endpoints than for mortality. Reasons for differences among findings on coarse-particle health effects reported for different cities are still poorly understood, but several of the locations where significant $PM_{10-2.5}$ effects have been observed (e.g., Phoenix, Mexico City, Santiago) tend to be in drier climates and may have contributions to observed effects due to higher levels of organic particles from biogenic processes (e.g., endotoxins, fungi, etc.) during warm months.

Other studies suggest that particles of crustal origin are generally unlikely to exert notable health effects under most ambient exposure conditions. Some exceptions may include situations where crustal particles have come to be heavily contaminated by metals originally emitted as fine particles from smelting operations but deposited over many years on soils around smelters, steel mills, etc. (see Item 10, below). Also, in some U.S. cities (especially in the NW and the SW) where $PM_{10-2.5}$ tends to be a large fraction of PM_{10}, measurements, coarse thoracic particles from woodburning are often an important source during at least some seasons. In such situations, the relationship between hospital admissions and PM_{10} may be an indicator of response to coarse thoracic particles from wood burning.

(4) Co-pollutant confounding and effects modification. Much progress has been made in sorting out contributions of ambient PM_{10} and its components to observed health effects relative to other co-pollutants; and, despite continuing uncertainties, the evidence overall tends to support the above conclusions that ambient PM_{10} and $PM_{2.5}$ are most clearly associated with mortality/morbidity effects, acting either alone or in combination with other covarying gaseous pollutants, with more limited support with regard to $PM_{10-2.5}$.

A major methodological issue affecting epidemiology studies of both short-term and long-term PM exposure effects relates to use of appropriate approaches for evaluating the extent to which other air pollutants correlated with ambient PM, including gaseous criteria pollutants (e.g, O_3, NO_2, SO_2, CO), air toxics, and/or bioaerosols, may confound or modify PM-related effects estimates. A variety of statistical methods for assessing potential confounding arising from these associations have been employed. However, no clear consensus yet exists as to what methods may be most appropriate or adequate for many specific cases. The inclusion of multiple pollutants often produces statistically unstable estimates (for PM, at times, and/or for other gaseous co-pollutants), such that this commonly applied approach has inherent limitations in disentangling the effects of highly correlated pollutants. Omission of other well correlated, potentially-contributing pollutants, on the other hand, may incorrectly attribute some of their independent effects to PM or obscure possible modifying of PM effects by them. Still, progress has been made in evaluating effects of ambient PM and those of other co-pollutants; and, overall, the new evidence tends to

substantiate that observed PM effects are at least partly due to ambient PM acting alone or in the presence of other covarying gaseous pollutants.

(5) Alternative Model Specifications for Meteorological Variables. The results of available epidemiologic studies, using a variety of approaches to control for weather effects, appear to demonstrate increased PM-related mortality and morbidity risks beyond those attributable to weather influences alone. However, there is no clear consensus at this time with regard to what constitutes appropriate or adequate model specifications to control for possible weather contributions to those human mortality/morbidity effects attributed to PM exposure and/or on how best to characterize possible joint (interactive) effects of weather and ambient PM or other air pollutants.

A wide variety of statistical approaches have been used in attempting to control for weather effects. Temperature extremes (hot or cold) are well known to cause increased morbidity and mortality, leading some investigations to simply characterize cities as "hot" or "cold" (based on annual mean temperatures) and to compare PM effect estimates across such categories. Others have included temperature and/or humidity as continuous linear variables in models and then tested for PM or gaseous pollutant effects on remaining risk residuals. Others have used widely varying model specifications for nonlinear temperature-response curves, with varying numbers of knot points, types of splines (natural, penalized, etc.), and numbers of degrees of freedom used in certain models (e.g. GAM). Still others have argued for and made at least preliminary attempts to use "synoptic weather categories" that define daily combinations of temperature, humidity, and/or other weather variables as constituting "offensive weather patterns" associated with increased risk of morbidity/mortality in a given city, with such "offensive" synoptic patterns varying from city to city in different regions. Higher temperatures and/or humidity combinations, for example, are required in certain southern U.S. cities (e.g. New Orleans, Miami, Atlanta, etc.) to reach "heat index" levels associated with increased risk of heat stroke and/or heat-related deaths than in northern U.S. cities (e.g. St. Louis, Chicago, New York, etc.). One study tested a large number of parametric and nonparametric models with different model specifications for weather variables and found very consistent PM effect size estimates (all statistically significant), even for those models using synoptic weather patterns in several of the models. It is not clear, however, as to what extent the PM effect estimates would be reduced in reanalyses of any of

the original GAM-related model runs in that study. New evidence is also emerging for possible weather-related modification of air pollution effects (or vice versa), such as results indicative of more deaths occurring on high temperature/humidity days that also have elevated PM or O_3 levels present than on high heat index days with cleaner air.

(6) Measurement Error. Newly available statistical simulation studies highlight the importance of considering differential measurement error in assessing and interpreting epidemiologic findings concerning the magnitude and precision of PM effect estimates, especially in relation to comparison of the relative strength or robustness of effect estimates attributed to one or another PM indicator (e.g., PM_{10}, $PM_{2,5}$, $PM_{10-2.5}$, etc.) or comparison of such to gaseous co-pollutant (e.g., O_3, NO_2, SO_2, CO) effect estimates.

The simulation studies indicate that the greater the measurement error associated with exposure estimates for a given pollutant or indicator, then the less precise the effect size estimate and the less robust it tends to be in multipollutant models. Of importance, directly measured PM_{10} and $PM_{2.5}$ values likely have less measurement error than $PM_{10-2.5}$ values derived by subtracting (differencing) between PM_{10} and $PM_{2.5}$ readings (or city-wide averages of them), especially if obtained from non-collocated PM_{10} and $PM_{2.5}$ monitors at different locations in a given urban area. Also, gaseous pollutant exposure estimates based on hourly or daily measurements at many monitoring sites in an urban area are likely subject to less measurement error than PM_{10} or $PM_{2.5}$ samples obtained on 1-in-6 day monitoring schedules at fewer locations or extrapolated from measures of other PM indicators (e.g. PM_{10} from TSP data) or other types of data (e.g., estimating fine particle or $PM_{2.5}$ levels based on airport visibility via use of light extinction calculations). Importantly, available simulation studies show that "transfer of effects", wherein the effects of one pollutant (e.g., one or another gaseous co-pollutant) are inappropriately attributed to another (e.g. PM_{10} or $PM_{2.5}$) in multipollutant models, can occur only under very unusual circumstances, e.g., with simultaneously very high positive or negative correlation ($r \geq .90$) between ambient PM indicators and co-pollutant levels and high negative correlations between their respective measurement errors, conditions not yet reported for real world data sets.

(7) Alternative Lag Structures. Different PM size components or particles with different composition or sources may produce effects by different mechanisms manifested at different lags, and different preexisting health conditions may lead to different delays between exposure and effect.

Thus, although maximum effect sizes for PM effects have often been reported for 0-1 day lags, evidence is also beginning to suggest that more consideration should be given to lags of several days. It is plausible that effects linked with PM may arise from different responses or PM-associated diseases with different characteristic lags, for example, that cardiovascular responses may arise almost immediately after exposure, within zero or one day lags or even within two hours (Peter et al., 2001a, for myocardial infarction). In contrast, a number of studies on respiratory symptoms have reported finding larger effect estimates with moving average lag models (for example, Mortimer et al., 2001). One would then expect to see different best-fitting lags for different effects, based on potentially different biological mechanisms as well as individual variability in responses. If various health effects are substantiated by toxicological evidence as likely occurring at different lag days, so that the risks for each lag day should be additive, then higher overall risks may exist that than are implied by maximum estimates for any given single day lag. In that case, multi-day averages or distributed lag models should be used to project more fully any potential PM-related public health risks.

(8) Cardiovascular Endpoints. Numerous time series studies indicate that increased cardiovascular-related mortality and/or morbidity risks are associated with short-term ($\leq$ 24-h) exposure to ambient particles (especially PM_{10} and/or $PM_{2.5}$).

Cardiovascular mortality risks appear to be increased most strongly (especially for those $\geq$ 65 years old) with $PM_{2.5}$ and occur within short lag times (0-1 day). Morbidity measures, e.g., cardiovascular hospital admissions and emergency department visits are also positively (but not as statistically significantly) related to short-term (24-h) $PM_{2.5}$ exposures. Several different panel studies (but not all) that evaluated temporal associations between PM exposures and measures of heart beat rhythm in elderly subjects found results suggestive of ambient PM exposure being associated with changes in electrocardiographic (ECG) markers of cardiac function, e.g., altered heart rate variability (HRV), shown in other studies to be indicators of increased risk for serious cardiovascular outcomes (e.g., heart attacks). However, conflicting implications of the specific alterations in ECG patterns indicative of likely predominance of sympathetic versus parasympathetic cardiac control preclude clear

conclusions. Other studies point toward changes in blood characteristics (e.g., alterations in C-reactive protein levels, fibrinogen levels, blood viscosity, etc.) related to increased risk of ischemic heart disease also being associated with ambient PM exposures. However, these heart rhythm and blood chemistry findings should currently be viewed as providing only very limited suggestive evidence indicative of potential pathophysiologic alterations contributing to serious PM-related cardiovascular effects (e.g., myocardial infarction, stroke, death).

(9) Respiratory Endpoints. Notable new evidence now exists which substantiates positive associations between ambient PM concentrations and (a) increased respiratory-related hospital admissions, emergency department, and other medical visits; (b) increased incidence of asthma and other respiratory symptoms; and (c) decrements in pulmonary functions.

Of much interest are new findings tending to implicate not only fine particle components but also coarse thoracic (e.g., $PM_{10-2.5}$) particles as likely contributing to exacerbation of various respiratory conditions (e.g., asthma). Also of much interest are emerging new findings indicative of likely increased occurrence of chronic bronchitis in association with (especially chronic) PM exposure. New reanalyses or extensions of earlier prospective cohort studies of long-term ambient PM exposure effects also show substantial evidence for increased lung cancer risk being associated with such PM exposures, especially exposure to fine PM or specific fine particles subcomponents (e.g., sulfates) and/or associated precursors (e.g., SO_2).

(10) Spatial Heterogeneity of PM Effects. There appears to be greater spatial heterogeneity in city-specific excess risk estimates for relationships between short-term ambient PM_{10} concentrations and acute health effects than was previously evident.

The reasons for such variation in effects estimates are not well understood. Factors likely contributing to the apparent heterogeneity include geographic differences in air pollution mixtures, composition of ambient PM components, and personal and sociodemographic factors potentially affecting PM exposure (such as use of air conditioning), as well as differences in PM mass concentration. For example, the Utah Valley studies showed that PM_{10} particles, known to be richer in metals during exposure periods while the steel mill was operating, were more highly associated with adverse health effects than was PM_{10} during

the PM exposure reduction while the steel mill was closed. In contrast, when PM_{10} and $PM_{2.5}$ samples were relatively higher in crustal particles during windblown dust episodes in Spokane and at three central Utah sites than at other times, they were not associated with higher total mortality during those periods. These differences require more research that may become more feasible as the $PM_{2.5}$ sampling network produces air quality data for speciated samples.

Certain classes of ambient particles appear to be distinctly less toxic than others and are unlikely to exert human health effects at typical ambient exposure concentrations (or perhaps only under special circumstances). For example, particles of crustal origin, which are predominately in the coarse fraction, are relatively non-toxic under most circumstances, compared to combustion-related particles (such as from coal and oil combustion, wood burning, etc.) However, under some conditions, crustal particles may become sufficiently toxic to cause human health effects. For example, resuspended crustal particles may be contaminated with toxic trace elements and other components from previously deposited fine PM, e.g., metals from smelters (Phoenix) or steel mills (Steubenville, Utah Valley), PAHs from automobile exhaust, or pesticides from agricultural lands. Fine particles of differing composition from different sources may also vary in toxic potency and in associated health risks. More research is needed to identify conditions under which one or another class of particles may cause little or no adverse health effects, as well as conditions under which particles may cause notable effects.

The above reasons suggest that it is inadvisable to pool epidemiology studies involving different locations, different time periods, different population subgroups, or different health endpoints, without assessing potential causes and the consequences of these differences. However, multicity analyses using common data bases, measurement devices, analytical strategies, and extensive independent external review (as carried out in the NMMAPS and APHEA studies) are useful. Quantitative meta-analyses of more diverse collections of independent studies of different cities, varying in methodologies used and/or in data quality or representativeness, are likely less credible.

(11) Effects of Long-term PM Exposure. Long-term PM exposure durations, on the order of months to years, are statistically associated with human health effects (indexed by mortality, development of chronic respiratory disease, and changes in lung function).

Notable uncertainties remain regarding the magnitude of and mechanisms underlying chronic health effects of long-term PM exposures and relationships between chronic exposure effects and acute responses to short-term exposures. Prospective cohort studies providing mortality risk estimates likely most representative of the general U.S. population report higher PM effect estimates for mortality associations with chronic long term exposures to $PM_{2.5}$ and/or sulfates than with acute short-term exposures to these fine particle indicators. Also, the most recent extension of the ACS study, more than doubling the original followup time, provides the strongest evidence to date for increased lung cancer mortality risk being significantly associated with long-term fine particle exposures. Studies that combine the features of cross-sectional and cohort studies provide some of the best evidence for noncancer morbidity effects of chronic PM exposure.

(12) Intervention Studies. Certain epidemiology evidence suggests that relatively sharp reductions in ambient PM concentrations may reduce a variety of health effects on a time scale from a few days to a few months.

This has been observed in epidemiology studies of "natural or "found experiments," such as in the Utah Valley, and by supporting toxicology studies using particle extracts from ambient community PM_{10} sampling filters from the Utah Valley. Another study in Dublin, Ireland also provides evidence for reductions in ambient PM air pollution (measured as British smoke) being associated with reductions in mortality rates. Another "found experiments" also provide evidence for decreases in mortality and/or morbidity being associated with notable declines in SO_2 as the result of interventions aimed at reducing air pollution.

(13) Concentration-Response Functions. The results from large multicity studies suggest that there is no strong evidence of a clear threshold for PM mortality effects. Some single city studies suggest a hint of a threshold, but not in a statistically clear manner. More data may need to be examined with alternative approaches (e.g., Smith et al.'s parametric model), but meanwhile, the use of a linear PM effect models appears to be appropriate.

Certain statistical simulation analyses have shown that increasing measurement error tends to flatten PM concentration-response curves somewhat and to increase uncertainty associated with estimates of potential thresholds (especially under extreme error scenarios). Nevertheless, it has been concluded that if thresholds exist, standard statistical analyses should be able to detect

them. Newly available evaluations of the shape of PM-related concentrations-response relationships provide very limited results suggestive of possible threshold(s) for health effects associated with low ambient PM concentrations (e.g., at ≤ 15 to 20 μg/m^3 for 24-h PM_{10} or ≤ 20 to 25 μg/m^3 24-h $PM_{2.5}$ levels). However, formal statistical tests comparing linear (no threshold) models versus various nonlinear or threshold models have not shown statistically significant distinctions between them or clear preference of one over the other. Results of analyses of NMMAPS data for the 20 largest U.S. cities, that compared a linear model for PM_{10}, a natural cubic spline model of PM_{10} with knots at 30 and 60 μg/m^3, and a threshold model with grid search in 5 μg/m^3 increments across 5 to 200 μg/m^3 PM_{10} suggested possible thresholds for daily total or cardiorespiratory mortality at PM_{10} levels below ~15 to 20 μg/m^3, but essentially zero probability of a threshold above ~25 μg/m^3. However, comparing AIC values across the models suggested that the linear (no-threshold) model would be preferred over the others. Other single-city analyses were suggestive of possible threshold change points in Birmingham and Chicago at 80 and ≥ 100 μg/m^3 PM_{10} but not statistically significantly so. In another single-city (Phoenix) study using a piecewise linear model or a B-spline model with 4 knots, some evidence was found to suggest a possible daily total mortality threshold(s) in the range of 20 to 25 μg/m^3 $PM_{2.5}$, but no evidence was found for threshold(s) for total mortality associations with $PM_{10-2.5}$ (perhaps reflecting greater measurement error for $PM_{10-2.5}$ exposure estimates in the analysis).

(14) Public Health Implications. Progress has been made in advancing our understanding of public health implications of PM mortality and morbidity effects, both in terms of (a) potential life shortening due to PM exposures and (b) a broader array of morbidity effects shown to be associated with ambient PM exposures.

Long-term exposures (on the order of years or decades) to thoracic particles in general and fine-fraction particles in particular appear to be associated with life shortening well beyond that accounted for by the simple accumulation of the more acute "harvesting" of effects of short-term PM exposures (on the order of a few days). Investigations of the public health implications of such long-term PM exposure-mortality effect estimates have been attempted. For example, preliminary life table calculations using risk estimates from long-term $PM_{2.5}$ exposure studies suggest that relatively small differences in long-term exposure to ambient PM can have substantial effects on life expectancy. To illustrate, based on the initial 1995 ACS study PM-

mortality risk estimates, a U.S. EPA calculation for the 1969-71 life table for U.S. white males projected that a chronic exposure increase of 10 $\mu g/m^3$ $PM_{2.5}$ could be associated with a reduction of 1.31 years for the entire U.S. population's life expectancy at age 25. However, such projections must be viewed with caution given their dependence on the specific PM effect-size estimates used in the calculations. The 1.31 year life expectancy reduction estimate, as an example, would need to be recalculated to a lower value based on lower (and presumably more credible) PM mortality risk estimates from the more recent Pope et al. (2002) extension of the ACS study.

PM-related health effects in infants and children are emerging as an area of more concern than in the 1996 PM AQCD; and ultimately, such health effects could have very substantial implications for life expectancy calculations. However, only very limited evidence currently exists about potential ambient PM relationships with some of the more serious pertinent health endpoints (low birth weight, preterm birth, neonatal and infant mortality, emergency hospital admissions, and mortality in older children). Also, little is yet known about involvement of PM exposure in the progression from less serious childhood conditions, such as asthma and respiratory symptoms, to more serious disease endpoints later in life. This is an important health issue, because childhood illness or death may cost a very large number of productive life-years.

Lastly, new epidemiologic studies of a broader array of health endpoints indicate ambient PM associations with increased nonhospital medical visits (physician visits) and asthma effects. Such new findings suggest likely much larger health impacts and costs to society due to ambient PM than just those indexed either by just hospital admissions/visits and/or mortality.

REFERENCES

Abbey, D. E.; Mills, P. K.; Petersen, F. F.; Beeson, W. L. (1991) Long-term ambient concentrations of total suspended particulates and oxidants as related to incidence of chronic disease in California Seventh-Day Adventists. Environ. Health Perspect. 94: 43-50.

Abbey, D. E.; Lebowitz, M. D.; Mills, P. K.; Petersen, F. F.; Beeson, W. L.; Burchette, R. J. (1995a) Long-term ambient concentrations of particulates and oxidants and development of chronic disease in a cohort of nonsmoking California residents. In: Phalen, R. F.; Bates, D. V., eds. Proceedings of the colloquium on particulate air pollution and human mortality and morbidity; January 1994; Irvine, CA. Inhalation Toxicol. 7: 19-34.

Abbey, D. E.; Ostro, B. E.; Fraser, G.; Vancuren, T.; Burchette, R. J. (1995b) Estimating fine particulates less that 2.5 microns in aerodynamic diameter ($PM_{2.5}$) from airport visibility data in California. J. Exposure Anal. Environ. Epidemiol. 5: 161-180.

Abbey, D. E.; Burchette, R. J.; Knutsen, S. F.; McDonnell, W. F.; Lebowitz, M. D.; Enright, P. L. (1998) Long-term particulate and other air pollutants and lung function in nonsmokers. Am. J. Respir. Crit. Care Med. 158: 289-298.

Abbey, D. E.; Nishino, N.; McDonnell, W. F.; Burchette, R. J.; Knutsen, S. F.; Beeson, W. L.; Yang, J. X. (1999) Long-term inhalable particles and other air pollutants related to mortality in nonsmokers. Am. J. Respir. Crit. Care Med. 159: 373-382.

Ackermann-Liebrich, U.; Leuenberger, P.; Schwartz, J.; Schindler, C.; Monn, C.; Bolognini, B.; Bongard, J. P.; Brändli, O.; Domenighetti, G.; Elsasser, S.; Grize, L.; Karrer, W.; Keller, R.; Keller-Wossidlo, H.; Künzli, N.; Martin, B. W.; Medici, T. C.; Perruchoud, A. P.; Schöni, M. H.; Tschopp, J. M.; Villiger, B.; Wüthrich, B.; Zellweger, J. P.; Zemp, E. (1997) Lung function and long term exposure to air pollutants in Switzerland. Am. J. Respir. Crit. Care Med. 155: 122-129.

Agócs, M. M.; White, M. C.; Ursicz, G.; Olson, D. R.; Vámos, A. (1997) A longitudinal study of ambient air pollutants and the lung peak expiratory flow rates among asthmatic children in Hungary. Int. J. Epidemiol. 26: 1272-1280.

Alberdi Odriozola, J. C.; Díaz Jiménez, J.; Montero Rubio, J. C.; Mirón Pérez, I. J.; Pajares Ortíz, M. S.; Ribera Rodrigues, P. (1998) Air pollution and mortality in Madrid, Spain: a time-series analysis. Int. Arch. Occup. Environ. Health 71: 543-549.

Anderson, H. R.; Ponce de Leon, A.; Bland, J. M.; Bower, J. S.; Strachan, D. P. (1996) Air pollution and daily mortality in London: 1987-92. Br. Med. J. 312: 665-669.

Anderson, H. R.; Spix, C.; Medina, S.; Schouten, J. P.; Castellsague, J.; Rossi, G.; Zmirou, D.; Touloumi, G.; Wojtyniak, B.; Ponka, A.; Bacharova, L.; Schwartz, J.; Katsouyanni, K. (1997) Air pollution and daily admissions for chronic obstructive pulmonary disease in 6 European cities: results from the APHEA project. Eur. Respir. J. 10: 1064-1071.

Anderson, H. R.; Ponce de Leon, A.; Bland, J. M.; Bower, J. S.; Emberlin, J.; Strachen, D. P. (1998) Air pollution, pollens, and daily admissions for asthma in London 1987-92. Thorax 53: 842-848.

Anderson, H. R.; Bremner, S. A.; Atkinson, R. W.; Harrison, R. M.; Walters, S. (2001) Particulate matter and daily mortality and hospital admissions in the west midlands conurbation of the United Kingdom: associations with fine and coarse particles, black smoke and sulphate. Occup. Environ. Med. 58: 504-510.

Archer, V. E. (1990) Air pollution and fatal lung disease in three Utah counties. Arch. Environ. Health 45: 325-334.

Atkinson, R. W.; Bremner, S. A.; Anderson, H. R.; Strachan, D. P.; Bland, J. M.; Ponce de Leon, A. (1999a) Short-term associations between emergency hospital admissions for respiratory and cardiovascular disease and outdoor air pollution in London. Arch. Environ. Health 54: 398-411.

Atkinson, R. W.; Anderson, H. R.; Strachan, D. P.; Bland, J. M.; Bremner, S. A.; Ponce de Leon, A. (1999b) Short-term associations between outdoor air pollution and visits to accident and emergency departments in London for respiratory complaints. Eur. Respir. J. 13: 257-265.

Atkinson, R. W.; Anderson, H. R.; Sunyer, J.; Ayres, J.; Baccini, M.; Vonk, J. M.; Boumghar, A.; Forastiere, F.; Forsberg, B.; Touloumi, G.; Schwartz, J.; Katsouyanni, K. (2001) Acute effects of particulate air pollution on respiratory admissions: results from APHEA 2 project. Am. J. Respir. Crit. Care Med. 164: 1860-1866.

Atkinson, R. W.; Anderson, H. R.; Sunyer, J.; Ayres, J.; Baccini, M.; Vonk, J. M.; Boumghar, A.; Forastiere, F.; Forsberg, B.; Touloumi, G.; Schwartz, J.; Katsouyanni, K. (2003) Acute effects of particulate air pollution on respiratory admissions. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 81-84. Available: http://www.healtheffects.org/Pubs/TimeSeries.pdf [18 October, 2004].

Avol, E. L.; Gauderman, W. J.; Tan, S. M.; London, S. J.; Peters, J. M. (2001) Respiratory effects of relocating to areas of differing air pollution levels. Am. J. Respir. Crit. Care Med. 164: 2067-2072.
Awasthi, S.; Glick, H. A.; Fletcher, R. H.; Ahmed, N. (1996) Ambient air pollution & respiratory symptoms complex in preschool children. Indian J. Med. Res. 104: 257-262.
Bailey, D. L. R.; Clayton, P. (1982) The measurement of suspended particle and total carbon concentrations in the atmosphere using standard smoke shade methods. Atmos. Environ. 16: 2683-2690.
Baldi, I.; Tessier, J. F.; Kauffmann, F.; Jacqmin-Gadda, H.; Nejjari, C.; Salamon, R. (1999) Prevalence of asthma and mean levels of air pollution: results from the French PAARC survey. Eur. Respir. J. 14: 132-138.
Barbone, F.; Bovenzi, M.; Cavalleri, F.; Stanta, G. (1995) Air pollution and lung cancer in Trieste, Italy. Am. J. Epidemiol. 141: 1161-1169.
Barker, D. J. P.; Gluckman, P. D.; Godfrey, K. M.; Harding, J. E.; Owens, J. A.; Robinson, J. S. (1993) Fetal nutrition and cardiovascular disease in adult life. Lancet 341: 938-941.
Basu, R.; Samet, J. M. (1999) A review of the epidemiological evidence on health effects of nitrogen dioxide exposure from gas stoves. J. Environ. Med. 1: 173-187.
Beckett, W. S. (2001) The air pollution detectives. Am. J. Respir. Crit. Care Med. 164: 515-516.
Beeson, W. L.; Abbey, D. E.; Knutsen, S. F. (1998) Long-term concentrations of ambient air pollutants and incident lung cancer in California adults: results from the AHSMOG study. Environ. Health Perspect. 106: 813-823.
Berglund, D. J.; Abbey, D. E.; Lebowitz, M. D.; Knutsen, S. F.; McDonnell, W. F. (1999) Respiratory symptoms and pulmonary function in an elderly nonsmoking population. Chest 115: 49-59.
Berkowitz, G. S.; Papiernik, E. (1993) Epidemiology of preterm birth. Epidemiol. Rev. 15: 414-443.
Beyer, U.; Franke, K.; Cyrys, J.; Peters, A.; Heinrich, J.; Wichmann, H. E.; Brunekreef, B. (1998) Air pollution and respiratory health of children: the PEACE panel study in Hettstedt and Zerbst, Eastern Germany. Eur. Respir. Rev. 8: 61-69.
Bobak, M.; Leon, D. A. (1992) Air pollution and infant mortality in the Czech Republic, 1986-1988. Lancet (8826): 1010-1014.
Bobak, M.; Leon, D. A. (1999) Pregnancy outcomes and outdoor air pollution: an ecological study in districts of the Czech Republic 1986-8. Occup. Environ. Med. 56: 539-543.
Bobak, M.; Roberts, A. (1997) Heterogeneity of air pollution effects is related to average temperature [letter]. Br. Med. J. 315: 1161.
Boezen, M.; Schouten, J.; Rijcken, B.; Vonk, J.; Gerritsen, J.; Van Der Zee, S.; Hoek, G.; Brunekreef, B.; Postma, D. (1998) Peak expiratory flow variability, bronchial responsiveness, and susceptibility to ambient air pollution in adults. Am. J. Respir. Crit. Care Med. 158: 1848-1854.
Boezen, H. M.; Van Der Zee, S. C.; Postma, D. S.; Vonk, J. M.; Gerritsen, J.; Hoek, G.; Brunekreef, B.; Rijcken, B.; Schouten, J. P. (1999) Effects of ambient air pollution on upper and lower respiratory symptoms and peak expiratory flow in children. Lancet 353: 874-878.
Borja-Aburto, V. H.; Loomis, D. P.; Bangdiwala, S. I.; Shy, C. M.; Rascon-Pacheco, R. A. (1997) Ozone, suspended particulates, and daily mortality in Mexico City. Am. J. Epidemiol. 145: 258-268.
Borja-Aburto, V. H.; Castillejos, M.; Gold, D. R.; Bierzwinski, S.; Loomis, D. (1998) Mortality and ambient fine particles in southwest Mexico City, 1993-1995. Environ. Health Perspect. 106: 849-855.
Braga, A. L. F.; Conceição, G. M. S.; Pereira, L. A. A.; Kishi, H. S.; Pereira, J. C. R.; Andrade, M. F.; Gonçalves, F. L. T.; Saldiva, P. H. N.; Latorre, M. R. D. O. (1999) Air pollution and pediatric respiratory hospital admissions in São Paulo, Brazil. J. Environ. Med. 1: 95-102.
Braga, A. L. F.; Zanobetti, A.; Schwartz, J. (2000) Do respiratory epidemics confound the association between air pollution and daily deaths? Eur. Respir. J. 16: 723-728.
Braga, A. L. F.; Zanobetti, A.; Schwartz, J. (2001a) The lag structure between particulate air pollution and respiratory and cardiovascular deaths in ten U.S. cities. J. Occup. Environ. Med. 43: 927-933.
Braga, A. L. F.; Zanobetti, A.; Schwartz, J. (2001b) The time course of weather-related deaths. Epidemiology 12: 662-667.
Braga, A. L. F.; Zanobetti, A.; Schwartz, J. (2002) The effect of weather on respiratory and cardiovascular deaths in 12 U.S. cities. Environ. Health Perspect. 110: 859-864.
Brauer, M.; Ebelt, S. T.; Fisher, T. V.; Brumm, J.; Petkau, A. J.; Vedal, S. (2001) Exposure of chronic obstructive pulmonary disease patients to particles: respiratory and cardiovascular health effects. J. Exposure Anal. Environ. Epidemiol. 11: 490-500.
Braun-Fahrländer, C.; Vuille, J. C.; Sennhauser, F. H.; Neu, U.; Künzle, T.; Grize, L.; Gassner, M.; Minder, C.; Schindler, C.; Varonier, H. S.; Wüthrich, B.; SCARPOL team. (1997) Respiratory health and long-term exposure to air pollutants in Swiss schoolchildren. Am. J. Respir. Crit. Care Med. 155: 1042-1049.

Bremner, S. A.; Anderson, H. R.; Atkinson, R. W.; McMichael, A. J.; Strachan, D. P.; Bland, J. M.; Bower, J. S. (1999) Short term associations between outdoor air pollution and mortality in London 1992-4. Occup. Environ. Med. 56: 237-244.

Brook, J. R.; Wiebe, A. H.; Woodhouse, S. A.; Audette, C. V.; Dann, T. F.; Callaghan, S.; Piechowski, M.; Dabek-Zlotorzynska, E.; Dloughy, J. F. (1997) Temporal and spatial relationships in fine particle strong acidity, sulphate, PM_{10}, and $PM_{2.5}$ across multiple Canadian locations. Atmos. Environ. 31: 4223-4236.

Brunekreef, B. (1997) Air pollution and life expectancy: is there a relation? Occup. Environ. Med. 54: 781-784.

Buffler, P. A.; Cooper, S. P.; Stinnett, S.; Contant, C.; Shirts, S.; Hardy, R. J.; Agu, V.; Gehan, B.; Burau, K. (1988) Air pollution and lung cancer mortality in Harris County, Texas, 1979-1981. Am. J. Epidemiol. 128: 683-699.

Burnett, R. T.; Goldberg, M. S. (2003) Size-fractionated particulate mass and daily mortality in eight Canadian cities. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 85-90. Available: http://www.healtheffects.org/news.htm [16 May, 2003].

Burnett, R. T.; Dales, R. E.; Raizenne, M. E.; Krewski, D.; Summers, P. W.; Roberts, G. R.; Raad-Young, M.; Dann, T.; Brook, J. (1994) Effects of low ambient levels of ozone and sulfates on the frequency of respiratory admissions to Ontario hospitals. Environ. Res. 65: 172-194.

Burnett, R. T.; Dales, R.; Krewski, D.; Vincent, R.; Dann, T.; Brook, J. R. (1995) Associations between ambient particulate sulfate and admissions to Ontario hospitals for cardiac and respiratory diseases. Am. J. Epidemiol. 142: 15-22.

Burnett, R. T.; Cakmak, S.; Brook, J. R.; Krewski, D. (1997a) The role of particulate size and chemistry in the association between summertime ambient air pollution and hospitalization for cardiorespiratory diseases. Environ. Health Perspect. 105: 614-620.

Burnett, R. T.; Dales, R. E.; Brook, J. R.; Raizenne, M. E.; Krewski, D. (1997b) Association between ambient carbon monoxide levels and hospitalizations for congestive heart failure in the elderly in 10 Canadian cities. Epidemiology 8: 162-167.

Burnett, R. T.; Brook, J. R.; Yung, W. T.; Dales, R. E.; Krewski, D. (1997c) Association between ozone and hospitalization for respiratory diseases in 16 Canadian cities. Environ. Res. 72: 24-31.

Burnett, R. T.; Cakmak, S.; Brook, J. R. (1998a) The effect of the urban ambient air pollution mix on daily mortality rates in 11 Canadian cities. Can. J. Public Health 89: 152-156.

Burnett, R. T.; Cakmak, S.; Raizenne, M. E.; Stieb, D.; Vincent, R.; Krewski, D.; Brook, J. R.; Philips, O.; Ozkaynak, H. (1998b) The association between ambient carbon monoxide levels and daily mortality in Toronto, Canada. J. Air Waste Manage. Assoc. 48: 689-700.

Burnett, R. T.; Smith-Doiron, M.; Stieb, D.; Cakmak, S.; Brook, J. R. (1999) Effects of particulate and gaseous air pollution on cardiorespiratory hospitalizations. Arch. Environ. Health 54:130-139.

Burnett, R. T.; Brook, J.; Dann, T.; Delocla, C.; Philips, O.; Cakmak, S.; Vincent, R.; Goldberg, M. S.; Krewski, D. (2000) Association between particulate- and gas-phase components of urban air pollution and daily mortality in eight Canadian cities. In: Grant, L. D., ed. PM2000: particulate matter and health. Inhalation Toxicol. 12(suppl. 4): 15-39.

Burnett, R.; Ma, R.; Jerrett, M.; Goldberg, M. S.; Cakmak, S.; Pope, C. A., III; Krewski, D. (2001a) The spatial association between community air pollution and mortality: a new method of analyzing correlated geographic cohort data. Environ. Health Perspect. Suppl. 109(3): 375-380.

Burnett, R. T.; Smith-Doiron, M.; Stieb, D.; Raizenne, M. E.; Brook, J. R.; Dales, R. E.; Leech, J. A.; Cakmak, S.; Krewski, D. (2001b) Association between ozone and hospitalization for acute respiratory diseases in children less than 2 years of age. Am. J. Epidemiol. 153: 444-452.

Cakmak, S.; Burnett, R. T.; Krewski, D. (1999) Methods for detecting and estimating population threshold concentrations for air pollution-related mortality with exposure measurement error. Risk Anal. 19: 487-496.

Calderón-Garcidueñas, L.; Mora-Tiscareño, A.; Chung, C. J.; Valencia, G.; Fordham, L. A.; García, R.; Osnaya, N.; Romero, L.; Acuña, H.; Villarreal-Calderón, A. (2000) Exposure to air pollution is associated with lung hyperinflation in healthy children and adolescents in southwest Mexico City: a pilot study. Inhalation Toxicol. 12: 537-561.

Carroll, R. J.; Ruppert, D.; Stefanski, L. A. (1995) Measurement error in nonlinear models. London, United Kingdom: Chapman & Hall. (Cox, D. R.; Hinkley, D. V.; Keiding, N.; Reid, N.; Rubin, D. B.; Silverman, B. W., eds. Monographs on statistics and applied probability: v. 63).

Carrothers, T. J.; Evans, J. S. (2000) Assessing the impact of differential measurement error on estimates of fine particle mortality. J. Air Waste Manage. Assoc. 50: 65-74.

Cassino, C.; Ito, K.; Bader, I.; Ciotoli, C.; Thurston, G.; Reibman, J. (1999) Cigarette smoking and ozone-associated emergency department use for asthma by adults in New York City. Am. J. Respir. Crit. Care Med. 159: 1773-1779.

Castillejos, M.; Borja-Aburto, V. H.; Dockery, D. W.; Gold, D. R.; Loomis, D. (2000) Airborne coarse particles and mortality. In: Phalen, R. F., ed. Inhalation toxicology: proceedings of the third colloquium on particulate air pollution and human health (first special issue); June, 1999; Durham, NC. Inhalation Toxicol. 12(suppl. 1): 61-72.

Checkoway, H.; Levy, D.; Sheppard, L.; Kaufman, J.; Koenig, J.; Siscovick, D. (2000) A case-crossover analysis of fine particulate matter air pollution and out-of-hospital sudden cardiac arrest. Cambridge, MA: Health Effects Institute; research report no. 99. Available: http://www.healtheffects.org/Pubs/Checkoway.pdf [18 October, 2004].

Chen, C.; Chock, D. P.; Winkler, S. L. (1999) A simulation study of confounding in generalized linear models for air pollution epidemiology. Environ. Health Perspect. 107: 217-222.

Chen, L.; Yang, W.; Jennison, B. L.; Omaye, S. T. (2000) Air particulate pollution and hospital admissions for chronic obstructive pulmonary disease in Reno, Nevada. Inhalation Toxicol. 12: 281-298.

Chew, F. T.; Goh, D. Y. T.; Ooi, B. C.; Saharom, R.; Hui, J. K. S.; Lee, B. W. (1999) Association of ambient air-pollution levels with acute asthma exacerbation among children in Singapore. Allergy (Copenhagen) 54: 320-329.

Chock, D. P.; Winkler, S.; Chen, C. (2000) A study of the association between daily mortality and ambient air pollutant concentrations in Pittsburgh, Pennsylvania. J. Air Waste Manage. Assoc. 50: 1481-1500.

Choudhury, A. H.; Gordian, M. E.; Morris, S. S. (1997) Associations between respiratory illness and PM_{10} air pollution. Arch. Environ. Health 52: 113-117.

Cifuentes, L. A.; Vega, J.; Köpfer, K.; Lave, L. B. (2000) Effect of the fine fraction of particulate matter versus the coarse mass and other pollutants on daily mortality in Santiago, Chile. J. Air Waste Manage. Assoc. 50: 1287-1298.

Clancy, L.; Goodman, P.; Sinclair, H.; Dockery, D. W. (2002) Effect of air pollution control on death rates in Dublin, Ireland: an intervention study. Lancet 360: 1210-1214.

Clench-Aas, J.; Bartonova, A.; Skjønsberg, O. H.; Leegaard, J.; Hagen, L. O.; Giæver, P.; Moseng, J.; Roemer, W. (1998) Air pollution and respiratory health of children: the PEACE study in Oslo, Norway. Eur. Respir. Rev. 8: 36-43.

Clyde, M. A. (1999) Bayesian model averaging and model search strategies. In: Bernardo, J. M.; Berger, J. O.; Dawid, A. P.; Smith, A. F. M., eds. Bayesian Statistics 6: proceedings of the Sixth Valencia International Meeting, June; pp. 157-185. Oxford, UK. Oxford, UK: Clarendon Press.

Clyde, M. (2000) Model uncertainty and health effect studies for particulate matter. Environmetrics 11: 745-763.

Clyde, M. A.; Guttorp, P.; Sullivan, E. (2000) Effects of ambient fine and coarse particles on mortality in Phoenix, Arizona. Seattle, WA: University of Washington, National Research Center for Statistics and the Environment; NRCSE technical report series, NRCSE-TRS no. 040. Available: http://www.nrcse.washington.edu/pdf/trs40_pm.pdf [18 October, 2004].

Cohen, A. J. (2000) Outdoor air pollution and lung cancer. Environ. Health Perspect. 108(suppl. 4): 743-750.

Cohen, A. J.; Pope, C. A., III. (1995) Lung cancer and air pollution. Environ. Health Perspect. Suppl. 103(8): 219-224.

Conceição, G. M. S.; Miraglia, S. G. E. K.; Kishi, H. S.; Saldiva, P. H. N.; Singer, J. M. (2001) Air pollution and child mortality: a time-series study in São Paulo, Brazil. Environ. Health Perspect. Suppl. 109(3): 347-350.

Cook, J. R.; Stefanski, L. A. (1994) Simulation-extrapolation estimation in parametric measurement error models. J. Am. Stat. Assoc. 89: 1314-1328.

Coull, B. A.; Schwartz, J.; Wand, M. P. (2001) Respiratory health and air pollution: additive mixed model analyses. Biostatistics 2: 337-349.

Coutant, R. W. (1977) Effect of environmental variables on collection of atmospheric sulfate. Environ. Sci. Technol. 11: 873-878.

Creason, J.; Neas, L.; Walsh, D.; Williams, R.; Sheldon, L.; Liao, D.; Shy, C. (2001) Particulate matter and heart rate variability among elderly retirees: the Baltimore 1998 PM study. J. Exposure Anal. Environ. Epidemiol. 11: 116-122.

Cropper, M. L.; Simon, N. B.; Alberini, A.; Arora, S.; Sharma, P. K. (1997) The health benefits of air pollution control in Delhi. Am. J. Agric. Econ. 79: 1625-1629.

Cuijpers, C. E. J.; Swaen, G. M. H.; Wesseling, G.; Wouters, E. F. M. (1994) Acute respiratory effects of summer smog in primary school children. Toxicol. Lett. 72: 227-235.

Dab, W.; Medina, S.; Quénel, P.; Le Moullec, Y.; Le Tertre, A.; Thelot, B.; Monteil, C.; Lameloise, P.; Pirard, P.; Momas, I.; Ferry, R.; Festy, B. (1996) Short term respiratory health effects of ambient air pollution: results of the APHEA project in Paris. In: St Leger, S., ed. The APHEA project. Short term effects of air pollution on health: a European approach using epidemiological time series data. J. Epidemiol. Community Health 50(suppl. 1): S42-S46.

Damiá, A. D.; Fabregas, M. L.; Tordera, M. P.; Torrero, L. C. (1999) Effects of air pollution and weather conditions on asthma exacerbation. Respiration 66: 52-58.

Daniels, M.; Dominici, F.; Samet, J. M.; Zeger, S. L. (2000) Estimating particulate matter-mortality dose-response curves and threshold levels: an analysis of daily time-series for the 20 largest US cities. Am. J. Epidemiol. 152: 397-406.

Daniels, M. J.; Lee, Y.-D.; Kaiser, M. (2001) Assessing sources of variability in measurement of ambient particulate matter. Environmetrics 12: 547-558.

Dejmek, J.; Selevan, S. G.; Beneš, I.; Solanský, I.; Šrám, R. J. (1999) Fetal growth and maternal exposure to particulate matter during pregnancy. Environ. Health Perspect. 107: 475-480.

Dejmek, J.; Solanský, I.; Beneš, I.; Leníček, J.; Šrám, R. J. (2000) The impact of polycyclic aromatic hydrocarbons and fine particles on pregnancy outcome. Environ. Health Perspect. 108: 1159-1164.

Delfino, R. J.; Coate, B. D.; Zeiger, R. S.; Seltzer, J. M.; Street, D. H.; Koutrakis, P. (1996) Daily asthma severity in relation to personal ozone exposure and outdoor fungal spores. Am. J. Respir. Crit. Care Med. 154: 633-641.

Delfino, R. J.; Murphy-Moulton, A. M.; Burnett, R. T.; Brook, J. R.; Becklake, M. R. (1997a) Effects of air pollution on emergency room visits for respiratory illnesses in Montreal, Quebec. Am. J. Respir. Crit. Care Med. 155: 568-576.

Delfino, R. J.; Zeiger, R. S.; Seltzer, J. M.; Street, D. H.; Matteucci, R. M.; Anderson, P. R.; Koutrakis, P. (1997b) The effect of outdoor fungal spore concentrations on daily asthma severity. Environ. Health Perspect. 105: 622-635.

Delfino, R. J.; Zeiger, R. S.; Seltzer, J. M.; Street, D. H. (1998a) Symptoms in pediatric asthmatics and air pollution: differences in effects by symptom severity, anti-inflammatory medication use and particulate averaging time. Environ. Health Perspect. 106: 751-761.

Delfino, R. J.; Murphy-Moulton, A. M.; Becklake, M. R. (1998b) Emergency room visits for respiratory illnesses among the elderly in Montreal: association with low level ozone exposure. Environ. Res. 76: 67-77.

Delfino, R. J.; Zeiger, R. S.; Seltzer, J. M.; Street, D. H.; McLaren, C. E. (2002) Association of asthma symptoms with peak particulate air pollution and effect modification by anti-inflammatory medication use. Environ. Health Perspect. 110: A607-A617.

Desqueyroux, H.; Pujet, J.-C.; Prosper, M.; Squinazi, F.; Momas, I. (2002) Short-term effects of low-level air pollution on respiratory health of adults suffering from moderate to severe asthma. Environ. Res. A 89: 29-37.

Díaz, J.; García, R.; Ribera, P.; Alberdi, J. C.; Hernández, E.; Pajares, M. S.; Otero, A. (1999) Modeling of air pollution and its relationship with mortality and morbidity in Madrid, Spain. Int. Arch. Occup. Environ. Health 72: 366-376.

Divon, M. Y.; Boldes, R.; McGahan, J. P. (1994) Assessment of intrauterine growth retardation. In: McGahan, J. P.; Porto, M., eds. Diagnostic obstetrical ultrasound. Philadelphia, PA: J. B. Lippincott; pp. 67-82.

Dockery, D. W.; Spengler, J. D. (1981) Personal exposure to respirable particulates and sulfates. J. Air Pollut. Control Assoc. 31: 153-159.

Dockery, D. W.; Speizer, F. E.; Stram, D. O.; Ware, J. H.; Spengler, J. D.; Ferris, B. G., Jr. (1989) Effects of inhalable particles on respiratory health of children. Am. Rev. Respir. Dis. 139: 587-594.

Dockery, D. W.; Schwartz, J.; Spengler, J. D. (1992) Air pollution and daily mortality: associations with particulates and acid aerosols. Environ. Res. 59: 362-373.

Dockery, D. W.; Pope, C. A., III; Xu, X.; Spengler, J. D.; Ware, J. H.; Fay, M. E.; Ferris, B. G., Jr.; Speizer, F. E. (1993) An association between air pollution and mortality in six U.S. cities. N. Engl. J. Med. 329: 1753-1759.

Dockery, D. W.; Cunningham, J.; Damokosh, A. I.; Neas, L. M.; Spengler, J. D.; Koutrakis, P.; Ware, J. H.; Raizenne, M.; Speizer, F. E. (1996) Health effects of acid aerosols on North American children: respiratory symptoms. Environ. Health Perspect. 104: 500-505.

Dockery, D. W.; Pope, C. A., III; Kanner, R. E.; Villegas, G. M.; Schwartz, J. (1999) Daily changes in oxygen saturation and pulse rate associated with particulate air pollution and barometric pressure. Cambridge, MA: Health Effects Institute; research report no. 83.

Dominici, F.; Samet, J. M.; Zeger, S. (2000a) Combining evidence on air pollution and daily mortality from the largest 20 US cities: a hierarchical modeling strategy. J. R. Stat. Soc. A 163: 263-302.

Dominici, F.; Zeger, S. L.; Samet, J. (2000b) A measurement error model for time-series studies of air pollution and mortality. Biostatistics 1: 157-175.

Dominici, F.; Daniels, M.; Zeger, S. L.; Samet, J. M. (2002) Air pollution and mortality: estimating regional and national dose-response relationships. J. Am. Stat. Assoc. 97: 100-111.

Dominici, F.; Daniels, M.; McDermott, A.; Zeger, S. L.; Samet, J. M. (2003a) Shape of the exposure-response relation and mortality displacement in the NMMAPS database. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 91-96. Available: http://www.healtheffects.org/Pubs/TimeSeries.pdf [12 May, 2004].

Dominici, F.; McDermott, A.; Daniels, M.; Zeger, S. L.; Samet, J. M. (2003b) Mortality among residents of 90 cities. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 9-24. Available: http://www.healtheffects.org/Pubs/TimeSeries.pdf [12 May, 2004].

Dominici, F.; McDermott, A.; Zeger, S. L.; Samet, J. M. (2003c) Airborne particulate matter and mortality: timescale effects in four US Cities. Am. J. Epidemiol. 157: 1055-1065.

Fairley, D. (1990) The relationship of daily mortality to suspended particulates in Santa Clara county, 1980-86. Environ. Health Perspect. 89: 159-168.

Fairley, D. (1999) Daily mortality and air pollution in Santa Clara County, California: 1989-1996. Environ. Health Perspect. 107: 637-641.

Fairley, D. (2003) Mortality and air pollution for Santa Clara County, California, 1989-1996. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 97-106. Available: http://www.healtheffects.org/Pubs/TimeSeries.pdf [18 October, 2004].

Forsberg, B.; Segerstedt, B.; Stjernberg, N.; Roemer, W. (1998) Air pollution and respiratory health of children: the PEACE panel study in Umeå, Sweden. Eur. Respir. Rev. 8: 12-19.

Friedman, M. S.; Powell, K. E.; Hutwagner, L.; Graham, L. M.; Teague, W. G. (2001) Impact of changes in transportation and commuting behaviors during the 1996 summer olympic games in Atlanta on air quality and childhood asthma. JAMA J. Am. Med. Assoc. 285: 897-905.

Frischer, T.; Studnicka, M.; Gartner, C.; Tauber, E.; Horak, F.; Veiter, A.; Spengler, J.; Kühr, J.; Urbanek, R. (1999) Lung function growth and ambient ozone: a three-year population study in school children. Am. J. Respir. Crit. Care Med. 160: 390-396.

Fung, K. Y.; Krewski, D. (1999) On measurement error adjustment methods in Poisson regression. Environmetrics 10: 213-224.

Fusco, D.; Forastiere, F.; Michelozzi, P.; Spadea, T.; Ostro, B.; Arca, M.; Perucci, C. A. (2001) Air pollution and hospital admissions for respiratory conditions in Rome, Italy. Eur. Respir. J. 17: 1143-1150.

Gamble, J. L. (1998) Effects of ambient air pollution on daily mortality: a time series analysis of Dallas, Texas, 1990-1994. Presented at: 91st annual meeting and exhibition of the Air & Waste Management Association; June; San Diego, CA. Pittsburgh, PA: Air & Waste Management Association; paper no. 98-MP26.03.

Garcia-Aymerich, J.; Tobias, A.; Anto, J. M.; Sunyer, J. (2000) Air pollution and mortality in a cohort of patients with chronic obstructive pulmonary disease: a time series analysis. J. Epidemiol. Community Health 54: 73-74.

Garty, B. Z.; Kosman, E.; Ganor, E.; Berger, V.; Garty, L.; Wietzen, T.; Waisman, Y.; Mimouni, M.; Waisel, Y. (1998) Emergency room visits of asthmatic children, relation to air pollution, weather, and airborne allergens. Ann. Allergy Asthma Immunol. 81: 563-570.

Gauderman, W. J.; Mcconnell, R.; Gilliland, F.; London, S.; Thomas, D.; Avol, E.; Vora, H.; Berhane, K.; Rappaport, E. B.; Lurmann, F.; Margolis, H. G.; Peters, J. (2000) Association between air pollution and lung function growth in southern California children. Am. J. Respir. Crit. Care Med. 162: 1383-1390.

Gauderman, W. J.; Gilliland, G. F.; Vora, H.; Avol, E.; Stram, D.; McConnell, R.; Thomas, D.; Lurmann, F.; Margolis, H. G.; Rappaport, E. B.; Berhane, K.; Peters, J. M. (2002) Association between air pollution and lung function growth in southern California children: results from a second cohort. Am. J. Respir. Crit. Care Med. 166: 76-84.

Gauvin, S.; Zmirou, D.; Pin, I.; Quentin, J.; Balducci, F.; Boudet, C.; Poizeau, D.; Brambilla, C. (1999) Short-term effect of exposure to suspended particulate matter (PM10) on the respiratory function of urban asthmatic and control adults. J. Environ. Med. 1: 71-79.

Gehring, U.; Cyrys, J.; Sedlmeir, G.; Brunekreef, B.; Bellander, T.; Fischer, P.; Bauer, C. P.; Reinhardt, D.; Wichmann, H. E.; Heinrich, J. (2002) Traffic-related air pollution and respiratory health during the first 2 yrs. of life. Eur. Respir. J. 19: 690-698.

Gherghinova, M.; Kostyanve, S.; Ivanova, M. (1989) Theoretic values of body plethysmography indices in healthy children between 7 and 14 years of age. Pediatria 28: 52-58.

Gielen, M. H.; Van Der Zee, S. C.; Van Wijnen, J. H.; Van Steen, C. J.; Brunekreef, B. (1997) Acute effects of summer air pollution on respiratory health of asthmatic children. Am. J. Respir. Crit. Care Med. 155: 2105-2108.

Gold, D. R.; Damokosh, A. I.; Pope, C. A., III; Dockery, D. W.; McDonnell, W. F.; Serrano, P.; Retama, A.; Castillejos, M. (1999) Particulate and ozone pollutant effects on the respiratory function of children in southwest Mexico City. Epidemiology 10: 8-16.

Gold, D. R.; Litonjua, A.; Schwartz, J.; Lovett, E.; Larson, A.; Nearing, B.; Allen, G.; Verrier, M.; Cherry, R.; Verrier, R. (2000) Ambient pollution and heart rate variability. Circulation 101: 1267-1273.

Gold, D. R.; Schwartz, J.; Litonjua, A.; Verrier, R.; Zanobetti, A. (2003) Ambient pollution and reduced heart rate variability. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 107-112. Available: http://www.healtheffects.org/Pubs/TimeSeries.pdf [18 October, 2004].

Goldberg, M. S.; Burnett, R. T. (2003) Revised analysis of the Montreal time-series study. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 113-132. Available: http://www.healtheffects.org/Pubs/TimeSeries.pdf [18 October, 2004].

Goldberg, M. S.; Bailar, J. C., III; Burnett, R. T.; Brook, J. R.; Tamblyn, R.; Bonvalot, Y.; Ernst, P.; Flegel, K. M.; Singh, R. K.; Valois, M.-F. (2000) Identifying subgroups of the general population that may be susceptible to short-term increases in particulate air pollution: a time-series study in Montreal, Quebec. Cambridge, MA: Health Effects Institute; research report 97. Available: http://www.healtheffects.org/Pubs/Goldberg.pdf [18 October, 2004].

Goldberg, M. S.; Burnett, R. T.; Bailar, J. C., III; Brook, J.; Bonvalot, Y.; Tamblyn, R.; Singh, R.; Valois, M.-F. (2001a) The association between daily mortality and ambient air particle pollution in Montreal, Quebec. 1. Nonaccidental mortality. Environ. Res. 86: 12-25.

Goldberg, M. S.; Burnett, R. T.; Bailar, J. C., III; Brook, J.; Bonvalot, Y.; Tamblyn, R.; Singh, R.; Valois, M.-F.; Vincent, R. (2001b) The association between daily mortality and ambient air particle pollution in Montreal, Quebec. 2. Cause-specific mortality. Environ. Res. 86: 26-36.

Goldberg, M. S.; Burnett, R. T.; Bailar, J. C., III; Tamblyn, R.; Ernst, P.; Flegel, K.; Brook, J.; Bonvalot, Y.; Singh, R.; Valois, M.-F.; Vincent, R. (2001c) Identification of persons with cardiorespiratory conditions who are at risk of dying from the acute effects of ambient air particles. Environ. Health Perspect. Suppl. 109(4): 487-494.

Goldberg, M. S.; Burnett, R. T.; Brook, J.; Bailar, J. C., III; Valois, M.-F.; Vincent, R. (2001d) Associations between daily cause-specific mortality and concentrations of ground-level ozone in Montreal, Quebec. Am. J. Epidemiol. 154: 817-826.

Goldberg, M. S.; Burnett, R. T.; Valois, M.-F.; Flegel, K.; Bailar, J. C., III; Brook, J.; Vincent, R.; Radon, K. (2003) Associations between ambient air pollution and daily mortality among persons with congestive heart failure. Environ. Res. 91: 8-20.

Gordian, M. E.; Özkaynak, H.; Xue, J.; Morris, S. S.; Spengler, J. D. (1996) Particulate air pollution and respiratory disease in Anchorage, Alaska. Environ. Health Perspect. 104: 290-297.

Gouveia, N.; Fletcher, T. (2000) Respiratory diseases in children and outdoor air pollution in Sao Paulo, Brazil: a time series analysis. Occup. Environ. Med. 57: 477-483.

Grievink, L.; Van der Zee, S. C.; Hoek, G.; Boezen, H. M.; Van't Veer, P.; Brunekreef, B. (1999) Modulation of the acute respiratory effects of winter air pollution by serum and dietary antioxidants: a panel study. Eur. Respir. J. 13: 1439-1446.

Güntzel, O.; Bollag, U.; Helfenstein, U. (1996) Asthma and exacerbation of chronic bronchitis: sentinel and environmental data in a time series analysis. Zentralbl. Hyg. Umweltmed. 198: 383-393.

Guo, Y. L.; Lin, Y.-C.; Sung, F.-C.; Huang, S.-L.; Ko, Y.-C.; Lai, J.-S.; Su, H.-J.; Shaw, C.-K.; Lin, R.-S.; Dockery, D. W. (1999) Climate, traffic-related air pollutants, and asthma prevalence in middle-school children in Taiwan. Environ. Health Perspect. 107: 1001-1006.

Gwynn, R. C.; Thurston, G. D. (2001) The burden of air pollution: impacts among racial minorities. Environ. Health Perspect. Suppl. 109(4): 501-506.

Gwynn, R. C.; Burnett, R. T.; Thurston, G. D. (2000) A time-series analysis of acidic particulate matter and daily mortality and morbidity in the Buffalo, New York, region. Environ. Health Perspect. 108: 125-133.

Hagen, J. A.; Nafstad, P.; Skrondal, A.; Bjørkly, S.; Magnus, P. (2000) Associations between outdoor air pollutants and hospitalization for respiratory diseases. Epidemiology 11: 136-140.

Hajat, S.; Haines, A.; Goubet, S. A.; Atkinson, R. W.; Anderson, H. R. (1999) Association of air pollution with daily GP consultations for asthma and other lower respiratory conditions in London. Thorax 54: 597-605.

Hajat, S.; Haines, A.; Atkinson, R. W.; Bremner, S. A.; Anderson, H. R.; Emberlin, J. (2001) Association between air pollution and daily consultations with general practitioners for allergic rhinitis in London, United Kingdom. Am. J. Epidemiol. 153: 704-714.

Haluszka, J.; Pisiewicz, K.; Miczynski, J.; Roemer, W.; Tomalak, W. (1998) Air pollution and respiratory health in children: the PEACE panel study in Kraków, Poland. Eur. Respir. Rev. 8: 94-100.
Harré, E. S. M.; Price, P. D.; Ayrey, R. B.; Toop, L. J.; Martin, I. R.; Town, G. I. (1997) Respiratory effects of air pollution in chronic obstructive pulmonary disease: a three month prospective study. Thorax 52: 1040-1044.
Harris, R. J. (1975) A primer of multivariate statistics. New York, NY: Academic Press; pp. 155-224.
Haverkate, F.; Thompson, S. G.; Pyke, S. D. M.; Gallimore, J. R.; Papys, M. B. (1997) Production of C-reactive protein and risk of coronary events in stable and unstable angina. Lancet 349: 462-466.
Health Effects Institute. (2000) Critique. Health Review Committee. In: Checkoway, H.; Levy, D.; Sheppard, L.; Kaufman, J.; Koenig, J.; Siscovick, D. A case-crossover analysis of fine particulate matter air pollution and out-of-hospital sudden cardiac arrest. Cambridge, MA: Health Effects Institute; research report no. 99; pp. 29-32. Available: http://www.healtheffects.org/Pubs/Checkoway.pdf [18 October, 2004].
Health Effects Institute. (2002) Reanalysis of National Morbidity, Mortality, and Air Pollution Study (NMMAPS) [letter with attachments]. Boston, MA: May 30.
Health Effects Institute. (2003a) Revised analyses of the National Morbidity, Mortality, and Air Pollution Study (NMMAPS), part II. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 9-72. Available: http://www.healtheffects.org/Pubs/TimeSeries.pdf [18 October, 2004].
Health Effects Institute. (2003b) Revised analyses of time-series studies of air pollution and health. Boston, MA: Health Effects Institute; special report. Available: Available: http://www.healtheffects.org/Pubs/TimeSeries.pdf [27 June 2003].
Health Effects Institute. (2003c) Commentary on revised analyses of selected studies. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 255-290. Available: http://www.healtheffects.org/Pubs/TimeSeries.pdf [18 October, 2004].
Hedley, A. J.; Wong, C.-M.; Thach, T. Q.; Ma, S.; Lam, T.-H.; Anderson, H. R. (2002) Cardiorespiratory and all-cause mortality after restrictions on sulphur content of fuel in Hong Kong: an intervention study. Lancet 360: 1646-1652.
Hefflin, B. J.; Jalaludin, B.; McClure, E.; Cobb, N.; Johnson, C. A.; Jecha, L.; Etzel, R. A. (1994) Surveillance for dust storms and respiratory diseases in Washington State, 1991. Arch. Environ. Health 49: 170-174.
Heinrich, J.; Hoelscher, B.; Wjst, M.; Ritz, B.; Cyrys, J.; Wichmann, H.-E. (1999) Respiratory diseases and allergies in two polluted areas in East Germany. Environ. Health Perspect. 107: 53-62.
Heinrich, J.; Hoelscher, B.; Wichmann, H. E. (2000) Decline of ambient air pollution and respiratory symptoms in children. Am. J. Respir. Crit. Care Med. 161: 1930-1936.
Heinrich, J.; Hoelscher, B.; Frye, C.; Meyer, I.; Pitz, M.; Cyrys, J.; Wjst, M.; Neas, L.; Wichmann, H.-E. (2002) Improved air quality in reunified Germany and decreases in respiratory symptoms. Epidemiology 13: 394-401.
Henderson, B. E.; Gordon, R. J.; Menck, H.; SooHoo, J.; Martin, S. P.; Pike, M. C. (1975) Lung cancer and air pollution in southcentral Los Angeles County. Am. J. Epidemiol. 101: 477-488.
Hill, A. B. (1965) The environment and disease: association or causation? Proc. R. Soc. Med. 58: 295-300.
Hiltermann, T. J. N.; de Bruijne, C. R.; Stolk, J.; Zwinderman, A. H.; Spieksma, F. Th. M.; Roemer, W.; Steerenberg, P. A.; Fischer, P. H.; van Bree, L.; Hiemstra, P. S. (1997) Effects of photochemical air pollution and allergen exposure on upper respiratory tract inflammation in asthmatics. Am. J. Respir. Crit. Care Med. 156: 1765-1772.
Hiltermann, T. J. N.; Stolk, J.; Van der Zee, S. C.; Brunekreef, B.; De Bruijne, C. R.; Fischer, P. H.; Ameling, C. B.; Sterk, P. J.; Hiemstra, P. S.; Van Bree, L. (1998) Asthma severity and susceptibility to air pollution. Eur. Respir. J. 11: 686-693.
Hoek, G. (2003) Daily mortality and air pollution in The Netherlands. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 133-142. Available: http://www.healtheffects.org/Pubs/TimeSeries.pdf [12 May, 2004].
Hoek, G.; Schwartz, J. D.; Groot, B.; Eilers, P. (1997) Effects of ambient particulate matter and ozone on daily mortality in Rotterdam, the Netherlands. Arch. Environ. Health 52: 455-463.
Hoek, G.; Dockery, D. W.; Pope, A.; Neas, L.; Roemer, W.; Brunekreef, B. (1998) Association between PM_{10} and decrements in peak expiratory flow rates in children: reanalysis of data from five panel studies. Eur. Respir. J. 11: 1307-1311.
Hoek, G.; Brunekreef, B.; Verhoeff, A.; van, Wijnen, J.; Fischer, P. (2000) Daily mortality and air pollution in the Netherlands. J. Air Waste Manage. Assoc. 50: 1380-1389.
Hoek, G.; Brunekreef, B.; Fischer, P.; Van Wijnen, J. (2001) The association between air pollution and heart failure, arrhythmia, embolism, thrombosis, and other cardiovascular causes of death in a time series study. Epidemiology 12: 355-357.

Hoek, G.; Brunekreef, B.; Goldbohm, S.; Fischer, P.; Van den Brandt, P. A. (2002) Association between mortality and indicators of traffic-related air pollution in the Netherlands: a cohort study. Lancet 360: 1203-1209.
Hodgkin, J. E.; Abbey, D. E.; Euler, G. L.; Magie, A. R. (1984) COPD prevalence in nonsmokers in high and low photochemical air pollution areas. Chest 86: 830-838.
Hoeting, J. A.; Madigan, D.; Raftery, A. E.; Volinsky, C. T. (1999) Bayesian model averaging: a tutorial. Stat. Sci. 14: 382-417.
Hong, Y.-C.; Leem, J.-H.; Ha, E.-H.; Christiani, D. C. (1999) PM_{10} exposure, gaseous pollutants, and daily mortality in Inchon, South Korea. Environ. Health Perspect. 107: 873-878.
Horak, F., Jr.; Studnicka, M.; Gartner, C.; Spengler, J. D.; Tauber, E.; Urbanek, R.; Veiter, A.; Frischer, T. (2002) Particulate matter and lung function growth in children: a 3-yr follow-up study in Austrian schoolchildren. Eur. Respir. J. 19: 838-845.
Howel, D.; Darnell, R.; Pless-Mulloli, T. (2001) Children's respiratory health and daily particulate levels in 10 nonurban communities. Environ. Res. 87: 1-9.
Ibald-Mulli, A.; Stieber, J.; Wichmann, H.-E.; Koenig, W.; Peters, A. (2001) Effects of air pollution on blood pressure: a population-based approach. Am. J. Public Health 91: 571-577.
Ilabaca, M.; Olaeta, I.; Campos, E.; Villaire, J.; Tellez-Rojo, M. M.; Romieu, I. (1999) Association between levels of fine particulate and emergency visits for pneumonia and other respiratory illnesses among children in Santiago, Chile. J. Air Waste Manage. Assoc. 49: 154-163.
Ito, K. (1990) An examination of the role of aerosol acidity in historical London, England daily mortality [dissertation]. Syracuse, NY: New York University. Available from: University Microfilms International, Ann Arbor, MI; AAD91-13012.
Ito, K. (2003) Associations of particulate matter components with daily mortality and morbidity in Detroit, Michigan. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 143-156. Available: http://www.healtheffects.org/Pubs/TimeSeries.pdf [12 May, 2004].
Ito, K.; Thurston, G. D. (1996) Daily PM_{10}/mortality associations: an investigation of at-risk subpopulations. J. Exposure Anal. Environ. Epidemiol. 6: 79-95.
Ito, K.; Thurston, G. D.; Hayes, C.; Lippmann, M. (1993) Associations of London, England, daily mortality with particulate matter, sulfur dioxide, and acidic aerosol pollution. Arch. Environ. Health 48: 213-220.
Ito, K.; Kinney, P.; Thurston, G. D. (1995) Variations in PM-10 concentrations within two metropolitan areas and their implications for health effects analyses. In: Phalen, R. F.; Bates, D. V., eds. Proceedings of the colloquium on particulate air pollution and human mortality and morbidity, part II; January 1994; Irvine, CA. Inhalation Toxicol. 7: 735-745.
Ito, K.; Thurston, G. D.; Nádas, A.; Lippmann, M. (2001) Monitor-to-monitor temporal correlation of air pollution and weather variables in the North-Central U.S. J. Exposure Anal. Environ. Epidemiol. 11: 21-32.
Jacobs, J.; Kreutzer, R.; Smith, D. (1997) Rice burning and asthma hospitalizations, Butte County, California, 1983-1992. Environ. Health Perspect. 105: 980-985.
Jalaludin, B. B.; Chey, T.; O'Toole, B. I.; Smith, W. T.; Capon, A. G.; Leeder, S. R. (2000) Acute effects of low levels of ambient ozone on peak expiratory flow rate in a cohort of Australian children. Int. J. Epidemiol. 29: 549-557.
Jamason, P. F.; Kalkstein, L. S.; Gergen, P. J. (1997) A synoptic evaluation of asthma hospital admissions in New York City. Am. J. Respir. Crit. Care Med. 156: 1781-1788.
Janssen, N. A. H.; Schwartz, J.; Zanobetti, A.; Suh, H. H. (2002) Air conditioning and source-specific particles as modifiers of the effect of PM_{10} on hospital admissions for heart and lung disease. Environ. Health Perspect. 110: 43-49.
Jedrychowski, W.; Flak, E. (1998) Separate and combined effects of the outdoor and indoor air quality on chronic respiratory symptoms adjusted for allergy among preadolescent children. Int. J. Occup. Med. Environ. Health 11: 19-35.
Jedrychowski, W.; Becher, H.; Wahrendorf, J.; Basa-Cierpialek, Z. (1990) A case-control study of lung cancer with special reference to the effect of air pollution in Poland. J. Epidemiol. Commun. Health 44: 114-120.
Jedrychowski, W.; Flak, E.; Mróz, E. (1999) The adverse effect of low levels of ambient air pollutants on lung function growth in preadolescent children. Environ. Health Perspect. 107: 669-674.
Joseph, K. S.; Kramer, M. S. (1996) Review of the evidence on fetal and early childhood antecedents of adult chronic disease. Epidemiol. Rev. 18: 158-174.
Just, J.; Ségala, C.; Sahraoui, F.; Priol, G.; Grimfeld, A.; Neukirch, F. (2002) Short-term health effects of particulate and photochemical air pollution in asthmatic children. Eur. Respir. J. 20: 899-906.

Kalandidi, A.; Gratziou, C.; Katsouyanni, K.; Manalis, N.; Tzala, L.; Pantazopoulou, A.; Efthimiou, M.; Roussos, C.; Roemer, W. (1998) Air pollution and respiratory health of children: the PEACE panel study in Athens, Greece. Eur. Respir. Rev. 8: 117-124.

Kalkstein, L. S. (1991) A new approach to evaluate the impact of climate on human mortality. Environ. Health Perspect. 96: 145-150.

Kalkstein, L. S.; Tan, G. (1995) Human health. In: Strzepek, K. M.; Smith, J. B., eds. As climate changes: international impacts and implications. New York, NY: Cambridge University Press, 124-145.

Kalkstein, L. S.; Barthel, C. D.; Ye, H.; Smoyer, K.; Cheng, S.; Greene, J. S.; Nichols, M. C. (1994) The differential impacts of weather and pollution on human mortality. Newark, DE: University of Delaware, Department of Geography, Center for Climatic Research; November.

Katsouyanni, K.; Touloumi, G. (1998) Causes of regional differences in air pollution effects are being studied further [letter]. Br. Med. J. 316: 1982.

Katsouyanni, K.; Karakatsani, A.; Messari, I.; Touloumi, G.; Hatzakis, A.; Kalandidi, A.; Trichopoulos, D. (1990) Air pollution and cause specific mortality in Athens. J. Epidemiol. Community Health 44: 321-324.

Katsouyanni, K.; Schwartz, J.; Spix, C.; Touloumi, G.; Zmirou, D.; Zanobetti, A.; Wojtyniak, B.; Vonk, J. M.; Tobias, A.; Pönkä, A.; Medina, S.; Bachárová, L.; Andersen, H. R. (1996) Short term effects of air pollution on health: a European approach using epidemiology time series data: the APHEA protocol. In: St Leger, S., ed. The APHEA project. Short term effects of air pollution on health: a European approach using epidemiological time series data. J. Epidemiol. Community Health 50(suppl. 1): S12-S18.

Katsouyanni, K.; Touloumi, G.; Spix, C.; Schwartz, J.; Balducci, F.; Medina, S.; Rossi, G.; Wojtyniak, B.; Sunyer, J.; Bachárová, L.; Schouten, J. P.; Pönkä, A.; Anderson, H. R. (1997) Short term effects of ambient sulphur dioxide and particulate matter on mortality in 12 European cities: results from time series data from the APHEA project. Br. Med. J. 314: 1658-1663.

Katsouyanni, K.; Touloumi, G.; Samoli, E.; Gryparis, A.; Le Tertre, A.; Monopolis, Y.; Rossi, G.; Zmirou, D.; Ballester, F.; Boumghar, A.; Anderson, H. R.; Wojtyniak, B.; Paldy, A.; Braunstein, R.; Pekkanen, J.; Schindler, C.; Schwartz, J. (2001) Confounding and effect modification in the short-term effects of ambient particles on total mortality: results from 29 European cities within the APHEA2 project. Epidemiology 12: 521-531.

Katsouyanni, K.; Touloumi, G.; Samoli, E.; Petasakis, Y.; Analitis, A.; Le Tertre, A.; Rossi, G.; Zmirou, D.; Ballester, F.; Boumghar, A.; Anderson, H. R.; Wojtyniak, B.; Paldy, A.; Braunstein, R.; Pekkanen, J.; Schindler, C.; Schwartz, J. (2003) Sensitivity analysis of various models of short-term effects of ambient particles on total mortality in 29 cities in APHEA2. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 157-164. Available: http://www.healtheffects.org/Pubs/TimeSeries.pdf [18 October, 2004].

Keatinge, W. R.; Donaldson, G. C. (2001) Mortality related to cold and air pollution in London after allowance for effects of associated weather patterns. Environ. Res. A 86: 209-216.

Keles, N.; Ilicali, Ö. C.; Deger, K. (1999) Impact of air pollution on prevalence of rhinitis in Istanbul. Arch. Environ. Health 54: 48-51.

Kelsall, J. E.; Samet, J. M.; Zeger, S. L.; Xu, J. (1997) Air pollution and mortality in Philadelphia, 1974-1988. Am. J. Epidemiol. 146: 750-762.

Kinney, P. L.; Ito, K.; Thurston, G. D. (1995) A sensitivity analysis of mortality/PM_{10} associations in Los Angeles. In: Phalen, R. F.; Bates, D. V., eds. Proceedings of the colloquium on particulate air pollution and human mortality and morbidity; January 1994; Irvine, CA. Inhalation Toxicol. 7: 59-69.

Kinney, P. L.; Aggarwal, M.; Northridge, M. E.; Janssen, N. A. H.; Shepard, P. (2000) Airborne concentrations of $PM_{2.5}$ and diesel exhaust particles on Harlem sidewalks: a community-based pilot study. Environ. Health Perspect. 108: 213-218.

Klemm, R. J.; Mason, R. M., Jr. (2000) Aerosol research and inhalation epidemiological study (ARIES): air quality and daily mortality statistical modeling—interim results. J. Air. Waste Manage. Assoc. 50: 1433-1439.

Klemm, R. J.; Mason, R. (2003) Replication of reanalysis of Harvard Six-City mortality study. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 165-172. Available: http://www.healtheffects.org/Pubs/TimeSeries.pdf [12 May, 2004].

Klemm, R. J.; Mason, R. M., Jr.; Heilig, C. M.; Neas, L. M.; Dockery, D. W. (2000) Is daily mortality associated specifically with fine particles? Data reconstruction and replication of analyses. J. Air Waste Manage. Assoc. 50: 1215-1222.

Koenig, J. Q.; Larson, T. V.; Hanley, Q. S.; Rebolledo, V.; Dumler, K.; Checkoway, H.; Wang, S.-Z.; Lin, D.; Pierson, W. E. (1993) Pulmonary function changes in children associated with fine particulate matter. Environ. Res. 63: 26-38.

Kontos, A. S.; Fassois, S. D.; Deli, M. F. (1999) Short-term effects of air pollution on childhood respiratory illness in Piraeus, Greece, 1987-1992: nonparametric stochastic dynamic analysis. Environ. Res. 81: 275-296.
Korrick, S. A.; Neas, L. M.; Dockery, D. W.; Gold, D. R.; Allen, G. A.; Hill, L. B.; Kimball, K. D.; Rosner, B. A.; Speizer, F. E. (1998) Effects of ozone and other pollutants on the pulmonary function of adult hikers. Environ. Health Perspect. 106: 93-99.
Kostianev, S.; Gerginova, M.; Ivanova, M. (1994) Reference values of lung function parameters in Bulgarian girls aged 7 to 14 years. Pediatria 33: 30-33.
Kotěšovec, F.; Skorkovský, J.; Brynda, J.; Peters, A.; Heinrich, J. (2000) Daily mortality and air pollution in northern Bohemia; different effects for men and women. Cent. Eur. J. Public Health 8: 120-127.
Kramer, M. S. (1987) Intrauterine growth and gestational duration determinants. Pediatrics 80: 502-511.
Krämer, U.; Behrendt, H.; Dolgner, R.; Ranft, U.; Ring, J.; Willer, H.; Schlipköter, H.-W. (1999) Airway diseases and allergies in East and West German children during the first 5 years after reunification: time trends and the impact of sulphur dioxide and total suspended particles. Int. J. Epidemiol. 28: 865-873.
Krewski, D.; Burnett, R. T.; Goldberg, M. S.; Hoover, K.; Siemiatycki, J.; Jerrett, M.; Abrahamowicz, M.; White, W. H. (2000) Reanalysis of the Harvard Six Cities study and the American Cancer Society study of particulate air pollution and mortality. A special report of the Institute's Particle Epidemiology Reanalysis Project. Cambridge, MA: Health Effects Institute.
Kunst, A. E.; Looman, C. W. N.; Mackenbach, J. P. (1993) Outdoor air temperature and mortality in the Netherlands: a time-series analysis. Am. J. Epidemiol. 137: 331-341.
Künzli, N.; Tager, I. B. (1997) The semi-individual study in air pollution epidemiology: a valid design as compared to ecologic studies. Environ. Health Perspect. 105: 1078-1083.
Künzli, N.; Ackermann-Liebrich, U.; Brändli, O.; Tschopp, J. M.; Schindler, C.; Leuenberger, P.; SAPALDIA Team. (2000) Clinically "small" effects of air pollution on FVC have a large public health impact. Eur. Respir. J. 15: 131-136.
Kwon, H.-J.; Cho, S.-H.; Nyberg, F.; Pershagen, G. (2001) Effects of ambient air pollution on daily mortality in a cohort of patients with congestive heart failure. Epidemiology 12: 413-419.
Laden, F.; Neas, L. M.; Dockery, D. W.; Schwartz, J. (2000) Association of fine particulate matter from different sources with daily mortality in six U.S. cities. Environ. Health Perspect. 108: 941-947.
Lave, L. B.; Seskin, E. P. (1977) Air pollution and human health. Baltimore, MD: The Johns Hopkins University Press.
Le Tertre, A.; Medina, S.; Samoli, E.; Forsberg, B.; Michelozzi, P.; Boumghar, A.; Vonk, J. M.; Bellini, A.; Atkinson, R.; Ayres, J. G.; Sunyer, J.; Schwartz, J.; Katsouyanni, K. (2002) Short term effects of particulate air pollution on cardiovascular diseases in eight European cities. J. Epidemiol. Community Health 56: 773-779.
Le Tertre, A.; Medina, S.; Samoli, E.; Forsberg, B.; Michelozzi, P.; Boumghar, A.; Vonk, J. M.; Bellini, A.; Atkinson, R.; Ayres, J. G.; Sunyer, J.; Schwartz, J.; Katsouyanni, K. (2003) Short-term effects of particulate air pollution on cardiovascular diseases in eight European cities. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 173-176. Available: http://www.healtheffects.org/Pubs/TimeSeries.pdf [18 October, 2004].
Lebowitz, M. D.; Collins, L.; Holberg, C. J. (1987) Time series analyses of respiratory responses to indoor and outdoor environmental phenomena. Environ. Res. 43: 332-341.
Lee, J.-T.; Schwartz, J. (1999) Reanalysis of the effects of air pollution on daily mortality in Seoul, Korea: a case-crossover design. Environ. Health Perspect. 107: 633-636.
Lee, J.-T.; Shy, C. M. (1999) Respiratory function as measured by peak expiratory flow rate and PM_{10}: six communities study. J. Exposure Anal. Environ. Epidemiol. 9: 293-299.
Lee, R. E., Jr.; Caldwell, J. S.; Morgan, G. B. (1972) The evaluation of methods for measuring suspended particulates in air. Atmos. Environ. 6: 593-622.
Lee, J.-T.; Shin, D.; Chung, Y. (1999) Air pollution and daily mortality in Seoul and Ulsan, Korea. Environ. Health Perspect. 107: 149-154.
Lee, J.-T.; Kim, H.; Hong, Y.-C.; Kwon, H.-J.; Schwartz, J.; Christiani, D. C. (2000) Air pollution and daily mortality in seven major cities of Korea, 1991-1997. Environ. Res. 84: 247-254.
Leonardi, G. S.; Houthuijs, D.; Steerenberg, P. A.; Fletcher, T.; Armstrong, B.; Antova, T. (2000) Immune biomarkers in relation to exposure to particulate matter: a cross-sectional survey in 17 cities of central Europe. In: Grant, L. D., ed. PM2000: particulate matter and health. Inhalation Toxicol. 12(suppl. 4): 1-14.
Levy, D. (1998) Fine particulate air pollution and out-of-hospital mortality in King County, Washington. In: Vostal, J. J., ed. Health effects of particulate matter in ambient air. Proceedings of an international conference; 1997; Prague, Czech Republic. Pittsburgh, PA: Air & Waste Management Association; pp. 262-271. (A&WMA publication VIP-80).

Levy, J. I.; Hammitt, J. K.; Spengler, J. D. (2000) Estimating the mortality impacts of particulate matter: what can be learned from between-study variability? Environ. Health Perspect. 108: 109-117.

Levy, D.; Sheppard, L.; Checkoway, H.; Kaufman, J.; Lumley, T.; Koenig, J.; Siscovick, D. (2001) A case-crossover analysis of particulate matter air pollution and out-of-hospital primary cardiac arrest. Epidemiology 12: 193-199.

Lewis, P. R.; Hensley, M. J.; Wlodarczyk, J.; Toneguzzi, R. C.; Westley-Wise, V. J.; Dunn, T.; Calvert, D. (1998) Outdoor air pollution and children's respiratory symptoms in the steel cities of New South Wales. Med. J. Aust. 169: 459-463.

Lewis, S. A.; Corden, J. M.; Forster, G. E.; Newlands, M. (2000) Combined effects of aerobiological pollutants, chemical pollutants and meteorological conditions on asthma admissions and A & E attendances in Derbyshire UK, 1993-96. Clin. Exp. Allergy 30: 1724-1732.

Liao, D.; Creason, J.; Shy, C.; Williams, R.; Watts, R.; Zweidinger, R. (1999) Daily variation of particulate air pollution and poor cardiac autonomic control in the elderly. Environ. Health Perspect. 107: 521-525.

Lin, C. A.; Martins, M. A.; Farhat, S. C. L.; Pope, C. A., III; Conceição, G. M. S.; Anastácio, V. M.; Hatanaka, M.; Andrade, W. C.; Hamaue, W. R.; Böhm, G. M.; Saldiva, P. H. N. (1999) Air pollution and respiratory illness of children in São Paulo, Brazil. Paediatr. Perinat. Epidemiol. 13: 475-488.

Lin, M.; Chen, Y.; Burnett, R. T.; Villeneuve, P. J.; Krewski, D. (2002) The influence of ambient coarse particulate matter on asthma hospitalization in children: case-crossover and time-series analyses. Environ. Health Perspect. 110: 575-581.

Linn, W. S.; Shamoo, D. A.; Anderson, K. R.; Peng, R.-C.; Avol, E. L.; Hackney, J. D.; Gong, H., Jr. (1996) Short-term air pollution exposures and responses in Los Angeles area schoolchildren. J. Exposure Anal. Environ. Epidemiol. 6: 449-472.

Linn, W. S.; Gong, H., Jr.; Clark, K. W.; Anderson, K. R. (1999) Day-to-day particulate exposures and health changes in Los Angeles area residents with severe lung disease. J. Air Waste Manage. Assoc. 49: PM108-PM115.

Linn, W. S.; Szlachcic, Y.; Gong, H., Jr.; Kinney, P. L.; Berhane, K. T. (2000) Air pollution and daily hospital admissions in metropolitan Los Angeles. Environ. Health Perspect. 108: 427-434.

Lipfert, F. W.; Morris, S. C. (2002) Temporal and spacial relationships between age-specific mortality and ambient air quality in the United States: preliminary results for counties, 1960-97. Occup. Environ. Med. 59: 156-174.

Lipfert, F. W.; Wyzga, R. E. (1996) The effects of exposure error on environmental epidemiology. In: Phalen, R. F.; Mannix, R. C.; Tonini, M. C., eds. The second colloquium on particulate air pollution & human mortality & morbidity: report to the California Air Resources Board; May; Park City, UT. Sacramento, CA: State of California, Air Resources Board; pp. 4-295--4-302; ARB contract no. 95-323. (University of California Air Pollution Health Effects Laboratory report no. 96-02). Available: http://www.arb.ca.gov/research/abstracts/95-323.htm#Ch95-323 (24 September 2002).

Lipfert, F. W.; Wyzga, R. E. (1997) Air pollution and mortality: the implications of uncertainties in regression modeling and exposure measurement. J. Air Waste Manage. Assoc. 47: 517-523.

Lipfert, F. W.; Morris, S. C.; Wyzga, R. E. (2000a) Daily mortality in the Philadelphia metropolitan area and size-classified particulate matter. J. Air Waste Manage. Assoc.: 1501-1513.

Lipfert, F. W.; Perry, H. M., Jr.; Miller, J. P.; Baty, J. D.; Wyzga, R. E.; Carmody, S. E. (2000b) The Washington University-EPRI veterans' cohort mortality study: preliminary results. In: Grant, L. D., ed. PM2000: particulate matter and health. Inhalation Toxicol. 12(suppl. 4): 41-73.

Lipfert, F. W.; Zhang, J.; Wyzga, R. E. (2000c) Infant mortality and air pollution: a comprehensive analysis of U.S. data for 1990. J. Air Waste Manage. Assoc. 50: 1350-1366.

Lipfert, F. W.; Perry, H. M., Jr.; Miller, J. P.; Baty, J. D.; Wyzga, R. E.; Carmody, S. E. (2003) Air pollution, blood pressure, and their long-term associations with mortality. Inhalation Toxicol. 15: 493-512.

Lippmann, M.; Thurston, G. D. (1996) Sulfate concentrations as an indicator of ambient particulate matter air pollution for health risk evaluations. J. Exposure Anal. Environ. Epidemiol. 6: 123-146.

Lippmann, M.; Lioy, P. J.; Leikauf, G.; Green, K. B.; Baxter, D.; Morandi, M.; Pasternack, B. S.; Fife, D.; Speizer, F. E. (1983) Effects of ozone on the pulmonary function of children. In: Lee, S. D.; Mustafa, M. G.; Mehlman, M. A., eds. International symposium on the biomedical effects of ozone and related photochemical oxidants; March 1982; Pinehurst, NC. Princeton, NJ: Princeton Scientific Publishers, Inc.; pp. 423-446. (Advances in modern environmental toxicology: v. 5).

Lippmann, M.; Ito, K.; Nádas, A.; Burnett, R. T. (2000) Association of particulate matter components with daily mortality and morbidity in urban populations. Cambridge, MA: Health Effects Institute; research report no. 95.

Lipsett, M.; Hurley, S.; Ostro, B. (1997) Air pollution and emergency room visits for asthma in Santa Clara County, California. Environ. Health Perspect. 105: 216-222.

Long, W.; Tate, R. B.; Neuman, M.; Manfreda, J.; Becker, A. B.; Anthonisen, N. R. (1998) Respiratory symptoms in a susceptible population due to burning of agricultural residue. Chest 113: 351-357.
Loomis, D.; Castillejos, M.; Gold, D. R.; McDonnell, W.; Borja-Aburto, V. H. (1999) Air pollution and infant mortality in Mexico City. Epidemiology 10: 118-123.
Lumley, T.; Heagerty, P. (1999) Weighted empirical adaptive variance estimators for correlated data regression. J. R. Stat. Soc. B 61(part 2): 459-477.
Lumley, T.; Sheppard, L. (2000) Assessing seasonal confounding and model selection bias in air pollution epidemiology using positive and negative control analyses. Environmetrics 11: 705-717.
Mackenbach, J. P.; Looman, C. W. N.; Kunst, A. E. (1993) Air pollution, lagged effects of temperature, and mortality: The Netherlands 1979-87. J. Epidemiol. Commun. Health 47: 121-126.
Magari, S. R.; Hauser, R.; Schwartz, J.; Williams, P. L.; Smith, T. J.; Christiani, D. C. (2001) Association of heart rate variability with occupational and environmental exposure to particulate air pollution. Circulation 104: 986-991.
Magari, S. R.; Schwartz, J.; Williams, P. L.; Hauser, R.; Smith, T. J.; Christiani, D. C. (2002) The association between personal measurements of environmental exposure to particulates and heart rate variability. Epidemiology 13: 305-310.
Mage, D.; Wilson, W.; Hasselblad, V.; Grant, L. (1999) Assessment of human exposure to ambient particulate matter. J. Air Waste Manage. Assoc. 49: 174-185.
Maisonet, M.; Bush, T. J.; Correa, A.; Jaakkola, J. J. K. (2001) Relation between ambient air pollution and low birth weight in the northeastern United States. Environ. Health Perspect. Suppl. 109(3): 351-356.
Mar, T. F.; Norris, G. A.; Koenig, J. Q.; Larson, T. V. (2000) Associations between air pollution and mortality in Phoenix, 1995-1997. Environ. Health Perspect. 108: 347-353.
Mar, T. F.; Norris, G. A.; Larson, T. V.; Wilson, W. E.; Koenig, J. Q. (2003) Air pollution and cardiovascular mortality in Phoenix, 1995-1997. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 177-182. Available: http://www.healtheffects.org/Pubs/TimeSeries.pdf [18 October, 2004].
Marcus, A. H.; Chapman, R. (1998) Estimating the health effects of fine particles from epidemiology studies: how serious are problems of measurement error, correlation, and confounding? In: Chow, J.; Koutrakis, P., eds. $PM_{2.5}$: a fine particle standard. Volume II: proceedings of an international specialty conference.; January; Long Beach, CA. Pittsburgh, PA: Air & Waste Management Association; pp. 899-919.
McConnell, R.; Berhane, K.; Gilliland, F.; London, S. J.; Vora, H.; Avol, E.; Gauderman, W. J.; Margolis, H. G.; Lurmann, F.; Thomas, D. C.; Peters, J. M. (1999) Air pollution and bronchitic symptoms in southern California children with asthma. Environ. Health Perspect. 107: 757-760.
McConnell, R.; Berhane, K.; Gilliland, F.; London, S. J.; Islam, T.; Gauderman, W. J.; Avol, E.; Margolis, H. G.; Peters, J. M. (2002) Asthma in exercising children exposed to ozone: a cohort study. Lancet 359: 386-391.
McDonnell, W. F.; Nishino-Ishikawa, N.; Petersen, F. F.; Chen, L. H.; Abbey, D. E. (2000) Relationships of mortality with the fine and coarse fractions of long-term ambient PM_{10} concentrations in nonsmokers. J. Exposure Anal. Environ. Epidemiol. 10: 427-436.
McGowan, J. A.; Hider, P. N.; Chacko, E.; Town, G. I. (2002) Particulate air pollution and hospital admissions in Christchurch, New Zealand. Aust. N. Z. J. Public Health 26: 23-29.
McGregor, G. R.; Walters, S.; Wordley, J. (1999) Daily hospital respiratory admissions and winter air mass types, Birmingham, UK. Int. J. Biometeorol. 43: 21-30.
Medina, S.; Le Tertre, A.; Quénel, P.; Le Moullec, Y.; Lameloise, P.; Guzzo, J. C.; Festy, B.; Ferry, R.; Dab, W. (1997) Air pollution and doctors' house calls: results from the ERPURS system for monitoring the effects of air pollution on public health in greater Paris, France, 1991-1995. Environ. Res. 75: 73-84.
Metzger, K. B.; Tolbert, P. E.; Klein, M.; Peel, J. L.; Flanders, W. D.; Todd, K. H.; Mulholland, J. A.; Ryan, P. B.; Frumkin , H. (2004) Ambient air pollution and cardiovascular emergency department visits. Epidemiology 15: 46-56.
Michelozzi, P.; Forastiere, F.; Fusco, D.; Perucci, C. A.; Ostro, B.; Ancona, C.; Pallotti, G. (1998) Air pollution and daily mortality in Rome, Italy. Occup. Environ. Med. 55: 605-610.
Miller, J. P.; Perry, H. M., Jr.; Rossiter, J. E.; Baty, J. D.; Carmody, S. E.; Sambhi, M. P. (1994) Regional differences in mortality during 15-year follow-up of 11,936 hypertensive veterans. Hypertension 23: 431-438.
Mills, P. K.; Abbey, D.; Beeson, W. L.; Petersen, F. (1991) Ambient air pollution and cancer in California Seventh-day Adventists. Arch. Environ. Health 46: 271-280.
Monn, C. (2001) Exposure assessment of air pollutants: a review on spatial heterogeneity and indoor/outdoor/personal exposure to suspended particulate matter, nitrogen dioxide and ozone. Atmos. Environ. 35: 1-32.

Monn, Ch.; Carabias, V.; Junker, M.; Waeber, R.; Karrer, M.; Wanner, H. U. (1997) Small-scale spatial variability of particulate matter <10 μm (PM_{10}) and nitrogen dioxide. Atmos. Environ. 31: 2243-2247.
Moolgavkar, S. H. (2000a) Air Pollution and Mortality in Three U.S. Counties. Environ. Health Perspect. 108: 777-784.
Moolgavkar, S. H. (2000b) Air pollution and hospital admissions for diseases of the circulatory system in three U.S. metropolitan areas. J. Air Waste Manage Assoc. 50: 1199-1206.
Moolgavkar, S. H. (2000c) Air pollution and hospital admissions for chronic obstructive pulmonary disease in three metropolitan areas in the United States. In: Grant, L. D., ed. PM2000: particulate matter and health. Inhalation Toxicol. 12(suppl. 4): 75-90.
Moolgavkar, S. H. (2003) Air pollution and daily deaths and hospital admissions in Los Angeles and Cook counties. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 183-198. Available: http://www.healtheffects.org/news.htm [16 May, 2003].
Moolgavkar, S. H.; Luebeck, E. G. (1996) A critical review of the evidence on particulate air pollution and mortality. Epidemiology 7: 420-428.
Moolgavkar, S. H.; Luebeck, E. G.; Anderson, E. L. (1997) Air pollution and hospital admissions for respiratory causes in Minneapolis-St. Paul and Birmingham. Epidemiology 8: 364-370.
Moolgavkar, S. H.; Hazelton, W.; Luebeck, G.; Levy, D.; Sheppard, L. (2000) Air pollution, pollens, and admissions for chronic respiratory disease in King County, Washington. In: Inhalation toxicology: proceedings of the third colloquium on particulate air pollution and human health; June, 1999; Durham, NC. Inhalation Toxicol. 12(suppl. 1): 157-171.
Morgan, G.; Corbett, S.; Wlodarczyk, J.; Lewis, P. (1998) Air pollution and daily mortality in Sydney, Australia, 1989 through 1993. Am. J. Public Health 88: 759-764.
Morris, R. D. (2001) Airborne particulates and hospital admissions for cardiovascular disease: a quantitative review of the evidence. Environ. Health Perspect. 109(suppl. 4): 495-500.
Morris, R. D.; Naumova, E. N. (1998) Carbon monoxide and hospital admissions for congestive heart failure: evidence of an increased effect at low temperatures. Environ. Health Perspect. 106: 649-653.
Morris, R. D.; Naumova, E. N.; Munasinghe, R. L. (1995) Ambient air pollution and hospitalization for congestive heart failure among elderly people in seven large US cities. Am. J. Public Health 85: 1361-1365.
Mortimer, K. M.; Redline, S.; Kattan, M.; Wright, E. C.; Kercsmar, C. M. (2001) Are peak flow and symptom measures good predictors of asthma hospitalizations and unscheduled visits? Pediatr. Pulmonol. 31: 190-197.
Mortimer, K. M.; Neas, L. M.; Dockery, D. W.; Redline, S.; Tager, I. B. (2002) The effect of air pollution on inner-city children with asthma. Eur. Respir. J. 19: 699-705.
Murray, C. J.; Nelson, C. R. (2000) State-space modeling of the relationship between air quality and mortality. J. Air Waste Manage. Assoc. 50: 1075-1080.
Naeher, L. P.; Holford, T. R.; Beckett, W. S.; Belanger, K.; Triche, E. W.; Bracken, M. B.; Leaderer, B. P. (1999) Healthy women's PEF variations with ambient summer concentrations of PM_{10}, $PM_{2.5}$, SO_4^{2-}, H^+, and O_3. Am. J. Respir. Crit. Care Med. 160: 117-125.
Nauenberg, E.; Basu, K. (1999) Effect of insurance coverage on the relationship between asthma hospitalizations and exposure to air pollution. Public Health Rep. 114: 135-148.
Neas, L. M.; Dockery, D. W.; Ware, J. H.; Spengler, J. D.; Ferris, B. G., Jr.; Speizer, F. E. (1994) Concentration of indoor particulate matter as a determinant of respiratory health in children. Am. J. Epidemiol. 139: 1088-1099.
Neas, L. M.; Dockery, D. W.; Koutrakis, P.; Tollerud, D. J.; Speizer, F. E. (1995) The association of ambient air pollution with twice daily peak expiratory flow rate measurements in children. Am. J. Epidemiol. 141: 111-122.
Neas, L. M.; Dockery, D. W.; Burge, H.; Koutrakis, P.; Speizer, F. E. (1996) Fungus spores, air pollutants, and other determinants of peak expiratory flow rate in children. Am. J. Epidemiol. 143: 797-807.
Neas, L. M.; Schwartz, J.; Dockery, D. (1999) A case-crossover analysis of air pollution and mortality in Philadelphia. Environ. Health Perspect. 107: 629-631.
Neukirch, F.; Ségala, C.; Le Moullec, Y.; Korobaeff, M.; Aubier, M. (1998) Short-term effects of low-level winter pollution on respiratory health of asthmatic adults. Arch. Environ. Health 53: 320-328.
Norris, G.; Young-Pong, S. N.; Koenig, J. Q.; Larson, T. V.; Sheppard, L.; Stout, J. W. (1999) An association between fine particles and asthma emergency department visits for children in Seattle. Environ. Health Perspect. 107: 489-493.
Norris, G.; Larson, T.; Koenig, J.; Claiborn, C.; Sheppard, L.; Finn, D. (2000) Asthma aggravation, combustion, and stagnant air. Thorax 55: 466-470.
Nyberg, F.; Gustavsson, P.; Järup, L.; Bellander, T.; Berglind, N.; Jakobsson, R.; Pershagen, G. (2000) Urban air pollution and lung cancer in Stockholm. Epidemiology 11: 487-495.

Ostro, B. (1995) Fine particulate air pollution and mortality in two Southern California counties. Environ. Res. 70: 98-104.
Ostro, B. D.; Lipsett, M. J.; Wiener, M. B.; Selner, J. C. (1991) Asthmatic responses to airborne acid aerosols. Am. J. Public Health 81: 694-702.
Ostro, B. D.; Lipsett, M. J.; Mann, J. K.; Braxton-Owens, H.; White, M. C. (1995) Air pollution and asthma exacerbations among African-American children in Los Angeles. In: Phalen, R. F.; Bates, D. V., eds. Proceedings of the colloquium on particulate air pollution and human mortality and morbidity, part II; January 1994; Irvine, CA. Inhalation Toxicol. 7: 711-722.
Ostro, B.; Chestnut, L.; Vichit-Vadakan, N.; Laixuthai, A. (1998) The impact of fine particulate matter in Bangkok, Thailand. In: Chow, J.; Koutrakis, P., eds. PM2.5: a fine particle standard. Volume II: proceedings of an international specialty conference; January; Long Beach, CA. Pittsburgh, PA: Air & Waste Management Association; pp. 939-949. (A&WMA publication VIP-81).
Ostro, B. D.; Hurley, S.; Lipsett, M. J. (1999a) Air pollution and daily mortality in the Coachella Valley, California: a study of PM_{10} dominated by coarse particles. Environ. Res. 81: 231-238.
Ostro, B. D.; Eskeland, G. S.; Sanchez, J. M.; Feyzioglu, T. (1999b) Air pollution and health effects: a study of medical visits among children in Santiago, Chile. Environ. Health Perspect. 107: 69-73.
Ostro, B. D.; Broadwin, R.; Lipsett, M. J. (2000) Coarse and fine particles and daily mortality in the Coachella Valley, CA: a follow-up study. J. Exposure Anal. Environ. Epidemiol.: 10: 412-419.
Ostro, B.; Lipsett, M.; Mann, J.; Braxtron-Owens, H.; White, M. (2001) Air pollution and exacerbation of asthma in African-American children in Los Angeles. Epidemiology 12: 200-208.
Ostro, B. D.; Broadwin, R.; Lipsett, M. J. (2003) Coarse particles and daily mortality in Coachella Valley, California. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 199-204. Available: http://www.healtheffects.org/Pubs/TimeSeries.pdf [18 October, 2004].
Osunsanya, T.; Prescott, G.; Seaton, A. (2001) Acute respiratory effects of particles: mass or number? Occup. Environ. Med. 58: 154-159.
Ott, W.; Wallace, L.; Mage, D. (2000) Predicting particulate (PM_{10}) personal exposure distributions using a random component superposition statistical model. J. Air Waste Manage. Assoc. 50: 1390-1406.
Özkaynak, H.; Xue, J.; Zhou, H.; Raizenne, M. (1996) Associations between daily mortality and motor vehicle pollution in Toronto, Canada. Boston, MA: Harvard University School of Public Health, Department of Environmental Health; March 25.
Pantazopoulou, A.; Katsouyanni, K.; Kourea-Kremastinou, J.; Trichopoulos, D. (1995) Short-term effects of air pollution on hospital emergency outpatient visits and admissions in the greater Athens, Greece area. Environ. Res. 69: 31-36.
Pekkanen, J.; Timonen, K. L.; Ruuskanen, J.; Reponen, A.; Mirme, A. (1997) Effects of ultrafine and fine particles in urban air on peak expiratory flow among children with asthmatic symptoms. Environ. Res. 74: 24-33.
Pekkanen, J.; Brunner, E. J.; Anderson, H. R.; Tiittanen, P.; Atkinson, R. W. (2000) Daily concentrations of air pollution and plasma fibrinogen in London. Occup. Environ. Med. 57: 818-822.
Penttinen, P.; Timonen, K. L.; Tiittanen, P.; Mirme, A.; Ruuskanen, J.; Pekkanen, J. (2001) Number concentration and size of particles in urban air: effects on spirometric lung function in adult asthmatic subjects. Environ. Health Perspect. 109: 319-323.
Pereira, L. A. A.; Loomis, D.; Conceição, G. M. S.; Braga, A. L. F.; Arcas, R. M.; Kishi, H. S.; Singer, J. M.; Böhm, G. M.; Saldiva, P. H. N. (1998) Association between air pollution and intrauterine mortality in São Paulo, Brazil. Environ. Health Perspect. 106: 325-329.
Perry, H. M., Jr.; Schnaper, H. W.; Meyer, G.; Swatzell, R. (1982) Clinical program for screening and treatment of hypertension in veterans. J. Natl. Med. Assoc. 74: 433-444.
Peters, A.; Goldstein, I. F.; Beyer, U.; Franke, K.; Heinrich, J.; Dockery, D. W.; Spengler, J. D.; Wichmann, H.-E. (1996) Acute health effects of exposure to high levels of air pollution in eastern Europe. Am. J. Epidemiol. 144: 570-581.
Peters, A.; Doring, A.; Wichmann, H.-E.; Koenig, W. (1997a) Increased plasma viscosity during an air pollution episode: a link to mortality? Lancet 349: 1582-1587.
Peters, A.; Wichmann, H. E.; Tuch, T.; Heinrich, J.; Heyder, J. (1997b) Respiratory effects are associated with the number of ultrafine particles. Am. J. Respir. Crit. Care Med. 155: 1376-1383.
Peters, A.; Dockery, D. W.; Heinrich, J.; Wichmann, H. E. (1997c) Short-term effects of particulate air pollution on respiratory morbidity in asthmatic children. Eur. Respir. J. 10: 872-879.

Peters, A.; Kotesovec, F.; Skorkovsky, J.; Brynda, J.; Heinrich, J. (1999a) Akute Auswirkung der Schwebstaubkonzentrationen in der Außenluft auf die Mortalität - Vergleichsstudie Nordost-Bayern / Nordböhmen. Abschlußbericht [Acute effects of suspended particle concentrations in the atmosphere on mortality - a study comparing northeast Bavaria and north Bohemia. Final report]. Bavaria, Federal Republic of Germany: Institut für Epidemiologie; report no. GSF-EP S 1/99.

Peters, J. M.; Avol, E.; Navidi, W.; London, S. J.; Gauderman, W. J.; Lurmann, F.; Linn, W. S.; Margolis, H.; Rappaport, E.; Gong, H., Jr.; Thomas, D. C. (1999b) A study of twelve southern California communities with differing levels and types of air pollution. I. Prevalence of respiratory morbidity. Am. J. Respir. Crit. Care Med. 159: 760-767.

Peters, J. M.; Avol, E.; Gauderman, W. J.; Linn, W. S.; Navidi, W.; London, S. J.; Margolis, H.; Rappaport, E.; Vora, H.; Gong, H., Jr.; Thomas, D. C. (1999c) A study of twelve southern California communities with differing levels and types of air pollution. II. Effects on pulmonary function. Am. J. Respir. Crit. Care Med. 159: 768-775.

Peters, A.; Liu, E.; Verrier, R. L.; Schwartz, J.; Gold, D. R.; Mittleman, M.; Baliff, J.; Oh, J. A.; Allen, G.; Monahan, K.; Dockery, D. W. (2000a) Air pollution and incidence of cardiac arrhythmia. Epidemiology 11: 11-17.

Peters, A.; Skorkovsky, J.; Kotesovec, F.; Brynda, J.; Spix, C.; Wichmann, H. E.; Heinrich, J. (2000b) Associations between mortality and air pollution in central Europe. Environ. Health Perspect. 108: 283-287.

Peters, A.; Dockery, D. W.; Muller, J. E.; Mittleman, M. A. (2001a) Increased particulate air pollution and the triggering of myocardial infarction. Circulation 103: 2810-2815.

Peters, A.; Fröhlich, M.; Döring, A.; Immervoll, T.; Wichmann, H.-E.; Hutchinson, W. L.; Pepys, M. B.; Koenig, W. (2001b) Particulate air pollution is associated with an acute phase response in men: results from the MONICA-Augsburg Study. Eur. Heart J. 22: 1198-1204.

Petroeschevsky, A.; Simpson, R. W.; Thalib, L.; Rutherford, S. (2001) Associations between outdoor air pollution and hospital admissions in Brisbane, Australia. Arch. Environ. Health 56: 37-52.

Pike, M. C.; Jing, J. S.; Rosario, I. P.; Henderson, B. E.; Menck, H. R. (1979) Occupation: "explanation" of an apparent air pollution related localized excess of lung cancer in Los Angeles County. In: Breslow, N. E.; Whitemore, A. S., eds. Energy and Health: proceedings of a conference sponsored by Siam Institute for Mathematics and Society; 1978; Alta, Utah. [SIAM-SIMS conference series 6].

Pless-Mulloli, T.; Howel, D.; King, A.; Stone, I.; Merefield, J.; Bessell, J.; Darnell, R. (2000) Living near opencast coal mining sites and children's respiratory health. Occup. Environ. Med. 57: 145-151.

Ponce de Leon, A.; Anderson, H. R.; Bland, J. M.; Strachan, D. P.; Bower, J. (1996) Effects of air pollution on daily hospital admissions for respiratory disease in London between 1987-88 and 1991-92. In: St Leger, S., ed. The APHEA project. Short term effects of air pollution on health: a European approach using epidemiological time series data. J. Epidemiol. Community Health 50(suppl. 1): S63-S70.

Pönkä, A.; Savela, M.; Virtanen, M. (1998) Mortality and air pollution in Helsinki. Arch. Environ. Health 53: 281-286.

Pope, C. A., III. (1989) Respiratory disease associated with community air pollution and a steel mill, Utah Valley. Am. J. Public Health 79: 623-628.

Pope, C. A., III. (1991) Respiratory hospital admissions associated with PM_{10} pollution in Utah, Salt Lake, and Cache Valleys. Arch. Environ. Health 46: 90-97.

Pope, C. A., III; Kalkstein, L S. (1996) Synoptic weather modeling and estimates of the exposure-response relationship between daily mortality and particulate air pollution. Environ. Health Perspect. 104: 414-420.

Pope, C. A., III; Dockery, D. W.; Spengler, J. D.; Raizenne, M. E. (1991) Respiratory health and PM_{10} pollution: a daily time series analysis. Am. Rev. Respir. Dis. 144: 668-674.

Pope, C. A., III; Schwartz, J.; Ransom, M. R. (1992) Daily mortality and PM10 pollution in Utah valley. Arch. Environ. Health 47: 211-217.

Pope, C. A., III; Thun, M. J.; Namboodiri, M. M.; Dockery, D. W.; Evans, J. S.; Speizer, F. E.; Heath, C. W., Jr. (1995) Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults. Am. J. Respir. Crit. Care Med. 151: 669-674.

Pope, C. A., III; Hill, R. W.; Villegas, G. M. (1999a) Particulate air pollution and daily mortality on Utah's Wasatch Front. Environ. Health Perspect. 107: 567-573.

Pope, C. A., III; Dockery, D. W.; Kanner, R. E.; Vollegas, G. M.; Schwartz, J. (1999b) Oxygen saturation, pulse rate, and particulate air pollution: a daily time-series panel study. Am. J. Respir. Crit. Care Med. 159: 365-372.

Pope, C. A., III; Verrier, R. L.; Lovett, E. G.; Larson, A. C.; Raizenne, M. E.; Kanner, R. E.; Schwartz, J.; Villegas, G. M.; Gold, D. R.; Dockery, D. W. (1999c) Heart rate variability associated with particulate air pollution. Am. Heart J. 138: 890-899.

Pope, C. A., III; Burnett, R. T.; Thun, M. J.; Calle, E. E.; Krewski, D.; Ito, K.; Thurston, G. D. (2002) Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. JAMA J. Am. Med. Assoc. 287: 1132-1141.

Prescott, G. J.; Cohen, G. R.; Elton, R. A.; Fowkes, F. G. R.; Agius, R. M. (1998) Urban air pollution and cardiopulmonary ill health: a 14.5 year time series study. Occup. Environ. Med. 55: 697-704.

Prescott, G. J.; Lee, R. J.; Cohen, G. R.; Elton, R. A.; Lee, A. J.; Fowkes, F. G. R.; Agius, R. M. (2000) Investigation of factors which might indicate susceptibility to particulate air pollution. Occup. Environ. Med. 57: 53-57.

Qian, Z. Chapman, R. S.; Tian, Q.; Chen, Y.; Lioy, P. J.; Zhang, J. (2000) Effects of air pollution on children's respiratory health in three Chinese cities. Arch. Environ. Health 55: 126-133.

Rahlenbeck, S. I.; Kahl, H. (1996) Air pollution and mortality in East Berlin during the winters of 1981-1989. Int. J. Epidemiol. 25: 1220-1226.

Raizenne, M.; Neas, L. M.; Damokosh, A. I.; Dockery, D. W.; Spengler, J. D.; Koutrakis, P.; Ware, J. H.; Speizer, F. E. (1996) Health effects of acid aerosols on North American children: pulmonary function. Environ. Health Perspect. 104: 506-514.

Ramlow, J. M.; Kuller, L. H. (1990) Effects of the summer heat wave of 1988 on daily mortality in Allegheny County, PA. Public Health Rep. 105: 283-289.

Ritz, B.; Yu, F.; Chapa, G.; Fruin, S. (2000) Effect of air pollution on preterm birth among children born in Southern California between 1989 and 1993. Epidemiology 11: 502-511.

Roemer, W. H.; Van Wijnen, J. H . (2001) Daily mortality and air pollution along busy streets in Amsterdam, 1987-1998. Epidemiology 12: 649-653.

Roemer, W.; Hoek, G.; Brunekreef, B. (1993) Effect of ambient winter air pollution on respiratory health of children with chronic respiratory symptoms. Am. Rev. Respir. Dis. 147: 118-124.

Roemer, W.; Hoek, G.; Brunekreef, B.; Haluszka, J.; Kalandidi, A.; Pekkanen, J. (1998) Daily variations in air pollution and respiratory health in a multicentre study: the PEACE project. Eur. Respir. J. 12: 1354-1361.

Roemer, W.; Hoek, G.; Brunekreef, B.; Clench-Aas, J.; Forsberg, B.; Pekkanen, J.; Schutz, A. (2000) PM_{10} elemental composition and acute respiratory health effects in European children (PEACE project). Eur. Respir. J. 15: 553-559.

Rogers, J. F.; Thompson, S. J.; Addy, C. L.; McKeown, R. E.; Cowen, D. J.; Decouflé, P. (2000) Association of very low birth weight with exposures to environmental sulfur dioxide and total suspended particulates. Am. J. Epidemiol. 151: 602-613.

Romieu, I.; Meneses, F.; Ruiz, S.; Sienra, J. J.; Huerta, J.; White, M. C.; Etzel, R. A. (1996) Effects of air pollution on the respiratory health of asthmatic children living in Mexico City. Am. J. Respir. Crit. Care Med. 154: 300-307.

Romieu, I.; Meneses, F.; Ruiz, S.; Huerta, J.; Sienra, J. J.; White, M.; Etzel, R.; Hernandez, M. (1997) Effects of intermittent ozone exposure on peak expiratory flow and respiratory symptoms among asthmatic children in Mexico City. Arch. Environ. Health 52: 368-376.

Rooney, C.; McMichael, A. J.; Kovats, R. S.; Coleman, M. P. (1998) Excess mortality in England and Wales, and in greater London, during the 1995 heatwave. J. Epidemiol. Community Health 52: 482-486.

Rosas, I.; McCartney, H. A.; Payne, R. W.; Calderon, C.; Lacey, J.; Chapela, R.; Ruiz-Velazco, S. (1998) Analysis of the relationships between environmental factors (aeroallergens, air pollution, and weather) and asthma emergency admissions to a hospital in Mexico City. Allergy (Copenhagen) 53: 394-401.

Rossi, G.; Vigotti, M. A.; Zanobetti, A.; Repetto, F.; Gianelle, V.; and Schwartz, J. (1999) Air pollution and cause-specific mortality in Milan, Italy, 1980-1989. Arch. Environ. Health 54: 158-164.

Rothman, K. J.; Greenland, S., eds. (1998) Modern epidemiology. 2nd ed. Philadelphia, PA: Lippincott-Raven Publishers.

Rutherford, S.; Clark, E.; McTainsh, G.; Simpson, R.; Mitchell, C. (1999) Characteristics of rural dust events shown to impact on asthma severity in Brisbane, Australia. Int. J. Biometeorol. 42: 217-225.

Samet, J. M.; Zeger, S. L.; Berhane, K. (1995) The association of mortality and particulate air pollution. In: Particulate air pollution and daily mortality: replication and validation of selected studies, the phase I report of the particle epidemiology evaluation project [preprint]. Cambridge, MA: Health Effects Institute; pp. 1-104.

Samet, J. M.; Zeger, S. L.; Kelsall, J. E.; Xu, J.; Kalkstein, L. S. (1996) Weather, air pollution and mortality in Philadelphia, 1973-1980, report to the Health Effects Institute on phase IB, Particle Epidemiology Evaluation Project. Cambridge, MA: Health Effects Institute; review draft.

Samet, J. M.; Zeger, S. L.; Dominici, F.; Curriero, F.; Coursac, I.; Dockery, D. W.; Schwartz, J.; Zanobetti, A. (2000a) The national morbidity, mortality, and air pollution study. Part II: morbidity, mortality, and air pollution in the United States. Cambridge, MA: Health Effects Institute; research report no. 94.

Samet, J. M.; Dominici, F.; Zeger, S. L.; Schwartz, J.; Dockery, D. W. (2000b) National morbidity, mortality, and air pollution study. Part I: methods and methodologic issues. Cambridge, MA: Health Effects Institute; research report no. 94.

Samet, J. M.; Dominici, F.; Curriero, F. C.; Coursac, I.; Zeger, S. L. (2000c) Fine particulate air pollution and mortality in 20 U.S. cities, 1987-1994. N. Engl. J. Med. 343: 1742-1749.

Samoli, E.; Schwartz, J.; Wojtyniak, B.; Touloumi, G.; Spix, C.; Balducci, F.; Medina, S.; Rossi, G.; Sunyer, J.; Bacharova, L.; Anderson, H. R.; Katsouyanni, K. (2001) Investigating regional differences in short-term effects of air pollution on daily mortality in the APHEA project: a sensitivity analysis for controlling long-term trends and seasonality. Environ. Health Perspect. 109: 349-353.

Samoli, E.; Schwartz, J.; Analitis, A.; Petasakis, Y.; Wojtyniak, B.; Touloumi, G.; Spix, C.; Balducci, F.; Medina, S.; Rossi, G.; Sunyer, J.; Anderson, H. R.; Katsouyanni, K. (2003) Sensitivity analyses of regional differences in short-term effects of air pollution on daily mortality in APHEA cities. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 205-210. Available: http://www.healtheffects.org/Pubs/TimeSeries.pdf [18 October, 2004].

Sarnat, J. A.; Koutrakis, P.; Suh, H. H. (2000) Assessing the relationship between personal particulate and gaseous exposures of senior citizens living in Baltimore, MD. J. Air Waste Manage. Assoc. 50: 1184-1198.

Sarnat, J. A.; Schwartz, J.; Catalano, P. J.; Suh, H. H. (2001) Gaseous pollutants in particulate matter epidemiology: confounders or surrogates? Environ. Health Perspect. 109: 1053-1061.

Scarlett, J. F.; Abbott, K. J.; Peacock, J. L.; Strachan, D. P.; Anderson, H. R. (1996) Acute effects of summer air pollution on respiratory function in primary school children in southern England. Thorax 51: 1109-1114.

Schouten, J. P.; Vonk, J. M.; de Graaf, A. (1996) Short term effects of air pollution on emergency hospital admissions for respiratory disease: results of the APHEA project in two major cities in The Netherlands, 1977-89. In: St Leger, S., ed. The APHEA project. Short term effects of air pollution on health: a European approach using epidemiological time series data. J. Epidemiol. Community Health 50(suppl. 1): S22-S29.

Schwartz, J. (1991) Particulate air pollution and daily mortality in Detroit. Environ. Res. 56: 204-213.

Schwartz, J. (1993) Air pollution and daily mortality in Birmingham, Alabama. Am. J. Epidemiol. 137: 1136-1147.

Schwartz, J. (1994a) PM_{10}, ozone, and hospital admissions for the elderly in Minneapolis, MN. Arch. Environ. Health 49: 366-374.

Schwartz, J. (1994b) Air pollution and hospital admissions for the elderly in Detroit, Michigan. Am. J. Respir. Crit. Care Med. 150: 648-655.

Schwartz, J. (1995) Short term fluctuations in air pollution and hospital admissions of the elderly for respiratory disease. Thorax 50: 531-538.

Schwartz, J. (1997a) Air pollution and hospital admissions for cardiovascular disease in Tucson. Epidemiology 8: 371-377.

Schwartz, J. (1997b) Health effects of air pollution from traffic: ozone and particulate matter. In: Fletcher, T.; McMichael, A. J., eds. Health at the crossroads: transport policy and urban health. [Proceedings of the] London School of Hygiene & Tropical Medicine fifth annual public health forum; April, 1995; London, United Kingdom. Chichester, United Kingdom: John Wiley & Sons Ltd.; pp. 61-85.

Schwartz, J. (1999) Air pollution and hospital admissions for heart disease in eight U.S. counties. Epidemiology 10: 17-22.

Schwartz, J. (2000a) Assessing confounding, effect modification, and thresholds in the association between ambient particles and daily deaths. Environ. Health Perspect. 108: 563-568.

Schwartz, J. (2000b) The distributed lag between air pollution and daily deaths. Epidemiology 11: 320-326.

Schwartz, J. (2000c) Harvesting and long term exposure effects in the relation between air pollution and mortality. Am. J. Epidemiol. 151: 440-448.

Schwartz, J. (2000d) Daily deaths are associated with combustion particles rather than SO_2 in Philadelphia. Occup. Environ. Med. 57: 692-697.

Schwartz, J. (2001) Air pollution and blood markers of cardiovascular risk. Environ. Health Perspect. Suppl. 109(3): 405-409.

Schwartz, J. (2003a) Daily deaths associated with air pollution in six US cities and short-term mortality displacement in Boston. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 219-226. Available: http://www.healtheffects.org/Pubs/TimeSeries.pdf [18 October, 2004].

Schwartz, J. (2003b) Airborne particles and daily deaths in 10 US cities. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 211-218. Available: http://www.healtheffects.org/Pubs/TimeSeries.pdf [18 October, 2004].

Schwartz, J.; Dockery, D. W. (1992) Increased mortality in Philadelphia associated with daily air pollution concentrations. Am. Rev. Respir. Dis. 145: 600-604.
Schwartz, J.; Marcus, A. (1990) Mortality and air pollution in London: a time series analysis. Am. J. Epidemiol. 131: 185-194.
Schwartz, J.; Morris, R. (1995) Air pollution and hospital admissions for cardiovascular disease in Detroit, Michigan. Am. J. Epidemiol. 142: 23-35.
Schwartz, J.; Neas, L. M. (2000) Fine particles are more strongly associated than coarse particles with acute respiratory health effects in schoolchildren. Epidemiology. 11: 6-10.
Schwartz, J.; Zanobetti, A. (2000) Using meta-smoothing to estimate dose-response trends across multiple studies, with application to air pollution and daily death. Epidemiology 11: 666-672.
Schwartz, J.; Dockery, D. W.; Neas, L. M.; Wypij, D.; Ware, J. H.; Spengler, J. D.; Koutrakis, P.; Speizer, F. E.; Ferris, B. G., Jr. (1994) Acute effects of summer air pollution on respiratory symptom reporting in children. Am. J. Respir. Crit. Care Med. 150: 1234-1242.
Schwartz, J.; Dockery, D. W.; Neas, L. M. (1996a) Is daily mortality associated specifically with fine particles? J. Air Waste Manage. Assoc. 46: 927-939.
Schwartz, J.; Spix, C.; Touloumi, G.; Bacharova, L.; Barumamdzadeh, T.; le Tertre, A.; Piekarksi, T.; Ponce de Leon, A.; Ponka, A.; Rossi, G.; Saez, M.; Schouten, J. P. (1996b) Methodological issues in studies of air pollution and daily counts of deaths or hospital admissions. In: St Leger, S., ed. The APHEA project. Short term effects of air pollution on health: a European approach using epidemiological time series data. J. Epidemiol. Community Health 50(suppl. 1): S3-S11.
Schwartz, J.; Norris, G.; Larson, T.; Sheppard, L.; Claiborne, C.; Koenig, J. (1999) Episodes of high coarse particle concentrations are not associated with increased mortality. Environ. Health Perspect. 107: 339-342.
Schwartz, J.; Zanobetti, A.; Bateson, T. (2003) Morbidity and mortality among elderly residents of cities with daily PM measurements. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 25-58. Available: http://www.healtheffects.org/Pubs/TimeSeries.pdf [18 October, 2004].
Seaton, A.; Soutar, A.; Crawford, V.; Elton, R.; McNerlan, S.; Cherrie, J.; Watt, M.; Agius, R.; Stout, R. (1999) Particulate air pollution and the blood. Thorax 54: 1027-1032.
Segala, C.; Fauroux, B.; Just, J.; Pascual, L.; Grimfeld, A.; Neukirch, F. (1998) Short-term effect of winter air pollution on respiratory health of asthmatic children in Paris. Eur. Respir. J. 11: 677-685.
Sheppard, L. (2003) Ambient air pollution and nonelderly asthma hospital admissions in Seattle, Washington, 1987-1994. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 227-230. Available: http://www.healtheffects.org/Pubs/TimeSeries.pdf [18 October, 2004].
Sheppard, L.; Damian, D. (2000) Estimating short-term PM effects accounting for surrogate exposure measurements from ambient monitors. Environmetrics 11: 675-687.
Sheppard, L.; Levy, D.; Norris, G.; Larson, T. V.; Koenig, J. Q. (1999) Effects of ambient air pollution on nonelderly asthma hospital admissions in Seattle, Washington, 1987-1994. Epidemiology 10: 23-30.
Sheppard, L.; Levy, D.; Checkoway, H. (2001) Correcting for the effects of location and atmospheric conditions on air pollution exposures in a case-crossover study. J. Exposure Anal. Environ. Epidemiol. 11: 86-96.
Shima, M.; Nitta, Y.; Ando, M.; Adachi, M. (2002) Effects of air pollution on the prevalence and incidence of asthma in children. Arch. Environ. Health 57: 529-535.
Shumway, R. H.; Tai, R. Y.; Tai, L. P.; Pawitan, Y. (1983) Statistical analysis of daily London mortality and associated weather and pollution effects. Sacramento, CA: California Air Resources Board; contract no. A1-154-33.
Shumway, R. H.; Azari, A. S.; Pawitan, Y. (1988) Modeling mortality fluctuations in Los Angeles as functions of pollution and weather effects. Environ. Res. 45: 224-241.
Simpson, R. W.; Williams, G.; Petroeschevsky, A.; Morgan, G.; Rutherford, S. (1997) Associations between outdoor air pollution and daily mortality in Brisbane, Australia. Arch. Environ. Health 52: 442-454.
Smith, R. L. (2003) Invited commentary: timescale-dependent mortality effects of air pollution. Am. J. Epidemiol. 157: 1066-1070.
Smith, M. A.; Jalaludin, B.; Byles, J. E.; Lim, L.; Leeder, S. R. (1996) Asthma presentations to emergency departments in western Sydney during the January 2194 bushfires. Int. J. Epidemiol. 25: 1227-1236.
Smith, R. L.; Davis, J. M.; Speckman, P. (1999) Human Health Effects of Environmental Pollution in the Atmosphere. London, England. New York, NY: Statistics for the Environment 4: Pollution Assessment and Control. Edited by V. Barrett, A, Stein and K.F. Turkman. Wiley. pp. 91-115.

Smith, R. L.; Spitzner, D.; Kim, Y.; Fuentes, M. (2000) Threshold dependence of mortality effects for fine and coarse particles in Phoenix, Arizona. J. Air Waste Manage. Assoc. 50: 1367-1379.
Smoyer, K. E.; Rainham, D. G. C.; Hewko, J. N. (2000a) Heat-stress-related mortality in five cities in southern Ontario: 1980-1996. Int. J. Biometeorol. 44: 190-197.
Smoyer, K. E.; Kalkstein, L. S.; Greene, J. S.; Ye, H. (2000b) The impacts of weather and pollution on human mortality in Birmingham, Alabama and Philadelphia, Pennsylvania. Int. J. Climatol. 20: 881-897.
Spinillo, A.; Capuzzo, E.; Egbe, T. O.; Fazzi, E.; Colonna, L.; Nicola, S. (1995) Pregnancies complicated by idiopathic intrauterine growth retardation: severity of growth failure, neonatal morbidity and two-year infant neurodevelopmental outcome. J. Reprod. Med. 40: 209-215.
Spix, C.; Heinrich, J.; Dockery, D.; Schwartz, J.; Volksch, G.; Schwinkowski, K.; Collen, C.; Wichmann, H. E. (1993) Air pollution and daily mortality in Erfurt, East Germany, 1980-1989. Environ. Health Perspect. 101: 518-526.
Spix, C.; Anderson, H. R.; Schwartz, J.; Vigotti, M. A.; LeTertre, A.; Vonk, J. M.; Touloumi, G.; Balducci, F.; Piekarski, T.; Bacharova, L.; Tobias, A.; Pönkä, A.; Katsouyanni, K. (1998) Short-term effects of air pollution on hospital admissions of respiratory diseases in Europe: a quantitative summary of APHEA study results. Arch. Environ. Health 53: 54-64.
Stieb, D. M.; Burnett, R. T.; Beveridge, R. C.; Brook, J. R. (1996) Association between ozone and asthma emergency department visits in Saint John, New Brunswick, Canada. Environ. Health Perspect. 104: 1354-1360.
Stieb, D. M.; Beveridge, R. C.; Rowe, B. H.; Walter, S. D.; Judek, S. (1998a) Assessing diagnostic classification in an emergency department: implications for daily time series studies of air pollution. Am. J. Epidemiol. 148: 666-670.
Stieb, D. M.; Brook, J. R.; Broder, I.; Judek, S.; Burnett, R. T.; Beveridge, R. C. (1998b) Personal exposure of adults with cardiorespiratory disease to particulate acid and sulfate in Saint John, New Brunswick, Canada. Appl. Occup. Environ. Hyg. 13: 461-468.
Stieb, D. M.; Beveridge, R. C.; Brook, J. R.; Smith-Doiron, M.; Burnett, R. T.; Dales, R. E.; Beaulieu, S.; Judek, S.; Mamedov, A. (2000) Air pollution, aeroallergens and cardiorespiratory emergency department visits in Saint John, Canada. J. Exposure Anal. Environ. Epidemiol. 10: 461-477.
Stölzel, M.; Peters, A.; Wichmann, H.-E. (2003) Daily mortality and fine and ultrafine particles in Erfurt, Germany. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 231-240. Available: http://www.healtheffects.org/Pubs/TimeSeries.pdf [18 October, 2004].
Styer, P.; McMillan, N.; Gao, F.; Davis, J.; Sacks, J. (1995) Effect of outdoor airborne particulate matter on daily death counts. Environ. Health Perspect. 103: 490-497.
Sunyer, J.; Basagaña, X. (2001) Particles, and not gases, are associated with the risk of death in patients with chronic obstructive pulmonary disease. Int. J. Epidemiol. 30: 1138-1140.
Sunyer, J.; Spix, C.; Quénel, P.; Ponce-de-León, A.; Pönka, A.; Barumandzadeh, T.; Touloumi, G.; Bacharova, L.; Wojtyniak, B.; Vonk, J.; Bisanti, L.; Schwartz, J.; Katsouyanni, K. (1997) Urban air pollution and emergency admissions for asthma in four European cities: the APHEA project. Thorax 52: 760-765.
Sunyer, J.; Schwartz, J.; Tobias, A.; Macfarlane, D.; Garcia, J.; Anto, J. M. (2000) Patients with chronic obstructive pulmonary disease are at increased risk of death associated with urban particle air pollution: a case-crossover analysis. Am. J. Epidemiol. 151: 50-56.
Taggart, S. C. O.; Custovic, A.; Francis, H. C.; Faragher, E. B.; Yates, C. J.; Higgins, B. G.; Woodcock, A. (1996) Asthmatic bronchial hyperresponsiveness varies with ambient levels of summertime air pollution. Eur. Respir. J. 9: 1146-1154.
Tan, W. C.; Qiu, D.; Liam, B. L.; Ng, T. P.; Lee, S. H.; Van Eeden, S. F.; D'Yachkova, Y.; Hogg, J. C. (2000) The human bone marrow response to acute air pollution caused by forest fires. Am. J. Respir. Crit. Care Med. 161: 1213-1217.
Tanaka, H.; Honma, S.; Nishi, M.; Igarashi, T.; Teramoto, S.; Nishio, F.; Abe, S. (1998) Acid fog and hospital visits for asthma: an epidemiological study. Eur. Respir. J. 11: 1301-1306.
Téllez-Rojo, M. M.; Romieu, I.; Ruiz-Velasco, S.; Lezana, M.-A.; Hernández-Avila, M. M. (2000) Daily respiratory mortality and PM10 pollution in Mexico City: importance of considering place of death. Eur. Respir. J. 16: 391-396.
Tenías, J. M.; Ballester, F.; Rivera, M. L. (1998) Association between hospital emergency visits for asthma and air pollution in Valencia, Spain. Occup. Environ. Med. 55: 541-547.
Thompson, S. G.; Kienast, J.; Pyke, S. D. M.; Haverkate, F.; Van De Loo, J. C. W. (1995) Hemostatic factors and the risk of myocardial infarction or sudden death in patients with angina pectoris. N. Engl. J. Med. 332: 635-641.

Thompson, A. J.; Shields, M. D.; Patterson, C. C. (2001) Acute asthma exacerbations and air pollutants in children living in Belfast, Northern Ireland. Arch. Environ. Health 56: 234-241.

Thurston, G. D.; Ito, K.; Hayes, C. G.; Bates, D. V.; Lippmann, M. (1994) Respiratory hospital admissions and summertime haze air pollution in Toronto, Ontario: consideration of the role of acid aerosols. Environ. Res. 65: 271-290.

Thurston, G. D.; Lippmann, M.; Scott, M. B.; Fine, J. M. (1997) Summertime haze air pollution and children with asthma. Am. J. Respir. Crit. Care Med. 155: 654-660.

Tiittanen, P.; Timonen, K. L.; Ruuskanen, J.; Mirme, A.; Pekkanen, J. (1999) Fine particulate air pollution, resuspended road dust and respiratory health among symptomatic children. Eur. Respir. J. 13: 266-273.

Timonen, K. L.; Pekkanen, J. (1997) Air pollution and respiratory health among children with asthmatic or cough symptoms. Am. J. Respir. Crit. Care Med. 156: 546-552.

Tobias, A.; Campbell, M. J. (1999) Modelling influenza epidemics in the relation between black smoke and total mortality. A sensitivity analysis. J. Epidemiol. Community Health 53: 583-584.

Tolbert, P. E.; Klein, M.; Metzger, K. B.; Flanders, W. D.; Todd, K.; Mulholland, J. A.; Ryan, P. B.; Frumkin, H. (2000a) Interim results of the study of particulates and health in Atlanta (SOPHIA). J. Exposure Anal. Environ. Epidemiol. 10: 446-460.

Tolbert, P. E.; Mulholland, J. A.; Maclntosh, D. L.; Xu, F.; Daniels, D.; Devine, O. J.; Carlin, B. P.; Klein, M.; Dorley, J.; Butler, A. J.; Nordenberg, D. F.; Frumkin, H.; Ryan, P. B.; White, M. C. (2000b) Air quality and pediatric emergency room visits for asthma in Atlanta, Georgia. Am. J. Epidemiol. 151: 798-810.

Touloumi, G.; Katsouyanni, K.; Zmirou, D.; Schwartz, J.; Spix, C.; Ponce de Leon, A.; Tobias, A.; Quennel, P.; Rabczenko, D.; Bacharova, L.; Bisanti, L.; Vonk, J. M.; Ponka, A. (1997) Short-term effects of ambient oxidant exposure on mortality: a combined analysis within the APHEA project. Am. J. Epidemiol. 146: 177-185.

Tsai, F. C.; Apte, M. G.; Daisey, J. M. (1999) An exploratory analysis of the relationship between mortality and the chemical composition of airborne particulate matter. Berkeley, CA: Lawrence Berkeley National Laboratory, Environmental Energy Technologies Division; report no. LBNL-43583.

Tsai, F. C.; Apte, M. G.; Daisey, J. M. (2000) An exploratory analysis of the relationship between mortality and the chemical composition of airborne particulate matter. Inhalation Toxicol. 12(suppl.): 121-135.

Turnovska, T.; Kostianev, S. (1999) Effects of reduced air pollution on children's pulmonary function. Cent. Eur. J. Public Health 7: 77-79.

U.S. Census Bureau. (1995) American housing survey for the United States in 1993. Washington, DC: U.S. Department of Commerce; current housing reports H150/93. Available: http://www.census.gov/hhes/www/housing/ahs/nationaldata.html [29 April, 2002].

U.S. Census Bureau. (2003) Internal migration of the older population: 1995 to 2000. Washington, DC: U.S. Department of Commerce. Available: http://www.census.gov/prod/2003pubs/censr-10.pdf [26 April, 2004].

U.S. Environmental Protection Agency. (1982) Air quality criteria for particulate matter and sulfur oxides. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; EPA report no. EPA-600/8-82-029aF-cF. 3v. Available from: NTIS, Springfield, VA; PB84-156777.

U.S. Environmental Protection Agency. (1986) Second addendum to air quality criteria for particulate matter and sulfur oxides (1982): assessment of newly available health effects information. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; EPA report no. EPA-600/8-86-020F. Available from: NTIS, Springfield, VA; PB87-176574.

U.S. Environmental Protection Agency. (1993) Air quality criteria for oxides of nitrogen. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; report nos. EPA/600/8-91/049aF-cF. 3v. Available from: NTIS, Springfield, VA; PB95-124533, PB95-124525, and PB95-124517.

U.S. Environmental Protection Agency. (1996a) Air quality criteria for particulate matter. Research Triangle Park, NC: National Center for Environmental Assessment-RTP Office; report nos. EPA/600/P-95/001aF-cF. 3v.

U.S. Environmental Protection Agency. (1996b) Air quality criteria for ozone and related photochemical oxidants. Research Triangle Park, NC: Office of Research and Development; report nos. EPA/600/AP-93/004aF-cF. 3v. Available from: NTIS, Springfield, VA; PB96-185582, PB96-185590, and PB96-185608. Available online at: www.epa.gov/ncea/ozone.htm.

U.S. Environmental Protection Agency. (2000a) Emissions and air quality data. Washington, DC: Technology Transfer Network. Available: http://www.epa.gov/ttn/naaqs/ozone/areas/ [20 May, 2003].

U.S. Environmental Protection Agency. (2000b) Air quality criteria for carbon monoxide. Research Triangle Park, NC: National Center for Environmental Assessment; report no. EPA/600/P-99/001F. Available: www.epa.gov/ncea/co/ [2000, October 6].

U.S. Environmental Protection Agency. (2002) Health assessment document for diesel engine exhaust. Washington, DC: Office of Research and Development, National Center for Environmental Assessment; report no. EPA/600/8-90/057F. Available: http://cfpub.epa.gov/ncea/ [22 May, 2003].
Van Der Zee, S. C.; Hoek, G.; Boezen, H. M.; Schouten, J. P.; Van Wijnen, J. H.; Brunekreef, B. (1999) Acute effects of urban air pollution on respiratory health of children with and without chronic respiratory symptoms. Occup. Environ. Med. 56: 802-813.
Van Der Zee, S. C.; Hoek, G.; Boezen, M. H.; Schouten, J. P.; Van Wijnen, J. H.; Brunekreef, B. (2000) Acute effects of air pollution on respiratory health of 50-70 yr old adults. Eur. Respir. J. 15: 700-709.
Vasan, R. S.; Larson, M. G.; Leip, E. P.; Kannel, W. B.; Levy, D. (2001) Assessment of frequency of progression to hypertension in non-hypertensive participants in the Framingham Heart Study: a cohort study. Lancet 358: 1682-1686.
Vedal, S.; Petkau, J.; White, R.; Blair, J. (1998) Acute effects of ambient inhalable particles in asthmatic and nonasthmatic children. Am. J. Respir. Crit. Care Med. 157: 1034-1043.
Vena, J. E. (1982) Air pollution as a risk factor in lung cancer. Am. J. Epidemiol. 116: 42-56.
Veterans Administration Cooperative Study Group on Antihypertensive Agents. (1967) Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. JAMA J. Am. Med. Assoc. 202: 1028-1034.
Veterans Administration Cooperative Study Group on Antihypertensive Agents. (1970) Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. JAMA J. Am. Med. Assoc. 213: 1143-1152.
Vigotti, M. A.; Rossi, G.; Bisanti, L.; Zanobetti, A.; Schwartz, J. (1996) Short term effects of urban air pollution on respiratory health in Milan, Italy, 1980-89. In: Leger, S., ed. The APHEA project. Short term effects of air pollution on health: a European approach using epidemiological time series data. J. Epidemiol. Community Health 50(suppl. 1): S71-S75.
Villeneuve, P. J.; Goldberg, M. S.; Krewski, D.; Burnett, R. T.; Chen, Y. (2002) Fine particulate air pollution and all-cause mortality within the Harvard six-cities study: variations in risk by period of exposure. Ann. Epidemiol. 12: 568-576.
Von Klot, S.; Wölke, G.; Tuch, T.; Heinrich, J.; Dockery, D. W.; Schwartz, J.; Kreyling, W. G.; Wichmann, H. E.; Peters, A. (2002) Increased asthma medication use in association with ambient fine and ultrafine particles. Eur. Respir. J. 20: 691-702.
Wallace, L. (2000) Real-time monitoring of particles, PAH, and CO in an occupied townhouse. Appl. Occup. Environ. Hyg. 15: 39-47.
Wang, B.; Peng, Z.; Zhang, X.; Xu, Y.; Wang, H.; Allen, G.; Wang, L.; Xu, X. (1999) Particulate matter, sulfur dioxide, and pulmonary function in never-smoking adults in Chongqing, China. Int. J. Occup. Environ. Health 5: 14-19.
Ward, D. J.; Miller, M. R.; Walters, S.; Harrison, R. M.; Ayres, J. G. (2000) Impact of correcting peak flow for nonlinear errors on air pollutant effect estimates from a panel study. Eur. Respir. J. 15: 137-140.
Ware, J. H.; Ferris, B. G., Jr.; Dockery, D. W.; Spengler, J. D.; Stram, D. O.; Speizer, F. E. (1986) Effects of ambient sulfur oxides and suspended particles on respiratory health of preadolescent children. Am. Rev. Respir. Dis. 133: 834-842.
Wichmann, H.-E.; Spix, C.; Tuch, T.; Wolke, G.; Peters, A.; Heinrich, J.; Kreyling, W. G.; Heyder, J. (2000) Daily mortality and fine and ultrafine particles in Erfurt, Germany. Part I: role of particle number and particle mass. Cambridge, MA: Health Effects Institute; Research Report no. 98.
Wilson, W. E.; Suh, H. H. (1997) Fine particles and coarse particles: concentration relationships relevant to epidemiologic studies. J. Air Waste Manage. Assoc. 47: 1238-1249.
Wilson, W. E.; Mage, D. T.; Grant, L. D. (2000) Estimating separately personal exposure to ambient and nonambient particulate matter for epidemiology and risk assessment: why and how. J. Air Waste Manage. Assoc. 50: 1167-1183.
Wjst, M.; Reitmeir, P.; Dold, S.; Wulff, A.; Nicolai, T.; Von Loeffelholz-Colberg, E. F.; Von Mutius, E. (1993) Road traffic and adverse effects on respiratory health in children. Br. Med. J. 307: 596-600.
Wolff, G. T.; Stroup, C. M.; Stroup, D. P. (1983) The coefficient of haze as a measure of particulate elemental carbon. J. Air Pollut. Control Assoc. 33: 746-750.
Wong, T. W.; Lau, T. S.; Yu, T. S.; Neller, A.; Wong, S. L.; Tam, W.; Pang, S. W. (1999a) Air pollution and hospital admissions for respiratory and cardiovascular diseases in Hong Kong. Occup. Environ. Med. 56: 679-683.
Wong, C. M.; Hu, Z. G.; Lam, T. H.; Hedley, A. J.; Peters, J. (1999b) Effects of ambient air pollution and environmental tobacco smoke on respiratory health of non-smoking women in Hong Kong. Int. J. Epidemiol. 28: 859-864.

Woodhouse, P. R.; Khaw, K. T.; Plummer, M.; Foley, A.; Meade, T. W. (1994) Seasonal variations of plasma fibrinogen and factor VII activity in the elderly: winter infections and death from cardiovascular disease. Lancet 343: 435-439.

Woodruff, T. J.; Grillo, J.; Schoendorf, K. C. (1997) The relationship between selected causes of postneonatal infant mortality and particulate air pollution in the United States. Environ. Health Perspect. 105: 608-612.

Wordley, J.; Walters, S.; Ayres, J. G. (1997) Short term variations in hospital admissions and mortality and particulate air pollution. Occup. Environ. Med. 54: 108-116.

World Health Organization. (1996) Climate change and human health. Geneva, Switzerland: United Nations Environment Programme.

Wyzga, R. E.; Lipfert, F. W. (1996) Ozone and daily mortality: the ramifications of uncertainties and interactions and some initial regression. In: Vostal, J. J., ed. Tropospheric ozone: critical issues in the regulatory process, proceedings of a specialty conference sponsored by the Air & Waste Management Association; May 1994; Orlando, FL. Pittsburgh, PA: Air & Waste Management Association; pp. 453-487. (A&WMA publication no. VIP-54).

Xu, Z.; Yu, D.; Jing, L.; Xu, X. (2000) Air pollution and daily mortality in Shenyang, China. Arch. Environ. Health 55: 115-120.

Yang, W.; Jennison, B. L.; Omaye, S. T. (1997) Air pollution and asthma emergency room visits in Reno, Nevada. Inhalation Toxicol. 9: 15-29.

Ye, F.; Piver, W. T.; Ando, M.; Portier, C. J. (2001) Effects of temperature and air pollutants on cardiovascular and respiratory diseases for males and females older than 65 years of age in Tokyo, July and August 1980-1995. Environ. Health Perspect. 109: 355-359.

Yu, O.; Sheppard, L.; Lumley, T.; Koenig, J. Q.; Shapiro, G. G. (2000) Effects of ambient air pollution on symptoms of asthma in Seattle-area children enrolled in the CAMP study. Environ. Health Perspect. 108: 1209-1214.

Zanobetti, A.; Schwartz, J. (2000) Race, gender, and social status as modifiers of the effects of PM_{10} on mortality. J. Occup. Environ. Med. 42: 469-474.

Zanobetti, A.; Schwartz, J. (2001) Are diabetics more susceptible to the health effects of airborne particles? Am. J. Respir. Crit. Care Med. 164: 831-833.

Zanobetti, A.; Schwartz, J. (2003a) Airborne particles and hospital admissions for heart and lung disease. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 241-248. Available: http://www.healtheffects.org/Pubs/TimeSeries.pdf [18 October, 2004].

Zanobetti, A.; Schwartz, J. (2003b) Multicity assessment of mortality displacement within the APHEA2 project. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 249-254. Available: http://www.healtheffects.org/Pubs/TimeSeries.pdf [18 October, 2004].

Zanobetti, A.; Schwartz, J.; Dockery, D. W. (2000a) Airborne particles are a risk factor for hospital admissions for heart and lung disease. Environ. Health Perspect. 108: 1071-1077.

Zanobetti, A.; Wand, M. P.; Schwartz, J.; Ryan, L. M. (2000b) Generalized additive distributed lag models: quantifying mortality displacement. Biostatistics 1: 279-292.

Zanobetti, A.; Schwartz, J.; Samoli, E.; Gryparis, A.; Touloumi, G.; Peacock, J.; Anderson, R. H.; Le Tertre, A.; Bobros, J.; Celko, M.; Goren, A.; Forsberg, B.; Michelozzi, P.; Rabczenko, D.; Hoyos, S. P.; Wichmann, H. E.; Katsouyanni, K. (2003) The temporal pattern of respiratory and heart disease mortality in response to air pollution. Environ. Health Perspect. 111: 1188-1193.

Zeger, S. L.; Dominici, F.; Samet, J. (1999) Harvesting-resistant estimates of air pollution effects on mortality. Epidemiology 10: 171-175.

Zeger, S. L.; Thomas, D.; Dominici, F.; Samet, J. M.; Schwartz, J.; Dockery, D.; Cohen, A. (2000) Exposure measurement error in time-series studies of air pollution: concepts and consequences. Environ. Health Perspect. 108: 419-426.

Zeghnoun, A.; Beaudeau, P.; Carrat, F.; Delmas, V.; Boudhabhay, O.; Gayon, F.; Guincetre, D.; Czernichow, P. (1999) Air pollution and respiratory drug sales in the city of Le Havre, France, 1993-1996. Environ. Res. 81: 224-230.

Zeghnoun, A.; Czernichow, P.; Beaudeau, P.; Hautemanière, A.; Froment, L.; Le Tertre, A.; Quénel, P. (2001) Short-term effects of air pollution on mortality in the cities of Rouen and Le Havre, France, 1990-1995. Arch. Environ. Health 56: 327-335.

Zemp, E.; Elsasser, S.; Schindler, C.; Künzli, N.; Perruchoud, A. P.; Domenighetti, G.; Medici, T.; Ackermann-Liebrich, U.; Leuenberger, P.; Monn, C.; Bolognini, G.; Bongard, J.-P.; Brändli, O.; Karrer, W.; Keller, R.; Schöni, M. H.; Tschopp, J.-M.; Villiger, B.; Zellweger, J.-P.; SAPALDIA Team. (1999) Long-term ambient air pollution and respiratory symptoms in adults (SAPALDIA study). Am. J. Respir. Crit. Care Med. 159: 1257-1266.

Zhang, J.; Qian, Z.; Kong, L.; Zhou, L.; Yan, L.; Chapman, R. S. (1999) Effects of air pollution on respiratory health of adults in three Chinese cities. Arch. Environ. Health 54: 373-381.

Zhang, H.; Triche, E.; Leaderer, B. (2000) Model for the analysis of binary time series of respiratory symptoms. Am. J. Epidemiol. 151: 1206-1215.

Zidek, J. V.; Wong, H.; Le, N. D.; Burnett, R. (1996) Causality, measurement error and multicollinearity in epidemiology. Environmetrics 7: 441-451.

Zmirou, D.; Schwartz, J.; Saez, M.; Zanobetti, A.; Wojtyniak, B.; Touloumi, G.; Spix, C.; Ponce de León, A.; Le Moullec, Y.; Bacharova, L.; Schouten, J.; Pönkä, A.; Katsouyanni, K. (1998) Time-series analysis of air pollution and cause-specific mortality. Epidemiology 9: 495-503.

APPENDICES 8A AND 8B

SHORT-TERM PARTICULATE MATTER EXPOSURE—MORTALITY AND PARTICULATE MATTER-MORBIDITY STUDIES: SUMMARY TABLES

APPENDIX 8A

SHORT-TERM PM EXPOSURE-MORTALITY STUDIES: SUMMARY TABLE

TABLE 8A-1. SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States			
Samet et al. (2000a,b).* 90 largest U.S. cities. 1987-1994. PM_{10} mean ranged from 15.3 (Honolulu) to 52.0 (Riverside).	Non-accidental total deaths and cause-specific (cardiac, respiratory, and the other remaining) deaths, stratified in three age groups (<65, 65-75, 75+), were examined for their associations with PM_{10}, O_3, SO_2, NO_2, and CO (single, two, and three pollutant models) at lags 0, 1, and 2 days. In the first stage of the hierarchical model, RRs for the pollutants for each city were obtained using GAM Poisson regression models, adjusting for temperature and dewpoint (0-day and average of 1-3 days for both variables), day-of-week, seasonal cycles, intercept and seasonal cycles for three age groups. In the second stage, between-city variation in RRs were modeled within region. The third stage modeled between-region variation (7 regions). Two alternative assumptions were made regarding the prior distribution: one with possibly substantial heterogeneity and the other with less or no heterogeneity within region. The weighted second-stage regression included five types of county-specific variables: (1) mean weather and pollution variables; (2) mortality rate; (3) socio-demographic variables; (4) urbanization; (5) variables related to measurement error.	The estimated city-specific coefficients were mostly positive at lag 0, 1, and 2 days (estimated overall effect size was largest at lag 1, with the estimated percent excess death rate per 10 $\mu g/m^3$ PM_{10} being about 0.5%). The posterior probabilities that the overall effects are greater than 0 at these lags were 0.99, 1.00, and 0.98, respectively. None of the county-specific variables (effect modifiers) in the second-stage regression significantly explained the heterogeneity of PM_{10} effects across cities. In the 3-stage regression model with the index for 7 geographical regions, the effect of PM_{10} varied somewhat across the 7 regions, with the effect in the Northeast being the greatest. Adding O_3 and other gaseous pollutants did not markedly change the posterior distributions of PM_{10} effects. O_3 effects, as examined by season, were associated with mortality in summer (0.5 percent per 10 ppb increase), but not in all season data (negative in winter).	Posterior mean estimates and 95% credible intervals for total mortality excess deaths per 50 $\mu g/m^3$ increase in PM_{10} at lag 1 day: 2.3% (0.1, 4.5) for "more heterogeneity" across-city assumption; 2.2% (0.5, 4.0) for "less or no heterogeneity" across cities assumption. The largest PM_{10} effect estimated for 7 U.S. regions was for the Northeast: 4.6% (2.7, 6.5) excess deaths per 50 $\mu g/m^3$ PM_{10} increment.
Dominici et al. (2002). Re-analysis of above study.	Illustration of the issues related to GAM convergence criteria using simulation; and re-analysis of above study using stringent convergence criteria as well as comparable GLM model with natural splines.	The overall estimate was reduced but major findings of the study were not changed. Sensitivity analysis using alternative degrees of freedom for temporal trends and weather terms showed that PM_{10} risk estimates were larger when smaller number of degrees of freedom were used.	Posterior mean estimates and 95% credible intervals for total mortality excess deaths per 50 $\mu g/m^3$ increase in PM_{10} at lag 1 day: 1.4% (0.9, 1.9) using GAM with stringent convergence criteria and 1.1 (0.5, 1.7) using GLM with natural splines. Northeast still has the largest PM_{10} risk estimate.

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Dominici et al. (2000a). +20 largest U.S. cities. 1987-1994. PM_{10} mean ranged from 23.8 $\mu g/m^3$ (San Antonio) to 52.0 $\mu g/m^3$ (Riverside).	Non-accidental total deaths (stratified in three age groups: <65, 65-75, 75+) were examined for their associations with PM_{10} and O_3 (single, 2, and 3 pollutant models) at lags 0, 1, and 2 days. In the first stage of the hierarchical model, RRs for PM_{10} and O_3 for each city were obtained using GAM Poisson regression models, adjusting for temperature and dewpoint (0-day and average of 1-3 days for both variables), day-of-week, seasonal cycles, intercept and seasonal cycles for three age groups. In the second stage, between-city variation in RRs were modeled as a function of city-specific covariates including mean PM_{10} and O_3 levels, percent poverty, and percent of population with age 65 and over. The prior distribution assumed heterogeneity across cities. To approximate the posterior distribution, a Markov Chain Monte Carlo (MCMC) algorithm with a block Gibbs sampler was implemented. The second stage also considered spatial model, in which RRs in closer cities were assumed to be more correlated.	Lag 1 day PM_{10} concentration positively associated with total mortality in most locations, though estimates ranged from 2.1% to –0.4% per 10 $\mu g/m^3$ PM_{10} increase. PM_{10} mortality associations changed little with the addition of O_3 to the model, or with the addition of a third pollutant in the model. The pattern of PM_{10} effects with respiratory and cardiovascular were similar to that of total mortality. The PM_{10} effect was smaller (and weaker) with other causes of deaths. The pooled analysis of 20 cities data confirmed the overall effect on total and cardiorespiratory mortality, with lag 1 day showing largest effect estimates. The posterior distributions for PM_{10} were generally not influenced by addition of other pollutants. In the data for which the distributed lags could be examined (i.e., nearly daily data), the sum of 7-day distributed lag coefficients was greater than each of single day coefficients. City-specific covariates did not predict the heterogeneity across cities. Regional model results suggested that PM_{10} effects in West U.S. were larger than in East and South.	Total mortality excess deaths per 50 $\mu g/m^3$ increase in PM_{10}: 1.8 (-0.5, 4.1) for lag 0; 1.9 (-0.4, 4.3) for lag 1; 1.2 (-1.0, 3.4) for lag 2. Cardiovascular disease excess deaths per 50 $\mu g/m^3$ PM_{10}: 3.4 (1.0, 5.9).
Daniels et al. (2000).* The largest U.S. 20 cities, 1987-1994.	This study examined the shape of concentration-response curve. Three log-linear GAM regression models were compared: (1) using a linear PM_{10} term; (2) using a natural cubic spline of PM_{10} with knots at 30 and 60 $\mu g/m^3$ (corresponding approximately to 25 and 75 percentile of the distribution); and, (3) using a threshold model with a grid search in the range between 5 and 200 $\mu g/m^3$ with 5 $\mu g/m^3$ increment. Covariates included the smoothing function of time, temperature and dewpoint, and day-of-week indicators. These models were fit for each city separately, and for model (1) and (2) the combined estimates across cities were obtained by using inverse variance weighting if there was no heterogeneity across cities, or by using a two-level hierarchical model if there was heterogeneity.	For total and cardiorespiratory mortality, the spline curves were roughly linear, consistent with the lack of a threshold. For mortality from other causes, however, the curve did not increase until PM_{10} concentrations exceeded 50 $\mu g/m^3$. The hypothesis of linearity was examined by comparing the AIC values across models. The results suggested that the linear model was preferred over the spline and the threshold models.	
Dominici et al. (2003a). Re-analysis of above study.	Re-analysis of above model using GLM/natural splines.	The shapes of concentration-response curves were similar to the original analysis.	

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Klemm et al. (2000). Replication study of the Harvard Six Cities time-series analysis by Schwartz et al. (1996).	Reconstruction and replication study of the Harvard Six Cities time-series study. The original investigators provided PM data; Klemm et al. reconstructed daily mortality and weather data from public records. Data analytical design (GAM Poisson model) was the same as that from the original study.	The combined PM effect estimates were essentially equivalent to the original results.	Total mortality percent excess risks: $PM_{10/15}$: 4.1(2.8, 5.4) per 50$\mu g/m^3$ $PM_{2.5}$: 3.3(2.3, 4.3) per 25 $\mu g/m^3$ $PM_{10-2.5}$: 1.0(-0.4, 2.4) per 25 $\mu g/m^3$
Klemm and Mason (2003). Re-analysis of the above study.	Re-analysis of the above study using GAM with stringent convergence criteria and GLM/natural splines. Sensitivity of results to alternative degrees of freedom were also examined.	When GAM with stringent convergence criteria were applied, PM effect estimates were reduced by 10 to 15%. GLM/natural splines, and increasing the degrees of freedom for temporal trends resulted in further reductions in PM coefficients.	Total mortality percent excess risks using GAM stringent convergence criteria: $PM_{10/15}$: 3.5(2.0, 5.1) per 50$\mu g/m^3$ $PM_{2.5}$: 3.0(2.1, 4.0) per 25 $\mu g/m^3$ $PM_{10-2.5}$: 0.8(-0.5, 2.0) per 25 $\mu g/m^3$ Using GLM/natural splines: $PM_{10/15}$: 2.0(0.3, 3.8) per 50$\mu g/m^3$ $PM_{2.5}$: 2.0(0.9, 3.2) per 25 $\mu g/m^3$ $PM_{10-2.5}$: 0.3(-1.2, 1.8) per 25 $\mu g/m$
Schwartz (2003a). Re-analysis of the Harvard Six Cities time-series analysis.	$PM_{2.5}$ data were re-analyzed using GAM with stringent convergence criteria, GLM/natural splines, B-splines, penalized splines, and thin-plate splines.	When GAM with stringent convergence criteria were applied, $PM_{2.5}$ effect estimates were reduced by ~5%. GLM/natural splines, B-splines, penalized splines, and thin-plate splines each resulted in further reductions in $PM_{2.5}$ excess risk estimates.	Total mortality percent excess risks using per 25 $\mu g/m^3$ $PM_{2.5}$: GAM (default):3.7(2.7, 4.7) GAM (stringent): 3.5(2.5, 4.5) Natural splines: 3.3(2.2, 4.3) B-splines: 3.0(2.0, 4.0) Penalized splines: 2.9(1.8, 4.) Thin-plate splines: 2.6(1.5, 3.8)
Zeger et al. (1999). Philadelphia, 1974-1988.	The implication of harvesting for PM regression coefficients, as observed in frequency domain, was illustrated using simulation. Three levels of harvesting, 3 days, 30 days, and 300 days were simulated. Real data from Philadelphia was then analyzed.	In the simulation results, as expected, the shorter the harvesting, the larger the PM coefficient in the higher frequency range. However, in the Philadelphia data, the regression coefficients increased toward the lower frequency range, suggesting that the extent of harvesting, if it exists, is not in the short-term range.	
Dominici et al. (2003a). Re-analysis of above study.	Re-analysis of above model using GLM/natural splines.	Results were essentially unchanged.	

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Braga et al. (2000). +Five U.S. cities: Pittsburgh, PA; Detroit, MI; Chicago, IL; Minneapolis-St. Paul, MN; Seattle, WA. 1986-1993. PM_{10} means were 35, 37, 37, 28, and 33 $\mu g/m^3$, respectively in these cities.	Potential confounding caused by respiratory epidemics on PM-total mortality associations was investigated in a subset of the 10 cities evaluated by Schwartz (2000a,b), as summarized below. GAM Poisson models were used to estimate city-specific PM_{10} effects, adjusting for temperature, dewpoint, barometric pressure, time-trend and day-of-week. A cubic polynomial was used to for each epidemic period, and a dummy variable was used to control for isolated epidemic days. Average of 0 and 1 day lags were used.	When respiratory epidemics were adjusted for, small decreases in the PM_{10} effect were observed (9% in Chicago, 11% in Detroit, 3% in Minneapolis, 5% in Pittsburgh, and 15% in Seattle).	The overall estimated percent excess deaths per 50 $\mu g/m^3$ increase in PM_{10} was 4.3% (3.0, 5.6) before controlling for epidemics and 4.0% (2.6, 5.3) after. Average of 0 and 1 day lags.
Braga et al. (2001a).* Ten U.S. cities. Same as Schwartz (2000b).	The study examined the lag structure of PM_{10} effects on respiratory and cardiovascular cause-specific mortality. Using GAM Poisson model adjusting for temporal pattern and weather, three types of lag structures were examined: (1) 7-day unconstrained distributed lags; (2) 2-day average (0- and 1-day lag); and (3) 0-day lag. The results were combined across 10 cities.	The authors reported that respiratory deaths were more affected by air pollution levels on the previous days, whereas cardiovascular deaths were more affected by same-day pollution. Pneumonia, COPD, all cardiovascular disease, and myocardial infarction were all associated with PM_{10} in the three types of lags examined. The 7-day unconstrained lag model did not always give larger effect size estimates compared others.	In the 7-day unconstrained distributed lag model, the estimated percent excess deaths per 50 $\mu g/m^3$ PM_{10} were 14.2%(7.8, 21.1) , 8.8%(0.6, 17.7), 5.1%(3.0, 7.2), and 3.0%(0.0, 6.2) for pneumonia, COPD, all cardiovascular, and myocardial infarction mortality, respectively.
Schwartz (2003b). Re-analysis of above study.	Re-analysis of above study using stringent convergence criteria as well as penalized splines.	Small changes in PM risk estimates. Original findings unchanged.	Above estimates using stringent convergence criteria were: 16.5%(8.3, 25.3), 9.9%(0.6, 20.0), 5.1%(2.8, 7.5), and 3.5%(-0.7, 8.0). Corresponding numbers for penalized splines were: 11.5%(3.1, 20.6), 7.2%(-2.6, 18.0), 4.6%(2.0, 7.2), and 2.5%(-2.2, 7.5).

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Schwartz (2000a).* Ten U.S. cities: New Haven, CT; Pittsburgh, PA; Detroit, MI; Birmingham, AL; Canton, OH; Chicago, IL; Minneapolis-St. Paul, MN; Colorado Springs, CO; Spokane, WA; and Seattle, WA. 1986-1993. PM_{10} means were 29, 35, 36, 37, 29, 37, 28, 27, 41, and 33, respectively in these cities.	Daily total (non-accidental) deaths (20, 19, 63, 60, 10, 133, 32, 6, 9, and 29, respectively in these cities in the order shown left). Deaths stratified by location of death (in or outside hospital) were also examined. For each city, a GAM Poisson model adjusting for temperature, dewpoint, barometric pressure, day-of-week, season, and time was fitted. The data were also analyzed by season (November through April as heating season). In the second stage, the PM_{10} coefficients were modeled as a function of city-dependent covariates including copollutant to PM_{10} regression coefficient (to test confounding), unemployment rate, education, poverty level, and percent non-white. Threshold effects were also examined. The inverse variance weighted averages of the ten cities' estimates were used to combine results.	PM_{10} was significantly associated with total deaths, and the effect size estimates were the same in summer and winter. Adjusting for other pollutants did not substantially change PM_{10} effect size estimates. Also, socioeconomic variables did not modify the estimates. The effect size estimate for the deaths that occurred outside hospitals was substantially greater than that for inside hospitals. The effect size estimate was larger for subset with PM_{10} less than 50 g/m^3.	The total mortality RR estimates combined across cities per 50 $\mu g/m^3$ increase of mean of lag 0- and 1-days PM_{10}: overall 3.4 (2.7, 4.1); summer 3.4 (2.4, 4.4); winter 3.3 (2.3, 4.4); in-hospital 2.5 (1.5, 3.4); out-of-hospital 4.5 (3.4, 5.6); days < 50 $\mu g/m^3$ 4.4 (3.1, 5.7); with SO_2 2.9 (1.2, 4.6); with CO 4.6 (3.2, 6.0); with O_3 3.5 (1.6, 5.3).
Schwartz (2003b). Re-analysis of above study.	Re-analysis of above study using stringent convergence criteria as well as natural splines. The case for in vs. out of hospital deaths and days $PM_{10} < 50$ $\mu g/m^3$ were not re-analyzed.		The total mortality RR estimates combined across cities per 50 $\mu g/m^3$ increase of mean of lag 0- and 1-days PM_{10}: overall 3.3 (2.6, 4.1); summer 3.4 (2.5, 4.4); winter 3.1 (2.0, 4.1); with SO_2 3.2 (1.7, 4.8); with CO 4.5 (2.7, 6.4); with O_3 3.5 (2.2, 4.8). Corresponding values for natural splines are: overall 2.8 (2.0, 3.6); summer 2.6 (1.6, 3.7); winter 2.9 (1.8, 4.1); with SO_2 2.8 (1.0, 4.6); with CO 3.7 (1.6, 5.8); with O_3 3.0 (1.6, 4.4).

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Schwartz (2000b).* Ten U.S. cities: New Haven, CT; Pittsburgh, PA; Birmingham, AL; Detroit, MI; Canton, OH; Chicago, IL; Minneapolis-St. Paul, MN; Colorado Springs, CO; Spokane, WA; and Seattle, WA. 1986-1993. PM_{10} means were 29, 35, 36, 37, 29, 37, 28, 27, 41, and 33, respectively in these cities.	The issue of distributed lag effects was the focus of this study. Daily total (non-accidental) deaths of persons 65 years of age and older were analyzed. For each city, a GAM Poisson model adjusting for temperature, dewpoint, barometric pressure, day-of-week, season, and time was fitted. Effects of distributed lag were examined using four models: (1) 1-day mean at lag 0 day; (2) 2-day mean at lag 0 and 1 day; (3) second-degree distributed lag model using lags 0 through 5 days; (4) unconstrained distributed lag model using lags 0 through 5 days. The inverse variance weighted averages of the ten cities' estimates were used to combine results.	The effect size estimates for the quadratic distributed model and unconstrained distributed lag model were similar. Both distributed lag models resulted in substantially larger effect size estimates than the single day lag, and moderately larger effect size estimates than the two-day average models.	Total mortality percent increase estimates combined across cities per 50 $\mu g/m^3$ increase in PM_{10}: 3.3 (2.5, 4.1) for 1-day mean at lag 0; 5.4 (4.4, 6.3) 2-day mean of lag 0 and 1; 7.3 (5.9, 8.6) for quadratic distributed lag; and 6.6 (5.3, 8.0) for unconstrained distributed lag.
Schwartz (2003b). Re-analysis of above study.	Re-analysis of above study using stringent convergence criteria as well as penalized splines. Only quadratic distributed lag and unconstrained distributed lag models were re-analyzed.	PM risk estimates were reduced but not substantially. Original findings unchanged.	Total mortality percent increase estimates combined across cities per 50 $\mu g/m^3$ increase in PM_{10}: 6.3 (4.9, 7.8) for quadratic distributed lag; and 5.8 (4.4, 7.3) for unconstrained distributed lag using stringent convergence criteria. Corresponding numbers for penalized splines were: 5.3%(4.2, 6.5) and 5.3%(3.9).
Schwartz and Zanobetti (2000). + Ten U.S. cities. Same as above.	The issue of a threshold in PM-mortality exposure-response curve was the focus of this study. First, a simulation was conducted to show that the "meta-smoothing" could produce unbiased exposure-response curves. Three hypothetical curves (linear, piecewise linear, and logarithmic curves) were used to generate mortality series in 10 cities, and GAM Poisson models were used to estimate exposure response curve. Effects of measurement errors were also simulated. In the analysis of actual 10 cities data, GAM Poisson models were fitted, adjusting for temperature, dewpoint, and barometric pressure, and day-of-week. Smooth function of PM_{10} with the same span (0.7) in each of the cities. The predicted values of the log relative risks were computed for 2 $\mu g/m^3$ increments between 5.5 $\mu g/m^3$ and 69.5 $\mu g/m^3$ of PM_{10} levels. Then, the predicted values were combined across cities using inverse-variance weighting.	The simulation results indicated that the "meta-smoothing" approach did not bias the underlying relationships for the linear and threshold models, but did result in a slight downward bias for the logarithmic model. Measurement error (additive or multiplicative) in the simulations did not cause upward bias in the relationship below threshold. The threshold detection in the simulation was not very sensitive to the choice of span in smoothing. In the analysis of real data from 10 cities, the combined curve did not show evidence of a threshold in the PM_{10}-mortality associations.	The combined exposure-response curve indicates that an increase of 50 $\mu g/m^3$ is associated with about a 4% increase in daily deaths. Avg. of 0 and 1 day lags.

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Zanobetti and Schwartz (2000).* Four U.S. cities: Chicago, IL; Detroit, MI; Minneapolis-St. Paul, MN; Pittsburgh, PA. 1986-1993. PM_{10} median = 33, 33, 25, and 31 respectively for these cities.	Separate daily counts of total non-accidental deaths, stratified by sex, race (black and white), and education (education > 12yrs or not), were examined to test hypothesis that people in each of these groups had higher risk of PM_{10}. GAM Poisson models adjusting for temperature, dewpoint, barometric pressure, day-of-week, season, and time were used. The mean of 0- and 1-day lag PM_{10} was used. The inverse variance weighted averages of the four cities' estimates were used to combine results.	The differences in the effect size estimates among the various strata were modest. The results suggest effect modification with the slope in female deaths one third larger than in male deaths. Potential interaction of these strata (e.g., black and female) were not investigated.	The total mortality RR estimates combined across cities per 50 $\mu g/m^3$ increase of mean of lag 0- and 1-days PM_{10}: white 5.0 (4.0, 6.0); black 3.9 (2.3, 5.4); male 3.8 (2.7, 4.9); female 5.5 (4.3, 6.7); education <12y 4.7 (3.3, 6.0); education > 12y 3.6 (1.0, 6.3).
Moolgavkar (2000a)* Cook County, Illinois Los Angeles County, CA Maricopa County, AZ 1987-1995 PM_{10}, CO, O_3, NO_2, SO_2 in all three locations. $PM_{2.5}$ in Los Angeles County. Cook Co: PM_{10} Median = 47 $\mu g/m^3$. Maricopa Co: PM_{10} Median = 41. Los Angeles Co: PM_{10} Median = 44; $PM_{2.5}$ Median = 22.	Associations between air pollution and time-series of daily deaths evaluated for three U.S. metropolitan areas with different pollutant mixes and climatic conditions. Daily total non-accidental deaths and deaths from cardiovascular disease (CVD), cerebrovascular (CrD), and chronic obstructive lung disease and associated conditions (COPD) were analyzed by generalized additive Poisson models in relation to 24-h readings for each of the air pollutants averaged over all monitors in each county. All models included an intercept term for day-of-week and a spline smoother for temporal trends. Effects of weather were first evaluated by regressing daily deaths (for each mortality endpoint) against temp and rel. humidity with lag times of 0 to 5 days. Then lags that minimized deviance for temp and rel. humidity were kept fixed for subsequent pollutant effect analyses. Each pollutant entered linearly into the regression and lags of between 0 to 5 days examined. Effects of two or more pollutants were then evaluated in multipollutant models. Sensitivity analyses were used to evaluate effect of degree of smoothing on results.	In general, the gases, especially CO (but not O_3) were much more strongly associated with mortality than PM. Specified pattern of results found for each county were as follows. For Cook Co., in single pollutant analyses PM_{10}, CO, and O_3 were all associated (PM_{10} most strongly on lag 0-2 days) with total mortality, as were SO_2 and NO_2 (strongest association on lag 1 day for the latter two). In joint analyses with one of gases, the coefficients for both PM_{10} and the gas were somewhat attenuated, but remained stat. sig. for some lags. With 3-pollutant models, PM_{10} coefficient became small and non-sig. (except at lag 0), whereas the gases dominated. For Los Angeles, PM_{10}, $PM_{2.5}$, CO, NO_2, and SO_2, (but not O_3), were all associated with total mortality. In joint analyses with CO or SO_2 and either PM_{10} or $PM_{2.5}$, PM metrics were markedly reduced and non-sig., whereas estimates for gases remained robust. In Maricopa Co. single-pollutant analyses, PM_{10} and each of the gases, (except O_3), were associated with total morality; in 2-pollutant models, coefficients for CO, NO_2, SO_2, were more robust than for PM_{10}. Analogous patterns of more robust gaseous pollutant effects were generally found for cause-specific (CVD, CrD, COPD) mortality analyses. Author concluded that while direct effect of individual components of air pollution cannot be ruled out, individual components best thought of as indices of overall pollutant mix.	In single pollutant models, estimated daily total mortality % excess deaths per 50 $\mu g/m^3$ PM_{10} was mainly in range of: 0.5-1.0% lags 0-2 Cook Co.; 0.25-1.0% lags 0-2 LA; 2.0% lag 2 Maricopa. Percent per 25 $\mu g/m^3$ $PM_{2.5}$ 0.5% lags 0, 1 for Los Angeles. Maximum estimated COPD % excess deaths (95% CI) per 50 $\mu g/m^3$ PM_{10}: Cook Co. 5.4 (0.3,10.7), lag 2; with O_3, 3.0 (-1.8, 8.1) lag 2; LA 5.9 (-1.6, 14.0) lag 1; Maricopa 8.2 (-4.2, 22.3) lag 1; per 25 $\mu g/m^3$ $PM_{2.5}$ in LA 2.7 (-3.4, 9.1). CVD % per 50 $\mu g/m^3$ PM_{10}: Cook 2.2 (0.4, 4.1) lag 3; with O_3, SO_2 1.99 (-0.06, 4.1) lag 3; LA 4.5 (1.7, 7.4) lag 2; with CO -0.56 (-3.8, 2.8) lag 2; Maricopa 8.9 (2.7, 15.4) lag 1; with NO_2 7.4 (-0.95, 16.3) lag 1. Percent per 25 $\mu g/m^3$ $PM_{2.5}$, LA 2.6 (0.4, 4.9) lag1; with CO 0.60 (-2.1, 3.4). CrD % per 50 $\mu g/m^3$ PM_{10}: Cook 3.3 (-0.12, 6.8) lag 2; LA 2.9 (-2.3, 8.4) lag 3; Maricopa 11.1 (0.54, 22.8) lag 5. Percent per 25 $\mu g/m^3$ $PM_{2.5}$, LA 3.6 (-0.6, 7.9) lag 3.

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Moolgavkar (2003). Re-analysis of above study, but Maricopa Co. data were not analyzed.	Re-analysis of above study using stringent convergence criteria as well as natural splines. Cerebrovascular deaths data were not analyzed. Ozone was not analyzed. In addition to the 30 degrees of freedom used for smoothing splines for temporal trends in the original analysis, results for 100 degrees of freedom were also presented. Two-pollutant model results were not reported for Cook county.	The sensitivity of results to the degrees of freedom was often greater than that to the GAM convergence criteria. The main conclusion of the original study remained the same.	Maximum estimated non-accidental deaths % excess deaths (95% CI) per 50 $\mu g/m^3$ PM_{10}: Cook Co. 2.4 (1.3,3.5), lag 0; LA 2.4 (0.5, 4.4) lag2; with CO, -1.6(-3.7, 0.6); per 25 $\mu g/m^3$ $PM_{2.5}$ in LA 1.5 (0, 3.0). Maximum estimated COPD % excess deaths (95% CI) per 50 $\mu g/m^3$ PM_{10}: Cook Co. 5.5 (0.3,11.0), lag 2; LA 4.4 (-3.1, 12.6) lag 1; per 25 $\mu g/m^3$ $PM_{2.5}$ in LA 1.9 (-10.0, 15.4). CVD % per 50 $\mu g/m^3$ PM_{10}: Cook 2.2 (0.3, 4.1) lag 3; LA 4.5 (1.6, 7.5) lag 2; Percent per 25 $\mu g/m^3$ $PM_{2.5}$, LA 2.6 (0.4, 4.9) lag1. All the estimates above are for 30 degrees of freedom cases.
Ostro et al. (1999a).+ Coachella Valley, CA. 1989-1992. PM_{10} (beta-attenuation) Mean = 56.8 $\mu g/m^3$.	Study evaluated total, respiratory, cardiovascular, non-cardiorespiratory and age >50 yr deaths (mean = 5.4, 0.6, 1.8, 3.0, and 4.8 per day, respectively). The valley is a desert area where 50-60% of PM_{10} estimated to be coarse particles. Correlation between gravimetric and beta-attenuation, separated by 25 miles, was high (r = 0.93). Beta-attenuation data were used for analysis. GAM Poisson models adjusting for temperature, humidity, day-of-week, season, and time were used. Seasonally stratified analyses were also conducted. Lags 0-3 days (separately) of PM_{10} along with moving averages of 3 and 5 days examined, as were O_3, NO_2, and CO.	Associations were found between 2- or 3-day lagged PM_{10} and all mortality categories examined, except non-cardiorespiratory series. The effect size estimates for total and cardiovascular deaths were larger for warm season (May through October) than for all year period. NO_2 and CO were significant predictor of mortality in single pollutant models, but in multi-pollutant models, none of the gaseous pollutants were significant (coefficients reduced), whereas PM_{10} coefficients remained the same and significant.	Total mortality percent excess deaths per 50 $\mu g/m^3$ PM_{10} at 2-day lag = 4.6 (0.6, 8.8). Cardiac deaths: 8.33 (2.14, 14.9) Respiratory deaths: 13.9 (3.25, 25.6)

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Ostro et al. (2000).* Coachella Valley, CA. 1989-1998. $PM_{2.5}$ = 16.8; $PM_{10-2.5}$ = 25.8 in Indio; $PM_{2.5}$ = 12.7; $PM_{10-2.5}$ = 17.9 in Palm Springs.	A follow-up study of the Coachella Valley data, with $PM_{2.5}$ and $PM_{10-2.5}$ data in the last 2.5 years. Both $PM_{2.5}$ and $PM_{10-2.5}$ were estimated for the remaining years to increase power of analyses. However, only $PM_{10-2.5}$ could be reliably estimated. Therefore, predicted $PM_{2.5}$ data were not used for mortality analysis. Thus, the incomparable sample size make it difficult to directly assess the relative importance of $PM_{2.5}$ and $PM_{10-2.5}$ in this data set.	Several pollutants were associated with all-cause mortality, including $PM_{2.5}$, CO, and NO_2. More consistent results were found for cardiovascular mortality, for which significant associations were found for $PM_{10-2.5}$ and PM_{10}, but not $PM_{2.5}$ (possibly due to low range of $PM_{2.5}$ concentrations and reduced sample size for $PM_{2.5}$ data).	Total percent excess deaths: PM_{10} (lag 0 or 2) = 2.0 (-1.0, 5.1) per 50 $\mu g/m^3$ $PM_{2.5}$ (lag 4) = 11.5 (0.2, 24.1) per 25 $\mu g/m^3$ $PM_{10-2.5}$ (lag 0 or 2) = 1.3 (-0.6, 3.5) per 25 $\mu g/m^3$ Cardio deaths: PM_{10} (lag 0) = 6.1 (2.0, 10.3) per 50 $\mu g/m^3$ $PM_{2.5}$ (lag 4) = 8.6 (-6.4, 25.8) per 25 $\mu g/m^3$ $PM_{10-2.5}$ (lag 0) = 2.6 (0.7, 4.5) per 25 $\mu g/m^3$ Respiratory deaths: PM_{10} (lag 3) = -2.0 (-11.4, 8.4) per 50 $\mu g/m^3$ $PM_{2.5}$ (lag 1) = 13.3 (-43.1, 32.1) per 25 $\mu g/m^3$ $PM_{10-2.5}$ (lag 3) = -1.3 (-6.2, 4.0) per 25 $\mu g/m^3$
Ostro et al. (2003). Re-analysis of above study.	Re-analysis of above study using stringent convergence criteria as well as natural splines. Only cardiovascular mortality data were analyzed. Additional sensitivity analyses were conducted.	The PM risk estimates were slightly reduced with stringent convergence criteria and GLM. Sensitivity analysis showed that results were not sensitive to alternative degrees of freedom for temporal trends and temperature. Multi-day averages for PM increased risk estimates.	Cardio deaths (GAM with stringent convergence criteria): PM_{10} (lag 0) = 5.5 (1.6, 9.5) per 50 $\mu g/m^3$ $PM_{2.5}$ (lag 4) = 10.2 (-5.3, 28.3) per 25 $\mu g/m^3$ $PM_{10-2.5}$ (lag 0) = 2.9 (0.7, 5.2) per 25 $\mu g/m^3$ Cardio deaths (GLM/natural splines): PM_{10} (lag 0) = 5.1 (1.2, 9.1) per 50 $\mu g/m^3$ $PM_{2.5}$ (only 0-2 day lags reported) $PM_{10-2.5}$ (lag 0) = 2.7 (0.5, 5.1) per 25 $\mu g/m^3$

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Fairley (1999).* Santa Clara County, CA 1989-1996. $PM_{2.5}$ (13); PM_{10} (34); $PM_{10-2.5}$ (11); COH (0.5 unit); NO_3 (3.0); SO_4 (1.8)	Total, cardiovascular, and respiratory deaths were regressed on PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, COH, nitrate, sulfate, O_3, CO, NO_2, adjusting for trend, season, and min and max temperature, using Poisson GAM model. Season-specific analysis was also conducted. The same approach was also used to re-analyze 1980-1986 data (previously analyzed by Fairley, 1990).	$PM_{2.5}$ and nitrate were most significantly associated with mortality, but all the pollutants (except $PM_{10-2.5}$) were significantly associated in single poll. models. In 2 and 4 poll. models with $PM_{2.5}$ or nitrate, other pollutants were not significant. The RRs for respiratory deaths were always larger than those for total or cardiovascular deaths. The difference in risk between season was not significant for $PM_{2.5}$. The 1980-1986 results were similar, except that COH was very significantly associated with mortality.	Total mortality per 25 $\mu g/m^3$ $PM_{2.5}$ at 0 d lag: 8% in one pollutant model; 9-12% in 2 pollutant model except with NO_3(~0) . Also, 8% per 50 $\mu g/m^3$ PM_{10} in one pollutant model and 2% per 25 $\mu g/m^3$ $PM_{10-2.5}$. Cardiovascular mortality: PM_{10} = 9% per 50 $\mu g/m^3$ $PM_{2.5}$ = 13% per 25 $\mu g/m^3$ $PM_{10-2.5}$ = 3% per 25 $\mu g/m^3$ Respiratory mortality: PM_{10} = 11% per 50 $\mu g/m^3$ $PM_{2.5}$ = 7% per 25 $\mu g/m^3$ $PM_{10-2.5}$ = 16% per 25 $\mu g/m^3$
Fairley (2003). Re-analysis of above study.	Re-analysis of above study using stringent convergence criteria as well as natural splines.	PM coefficients were either unchanged, slightly decreased, or slightly increased. Original findings, including the pattern in two-pollutant models unchanged.	Percent excess mortality for GAM (stringent) and GLM/natural splines, respectively per 50 $\mu g/m^3$ for PM_{10} and 25 $\mu g/m^3$ for $PM_{2.5}$ and $PM_{10-2.5}$. Total mortality: PM_{10} =7.8(2.8,13.1); 8.3(2.9, 13.9) $PM_{2.5}$ = 8.2(1.6, 15.2); 7.1(1.4, 13.1) $PM_{10-2.5}$ = 4.5(-7.6, 18.1); 3.3(-5.3, 12.7) Cardiovascular mortality: PM_{10} = 8.5(0.6, 17.0); 8.9(1.3, 17.0) $PM_{2.5}$ = 6.4(-4.1, 18.1); 6.8(-2.5, 16.9) $PM_{10-2.5}$ = 5.1(-13.4, 27.4); (no GLM) Respiratory mortality: PM_{10} = 10.7(-3.7, 27.2); 10.8(-3.4, 27.1) $PM_{2.5}$ = 11.8(-9.9, 38.7); 13.6(-3.7, 34.1) $PM_{10-2.5}$ = 32.2(-12.1, 98.6); (no GLM)

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Schwartz et al. (1999). Spokane, WA 1989-1995 PM_{10}: "control" days: 42 $\mu g/m^3$; dust-storm days: 263	Effects of high concentration of coarse crustal particles were investigated by comparing death counts on 17 dust storm episodes to those on non-episode days on the same day of the years in other years, adjusting for temperature, dewpoint, and day-of-week, using Poisson regression.	No association was found between the mortality and dust storm days on the same day or the following day.	0% (-4.5, 4.7) for dust storm days at 0 day lag (50 $\mu g/m^3$ PM_{10}) (lagged days also reported to have no associations).
Pope et al. (1999a). + Ogden, Salt Lake City, and Provo/Orem, UT 1985-1995 PM_{10} (32 for Ogden; 41 for SLC; 38 for P/O)	Associations between PM_{10} and total, cardiovascular, and respiratory deaths studied in three urban areas in Utah's Wasatch Front, using Poisson GAM model and adjusting for seasonality, temperature, humidity, and barometric pressure. Analysis was conducted with or without dust (crustal coarse particles) storm episodes, as identified on the high "clearing index" days, an index of air stagnation.	Salt Lake City (SLC), where past studies reported little PM_{10}-mortality associations, had substantially more dust storm episodes. When the dust storm days were screened out from analysis and PM_{10} data from multiple monitors were used, comparable RRs were estimated for SLC and Provo/Orem (P/O).	Ogden PM_{10} Total (0 d) = 12.0% (4.5, 20.1) CVD (0-4 d) = 1.4% (-8.3, 12.2) Resp. (0-4 d) = 23.8 (2.8, 49.1) SLC PM_{10} Total (0 d) = 2.3% (0.47) CVD (0-4 d) = 6.5% (2.2, 11.0) Resp. (0-4 d) = 8.2 (2.4, 15.2) Provo/Ovem PM_{10} Total (0 d) = 1.9% (-2.1, 6.0) CVD (0-4 d) = 8.6% (2.4, 15.2) Resp. (0-4 d) = 2.2% (-9.8, 15.9) Note: Above % for $PM_{2.5}$ and $PM_{10-2.5}$ all per 25 $\mu g/m^3$; all PM_{10} % per 50 $\mu g/m^3$.
Schwartz and Zanobetti (2000) +Chicago 1988-1993. PM_{10}. Median = 36 $\mu g/m^3$.	Total (non-accidental), in-hospital, out-of-hospital deaths (median = 132, 79, and 53 per day, respectively), as well as heart disease, COPD, and pneumonia elderly hospital admissions (115, 7, and 25 per day, respectively) were analyzed to investigate possible "harvesting" effect of PM_{10}. GAM Poisson models adjusting for temperature, relative humidity, day-of-week, and season were applied in baseline models using the average of the same day and previous day's PM_{10}. The seasonal and trend decomposition techniques called STL was applied to the health outcome and exposure data to decompose them into different time-scales (i.e, short-term to long-term), excluding the long, seasonal cycles (120 day window). The associations were examined with smoothing windows of 15, 30, 45, and 60 days.	The effect size estimate for deaths outside of the hospital is larger than for deaths inside the hospital. All cause mortality shows an increase in effect size at longer time scales. The effect size for deaths outside of hospital increases more steeply with increasing time scale than the effect size for deaths inside of hospitals.	Mortality RR estimates per 50 $\mu g/m^3$ increase of mean of lag 0- and 1-days PM_{10}: total deaths 4.5 (3.1, 6.0); in-hospital 3.9 (2.1, 5.8); out-of-hospital 6.3 (4.1, 8.6). For total deaths, the RR approximately doubles as the time scale changes from 15 days to 60 days. For out-of-hospital deaths, it triples from15 days to 60 days time scale.

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Lippmann et al. (2000).* Detroit, MI. 1992-1994. PM_{10} = 31; $PM_{2.5}$ = 18; $PM_{10-2.5}$ = 13.	For 1992-1994 study period, total (non-accidental), cardiovascular, respiratory, and other deaths were analyzed using GAM Poisson models, adjusting for season, temperature, and relative humidity. The air pollution variables analyzed were: PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, sulfate, H^+, O_3, SO_2, NO_2, and CO.	PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ were more significantly associated with mortality outcomes than sulfate or H^+. PM coefficients were generally not sensitive to inclusion of gaseous pollutants. PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ effect size estimates were comparable per same distributional increment (5^{th} to 95^{th} percentile).	Percent excess mortality per 50 $\mu g/m^3$ for PM_{10} and 25 $\mu g/m^3$ for $PM_{2.5}$ and $PM_{10-2.5}$: Total mortality: PM_{10} (1 d) = 4.4(-1.0,10.1) $PM_{2.5}$ (3 d) = 23.1(-0.6, 7.0) $PM_{10-2.5}$ (1 d) = 4.0(-1.2, 9.4)
For 1985-1990 period TSP, PM_{10}, TSP-PM_{10}, Sulfate from TSP (TSP-$SO_4^=$)	For earlier 1985-1990 study period, total non-accidental, circulatory, respiratory, and "other" (non-circulatory or respiratory non-accidental) mortality were evaluated versus noted PM indices and gaseous pollutants.	Both PM_{10} (lag 1 and 2 day) and TSP (lag 1 day) but not TSP-PM_{10} or TSP-$SO_4^=$ significantly associated with respiratory mortality for 1985-1990 period. The simultaneous inclusions of gaseous pollutants with PM_{10} or TSP reduced PM effect size by 0 to 34%. Effect size estimates for total, circulatory, and "other" categories were smaller than for respiratory mortality.	Circulatory mortality: PM_{10} (1 d) = 6.9(-1.3, 15.7) $PM_{2.5}$ (1 d) = 3.2 (-2.3, 8.9) $PM_{10-2.5}$ (1 d) = 7.8 (0, 16.2) Respiratory mortality: PM_{10} (0 d) = 7.8(-10.2, 29.5) $PM_{2.5}$ (0 d) = 2.3 (-10.3, 16.6) $PM_{10-2.5}$ (2 d) = 7.4(-9.1, 26.9)

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Ito (2003). Re-analysis of above study.	Re-analysis of above study using stringent convergence criteria as well as natural splines. Additional sensitivity analysis examined alternative weather models and influence of the degrees of freedom in a limited data sets.	PM coefficients were often reduced (but sometimes unchanged or increased) somewhat when GAM with stringent convergence criteria or GLM/natural splines were used. The reductions in coefficients were not differential across PM components; the original conclusion regarding the relative importance of PM components remained the same.	Percent excess mortality for GAM (stringent) and GLM/natural splines, respectively per 50 $\mu g/m^3$ for PM_{10} and 25 $\mu g/m^3$ for $PM_{2.5}$ and $PM_{10-2.5}$: Total mortality: PM_{10} (1 d) = 3.3(-2.0, 8.9); 3.1(-2.2, 8.7) $PM_{2.5}$ (3 d) = 1.9 (-1.8,5.7); 2.0(-1.7, 5.8) $PM_{10-2.5}$ (1 d) = 3.2(-1.9, 8.6); 2.8(-2.2, 8.1) Circulatory mortality: PM_{10} (1 d) = 5.4(-2.6, 14.0); 4.9(-3.0, 13.5) $PM_{2.5}$ (1 d) = 2.2 (-3.2, 7.9); 2.0(-3.4, 7.7) $PM_{10-2.5}$ (1 d) = 6.7 (-1.0, 15.0); 6.0(-1.6, 14.3) Respiratory mortality: PM_{10} (0 d) = 7.5(-10.5, 29.2); 7.9(-10.2, 29.7) $PM_{2.5}$ (0 d) = 2.3 (-10.4, 16.7); 3.1(-9.7, 17.7) $PM_{10-2.5}$ (2 d) = 7.0(-9.5, 26.5); 6.4(-10.0, 25.7)

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in μg/m^3.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Chock et al. (2000). 1989-1991 Pittsburgh, PA PM_{10} (daily) $PM_{2.5}$ (every 2 days)	Study evaluated associations between daily mortality and several air pollution variables (PM_{10}, $PM_{2.5}$, CO, O_3, NO_2, SO_2) in two age groups (<75 yr., 75 yr.) in Pittsburgh, PA, during 3-yr. period. Poisson GLM regression used, including filtering of data based on cubic B-spline basis functionsas adjustments for seasonal trends. Day-of-week effects, temperature was modeled as a V-shape terms. Single- and multi-pollutant models run for 0, 1, 2, and 3 day lags. $PM_{2.5}/PM_{10}$ 0.67.	Issues of seasonal dependence of correlation among pollutants, multi-collinearity among pollutants, and instability of coefficients emphasized. Single- and multi-pollutant non-seasonal models show significant positive association between PM_{10} and daily mortality, but seasonal models showed much multi-collinearity, masking association of any pollutant with mortality. Also, based on data set half the size for PM_{10}, the $PM_{2.5}$ coefficients were highly unstable and, since no consistently significant associations found in this small data set stratified by age group and season, no conclusions drawn on relative role of $PM_{2.5}$ vs. $PM_{10-2.5}$.	Total mortality percent increase per 25 μg/m^3 for aged <75 yrs: $PM_{2.5}$ = 2.6% (2.0, 7.3) $PM1_{0-2.5}$ = 0.7% (-1.7, 3.7) Total mortality percent increase per 25 μg/m^3 for aged >75 yrs: $PM_{2.5}$ = 1.5% (-3.0, 6.3) $PM1_{0-2.5}$ = 1.3% (-1.3, 3.8)
Klemm and Mason (2000). Atlanta, GA 1998-1999 $PM_{2.5}$ mean=19.9; $PM_{2.5}/PM_{10}$ =0.65. Nitrate, EC, OC, and oxygenated HC.	Reported "interim" results for 1 yr period of observations regarding total mortality in Atlanta, GA during 1998-1999. Poisson GLM model with natural splines used to assess effects of $PM_{2.5}$ vs $PM_{10-2.5}$, and for nitrate, EC, OC and oxygenated HC components.	No significant associations were found for any of the pollutants examined, possibly due to a relatively short study period (1-year). The coefficient and t-ratio were larger for $PM_{2.5}$ than for $PM_{10-2.5}$.	Total mortality percent increase per 25 μg/m^3 for: $PM_{2.5}$ = 4.8% (-3.2, 13.4) $PM_{10-2.5}$ = 1.4% (-11.3, 15.9)
Gwynn et al. (2000). +Buffalo, N.Y. 1988-1990. PM_{10} (24); COH (0.2 /1000ft); SO_4 = (62 nmoles/m3)	Total, circulatory, and respiratory mortality and unscheduled hospital admissions were analyzed for their associations with H+, SO_4=, PM_{10}, COH, O_3, CO, SO_2, and NO_2, adjusting for seasonal cycles, day-of-week, temperature, humidity, using. Poisson and negative binomial GAM models.	For total mortality, all the PM components were significantly associated, with H+ being the most significant, and COH the least significant predictors. The gaseous pollutants were mostly weakly associated with total mortality.	12% (2.6, 22.7) per 50 μg/m^3 PM_{10} at 2-day lag.
Schwartz (2000c).* Boston, MA. 1979-1986. $PM_{2.5}$ mean = 15.6.	Non-accidental total, pneumonia, COPD, and ischemic heart disease mortality were examined for possible "harvesting" effects of PM. The mortality, air pollution, and weather time-series were separated into seasonal cycles (longer than 2-month period), midscale, and short-term fluctuations using STL algorithm. Four different midscale components were used (15, 30, 45, and 60 days) to examine the extent of harvesting. GAM Poisson regression analysis was performed using deaths, pollution, and weather for each of the four midscale periods.	For COPD deaths, the results suggest that most of the mortality was displaced by only a few months. For pneumonia, ischemic heart disease, and total mortality, the effect size increased with longer time scales.	Total mortality percent increase per 25 μg/m^3 increase in $PM_{2.5}$: 5.8(4.5, 7.2) for 15-day window fluctuations; 9.6 (8.2, 11.1) for the 60 day window.

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Schwartz (2003a). Re-analysis of above study.	Reanalysis of above study using GLM/natural splines.	PM risk estimates at different time scales changed only slightly (more often increased). Increase in standard error of PM coefficients was also small (<3%). Original findings unchanged.	Total mortality percent increase per 25 $\mu g/m^3$ increase in $PM_{2.5}$: 5.8 (4.5, 7.3) for 15-day window; 9.7 (8.2, 11.2) for the 60 day window.
Lipfert et al. (2000a). Philadelphia (7 county Metropolitan area), 1992-1995. Harvard PM measurements: $PM_{2.5}$ (17.3); PM_{10} (24.1); $PM_{10-2.5}$ (6.8), sulfate (53.1 nmol/m3); H^+ (8.0 nmol/m3).	12 mortality variables, as categorized by area, age, and cause, were regressed on 29 pollution variables (PM components, O_3, SO_2, NO_2, CO, and by sub-areas), yielding 348 regression results. Both dependent and explanatory variables were pre-filtered using the19-day-weighted average filter prior to OLS regression. Covariates were selected from filtered temperature (several lagged and averaged values), indicator variables for hot and cold days and day-of-week using stepwise procedure. The average of current and previous days' pollution levels were used.	Significant associations were found for a wide variety gaseous and particulate pollutants, especially for peak O_3. No systematic differences were seen according particle size or chemistry. Mortality for one part of the metropolitan area could be associated with air quality from another, not necessarily neighboring part.	The fractional Philadelphia mortality risk attributed to the pollutant levels: "average risk" was 0.0423 for 25 $\mu g/m^3$ $PM_{2.5}$; 0.0517 for 25 $\mu g/m^3$ $PM_{10-2.5}$; 0.0609 for 50 $\mu g/m^3$ PM_{10}, using the Harvard PM indices at avg. of 0 and 1 d lags.
Laden et. al. (2000)* Six Cities (means): Watertown, MA (16.5); Kingston-Harriman, TN (21.1); St. Louis, MO (19.2); Steubenville, OH (30.5); Portage, WI (11.3); Topeka, KS (12.2). 1979-1988?. 15 trace elements in the dichot $PM_{2.5}$: Si, S, Cl, K, Ca, V, Mn, Al, Ni, Zn, Se, Br, Pb, Cu, and Fe.	Total (non-accidental), ischemic heart disease, pneumonia, and COPD (mean daily total deaths for the six cities: 59, 12, 55, 3, 11, and 3, respectively in the order shown left). A factor analysis was conducted on the 15 elements in the fine fraction of dichot samplers to obtain five common factors; factors were rotated to maximize the projection of the single "tracer" element (as in part identified from the past studies conducted on these data) for each factor; $PM_{2.5}$ was regressed on the identified factors scores so that the factor scores could be expressed in the mass scale. Using GAM Poisson models adjusting for temperature, humidity, day-of-week, season, and time, mortality was regressed on the factor scores in the mass scale. The mean of the same-day and previous day (increasing the sample size from 6,211 to 9,108 days) mass values were used. The city-specific regression coefficients were combined using inverse variance weights.	Three sources of fine particles were defined in all six cities with a representative element for each source type: Si for soil and crustal material; Pb for motor vehicle exhaust; and Se for coal combustion sources. In city-specific analysis, additional sources (V for fuel oil combustion, Cl for salt, etc.) were considered. Five source factors were considered for each city, except Topeka with the three sources. Coal and mobile sources account for the majority of fine particles in each city. In all of the metropolitan areas combined, 46% of the total fine particle mass was attributed to coal combustion and 19% to mobile sources. The strongest increase in daily mortality was associated with the mobile source factor. The coal combustion factor was positively associated with mortality in all metropolitan areas, with the exception of Topeka. The crustal factor from the fine particles was not associated with mortality.	Percent excess total mortality per 25µg/m3 increase in PM2.5 from source types: Crustal: -5.6(-13.6, 3.1) Traffic: 8.9(4.2, 13.8) Coal: 2.8(0.8, 4.8) Residual oil: 6.3(0.4, 12.5)

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Schwartz (2003a). Re-analysis of above study.	Re-analysis of above study using penalized splines.	The change in risk estimates for each source-apportioned $PM_{2.5}$ in each city were either positive or negative, but the combined estimates across cities increased for traffic factor and decreased for coal factor and residual oil factor.	Percent excess total mortality per 25µg/m3 increase in PM2.5 from source types: Crustal: -5.1(-13.9, 4.6) Traffic: 9.3(4.0, 14.9) Coal: 2.0(-0.3, 4.4) Residual oil: 5.9(-0.9, 13.2)
Levy (1998). King County, WA. 1990-1994. PM_{10} Nephelometer (30); (0.59 bsp unit)	Out-of-hospital deaths (total, respiratory, COPD, ischemic heart disease, heart failure, sudden cardiac death screening codes, and stroke) were related to PM_{10}, nephelometer (0.2 - 1.0 m fine particles), and PM_{10}. The nephelometer measures were converted to gravimetric units based on a regression. SO_2, and CO, adjusting for day-of-week, month of the year, temperature and dewpoint, using Poisson GLM regression.	Nephelometer data were not associated with mortality. Cause-specific death analyses suggest PM associations with ischemic heart disease deaths. Associations of mortality with SO_2 and CO not mentioned. Mean daily death counts were small (e.g., 7.7 for total; 1.6 for ischemic heart disease). This is an apparently preliminary analysis.	Total mortality percent excess: 5.6% (-2.4, 14.3) per 50 $\mu g/m^3$ PM_{10} at avg. of 2 to 4 d lag; 7.2% (-6.3, 22.8) with SO_2 CO. 1.8% (-3.5, 7.3) per 25 $\mu g/m^3$ PM_1; -1.0 (-8.7,. 7.7) with SO_2 and CO.
Mar et al. (2000).* Phoenix, AZ. 1995-1997. PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ (TEOM), with means = 46.5, 13.0, and 33.5, respectively; and $PM_{2.5}$ (DFPSS), mean = 12.0.	Total (non-accidental) and cardiovascular deaths (mean = 8.6 and 3.9, respectively) for only those who resided in the zip codes located near the air pollution monitor were included. GAM Poisson models were used, adjusting for season, temperature, and relative humidity. Air pollution variables evaluated included: O_3, SO_2, NO_2, CO, TEOM PM_{10}, TEOM $PM_{2.5}$, TEOM $PM_{10-2.5}$, DFPSS $PM_{2.5}$, S, Zn, Pb, soil, soil-corrected K (KS), nonsoil PM, OC, EC, and TC. Lags 0 to 4 days evaluated. Factor analysis also conducted on chemical components of DFPSS $PM_{2.5}$ (Al, Si, S, Ca, Fe, Zn, Mn, Pb, Br, KS, OC, and EC); and factor scores included in mortality regression.	Total mortality was significantly associated with CO and NO_2 and weakly associated with SO_2, PM_{10}, $PM_{10-2.5}$, and EC. Cardiovascular mortality was significantly associated with CO, NO_2, SO_2, $PM_{2.5}$, PM_{10}, $PM_{10-2.5}$, OC and EC. Combustion-related factors and secondary aerosol factors were also associated with cardiovascular mortality. Soil-related factors, as well as individual variables that are associated with soil were negatively associated with total mortality.	Total mortality percent excess: 5.4 (0.1, 11.1) for PM_{10} (TEOM) 50 $\mu g/m^3$ at lag 0 d; 3.0 (-0.5, 6.6) for $PM_{10-2.5}$ (TEOM) 25 $\mu g/m^3$ at lag 0 d; 3.0 (-0.7, 6.9) for $PM_{2.5}$ (TEOM) 25 $\mu g/m^3$ at lag 0 d. Cardiovascular mortality RRs: 9.9 (1.9, 18.4) for PM_{10} (TEOM) 50 $\mu g/m^3$ at lag 0 d; 18.7 (5.7, 33.2) for $PM_{2.5}$ (TEOM) 25 $\mu g/m^3$ at lag 1 d; and 6.4 (1.4, 11.7) PM_{10} (TEOM) 25 $\mu g/m^3$ $PM_{10-2.5}$ at lag 0 d.
Mar et al. (2003). Re-analysis of above study.	Re-analysis of above study using stringent convergence criteria as well as natural splines. Only cardiovascular mortality was re-analyzed.	Reductions on PM risk estimates for PM mass concentration indices in the GAM/stringent convergence criteria or GLM/natural splines were small. The change in coefficient for source factors varied: moderate reductions for motor vehicle factor, but slight increase for regional sulfate factor. EC and OC coefficients were also slightly reduced.	Percent excess cardiovascular mortality per 50 $\mu g/m^3$ PM_{10}; 25 $\mu g/m^3$ for $PM_{2.5}$ and $PM_{10-2.5}$: GAM with stringent convergence criteria and GLM/natural splines, respectively: PM_{10} (0 d): 9.7(1.7, 18.3); 9.5(0.6, 19.3) $PM_{2.5}$ (1 d): 18.0(4.9, 32.6); 19.1(3.9, 36.4) $PM_{10-2.5}$ (0 d): 6.4(1.3, 11.7); 6.2(0.8, 12.0)

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Clyde et al. (2000). Phoenix, AZ. 1995-1998. PM_{10}, and $PM_{2.5}$, (from TEOM), with means = 45.4, and 13.8. $PM_{10-2.5}$ computed as PM_{10}-$PM_{2.5}$.	Elderly (age 65 years) non-accidental mortality for three regions of increasing size in Phoenix urban area analyzed to evaluate influence of spatial uniformity of PM_{10} and $PM_{2.5}$. All-age accidental deaths for the metropolitan area also examined as a "control". GAM Poisson models adjusting for season (smoothing splines of days), and parametric terms for temperature, specific humidity, and lags 0- to 3-d of weather variables. PM indices for lags 0-3 d considered. Bayesian Model Averaging (BMA) produces posterior mean relative risks by weighting each model (out of all possible model specifications examined) based on support received from the data.	The BMA results suggest that a weak association was found only for the mortality variable defined over the region with uniform $PM_{2.5}$, with a 0.91 probability that RR is greater than 1. The other elderly mortality variables, including the accidental deaths ("control"), had such probabilities in the range between 0.46 to 0.77. Within the results for the mortality defined over the region with uniform $PM_{2.5}$, the results suggested that effect was primarily due to coarse particles rather than fine; only the lag 1 coarse PM was consistently included in the highly ranked models.	Posterior mean RRs and 90% probability intervals per changes of 25 $\mu g/m^3$ in all lags of fine and coarse PM for elderly mortality for uniform PM_{10} region: 1.06 (1+, 1.11).
Smith et al. (2000). Phoenix, AZ. 1995-1997	Study evaluated effects of daily and 2- to 5-day average coarse ($PM_{10-2.5}$) and fine ($PM_{2.5}$) particles from an EPA-operated central monitoring site on nonaccidental mortality among elderly (65+ years), using time-series analyses for residents within city of Phoenix and, separately, for region of circa 50 mi around Phoenix. Mortality was square-root transformed.Initial model selected to represent long-term trends (using B-splines) and weather variables (e.g., ave. daily temp., max daily temp., daily mean specific humidity, etc.); then PM variables added to model one at a time to ascertain which had strongest effect. Piecewise linear analysis and spline analysis used to evaluate possible nonlinear PM-mortality relationship and to evaluate threshold possibilities. Data analyzed most likely same as Clyde's or Mar's Phoenix data.	In linear PM effect model, a statistically significant mortality association found with $PM_{10-2.5}$, but not with $PM_{2.5}$. In the model allowing for a threshold, evidence suggestive of possible threshold for $PM_{2.5}$ (in the range of 20-25 $\mu g/m^3$) found, but not for $PM_{10-2.5}$. A seasonal interaction in the $PM_{10-2.5}$ effect was also reported: the effect being highest in spring and summer when anthropogenic concentration of $PM_{10-2.5}$ is lowest.	—

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Tsai et al. (2000). Newark, Elizabeth, and Camden, NJ. 1981-1983. PM_{15}: 55.5, 47.0, 47.5; and $PM_{2.5}$: 42.1, 37.1, 39.9, for Newark, Elizabeth, and Camden, respectively.	Factor analysis-derived source type components were examined for their associations with mortality in this study. Non-accidental total deaths and cardiorespiratory deaths were examined for their associations with PM_{15}, $PM_{2.5}$ sulfate, trace metals from PM_{15}, three fractions of extractable organic matter, and CO. Data were analyzed with Poisson GEE regression models with autoregressive correlation structure, adjusting for temperature, time-of-week, and season indicator variables. Individual pollution lag days from 0 to 3, as well as the average concentrations of current and preceding 3 days were considered. Factor analysis of the trace elements, sulfate, and CO data was conducted, and mortality series were regressed on these factor scores.	Factor analysis identified several source types with tracer elements. In Newark, oil burning factor, industrial source factor, and sulfate factor were positively associated with total mortality; and sulfate was associated with cardio-respiratory mortality. In Camden, oil burning and motor vehicle factors were positively associated with total mortality; and, oil burning, motor vehicles, and sulfate were associated with cardio-respiratory mortality. In Elizabeth, resuspended dust was not associated with total mortality; and industrial source (traced by Cd) showed positive associations with cardio-respiratory mortality. On the mass basis (source-contributed mass), the RRs estimates per 10 $\mu g/m^3$ were larger for specific sources (e.g., oil burning, industry, etc.) than for total mass. The choice of lag/averaging reported to be not important.	Percent excess deaths per 50 $\mu g/m^3$ increase in current day PM_{15}: in Newark, 5.7 (4.6, 6.7) for total mortality, 7.8 (3.6, 12.1) for cardioresp. mortality; in Camden, 11.1 (0.7, 22.5) and 15.0 (4.3, 26.9); and in Elizabeth, -4.9 (-17.9, 10.9) and 3.0 (-11.0, 19.4), respectively. Percent excess deaths per 25 $\mu g/m^3$ $PM_{2.5}$; in Newark, 4.3 (2.8, 5.9) for total and 5.1 (3.1, 7.2) for cardiorespiratory mortality; in Camden, 5.7 (0.1, 11.5) and 6.2 (0.6, 12.1); in Elizabeth, 1.8 (-5.4, 9.5) and 2.3 (-5.0, 10.1), respectively.
Gamble (1998). Dallas, TX. 1990-1994. PM_{10} (25)	Relationships of total, respiratory, cardiovascular, cancer, and remaining non-accidental deaths to PM_{10}, O_3, NO_2, SO_2, and CO evaluated, adjusting for temperature, dewpoint, day-of-week, and seasonal cycles (trigonometric terms) using Poisson GLM regression. Daily PM_{10} concentrations were estimated from the every-sixth-day measures by an estimation model.	O_3 (avg. of 1-2 day lags), NO_2 (avg.. 4 -5 day lags), and CO (avg. of lags 5- 6 days) were significantly positively associated with total mortality. PM_{10} and SO_2 were not significantly associated with any deaths.	-3.6% (-12.7, 6.6) per 50 $\mu g/m^3$ PM_{10} at 0 lag (other lags also reported to have no associations)
Ostro (1995). San Bernardino and Riverside Counties, CA, 1980-1986. $PM_{2.5}$ (estimated from visual range). Mean = 32.5.	Study evaluated total, respiratory, cardiovascular, and age > = 65 deaths (mean = 40.7, 3.8, 18.7, and 36.4 per day, respectively). $PM_{2.5}$ estimated based on airport visual range and previously published empirical formula. Autoregressive OLS (for total) and Poisson (for sub-categories) regressions used, adjusting for season (sine/cosine with cycles from 1 yr to 0.75 mo; prefiltering with 15-day moving ave.; dichotomous variables for each year and month; smooth function of day and temp.), day-of-week, temp. and dewpoint. Evaluated lags 0, 1, and 2 of estimated $PM_{2.5}$, as well as moving averages of 2, 3, and 4 days and O_3.	The results were dependent on season. No $PM_{2.5}$ – mortality association found for the full year-round period. Associations between estimated $PM_{2.5}$ (same-day) and total and respiratory deaths found during summer quarters (April - Sept.). Correlation between the estimated $PM_{2.5}$ and daily max temp. was low (r = 0.08) during the summer quarters. Ozone was also associated with mortality, but was also relatively highly correlated with temp. r = 0.73). Moving averages of $PM_{2.5}$ did not improve the associations.	Percent excess deaths per 25 µg/m3 of estimated $PM_{2.5}$, lag 0: Full year: 0.3 (-0.6, 1.2) for total; 2.1 (-0.3, 4.5) for respiratory; and 0.7 (-0.3, 1.7) for circulatory. Summer quarters: 1.6 (0.03, 3.2) for total; 5.5 (1.1, 10.0) for respiratory; and 0 (-1.0, 1.0) for circulatory.
Kelsall et al. (1997). +Philadelphia, PA 1974-1988. TSP (67)	Total, cardiovascular, respiratory, and by-age mortality regressed on TSP, SO_2, NO_2, O_3, and CO, adjusting for temporal trends and weather, using Poisson GAM model.	TSP, SO_2, O_3, and 1-day lagged CO individually showed statistically significant associations with total mortality. No NO_2 associations unless SO_2 or TSP was also considered. The effects of TSP and SO_2 were diminished when both pollutants were included.	Total mortality excess risk: 3.2% (0, 6.1) per 100 $\mu g/m^3$ TSP at 0 day lag.

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Moolgavkar and Luebeck (1996). Philadelphia, PA. 1973-1988. TSP (68)	A critical review paper, with an analysis of total daily mortality for its association with TSP, SO_2, NO_2, and O_3, adjusting for temporal trends, temperature, and also conducting analysis by season, using Poisson GAM model. (Only one non-parametric smoothing terms in GAM models)	RR results presented as figures, and seasonal difference noted. TSP, SO_2, O_3 - mortality associations varied across season. TSP associations were stronger in summer and fall. NO_2 was the most significant predictor.	Total mortality excess risk: ranged 0 (winter) to 4% (summer) per 100 $\mu g/m^3$ TSP at 1 day lag.
Murray and Nelson (2000). Philadelphia, PA, 1973-1990.	Kalman filtering used to estimate hazard function in a state space model. The model framework, which assumes harvesting effect, allows estimation of at-risk population and the effect of changes in air quality on the life expectancy of the at-risk population. The model was first verified by simulation. Combinations of TSP, linear temperature, squared temperature, and interaction of TSP and temperature were considered in six models.	Both TSP and the product of TSP and average temperature are significant, but not together. The size of at-risk population estimated was about 500 people, with its life expectancy between 11.8 to 14.3 days, suggesting that the hazard causing agent making the difference of 2.5 days in the at-risk population.	The coefficients obtained in the models cannot be directly compared to the relative risk per $\mu g/m^3$ PM obtained in other time-series models.
Smith et al. (1999). Birmingham, AL 1985-1988; Chicago (Cook Co.), IL, 1986-1990. PM_{10} median = 45 $\mu g/m^3$ for Birmingham and 37.5 $\mu g/m^3$ for Chicago.	Study evaluated associations between lagged/averaged PM_{10} and non-accidental mortality in two cities. Mortality was square root-transformed in Birmingham data, and log-transformed in Chicago data. Seasonal cycles were modeled using B-splines. Temperature was modeled using piece-wise linear terms with a change point. PM_{10} data were included in the models at lag 0 through 3 and 3-day averages at these lags. Also, to examine the possible existence of a threshold, PM_{10} was modeled using a B-spline representation, and also using parametric threshold model, with the profile log likelihood evaluated at changing threshold points. In addition, the possibility of mortality displacement was examined with a model that attempts to estimate the frail population size through Bayesian techniques using Monte Carlo sampling.	The authors reported that, while significantly positive associations were found in both cities, the results were sensitive to the choice of lags. The PM_{10}-mortality associations were more stable in Chicago (perhaps in part due to sample size). The non-linear estimates of relative risk using B-splines suggest that an increasing effect above 80$\mu g/m^3$ for Birmingham, and above 100 $\mu g/m^3$ for Chicago. The threshold model through examination of log likelihood at various possible threshold levels also suggested similar change points, but not to the extent that could achieve statistical distinctions. The mortality displacement model in Chicago data suggested that the size of the frail population was very small (mean ~765), and the mean lifetime within the frail population short (< 10 days).	Birmingham: 4.8%(t=1.98) per 50$\mu g/m^3$ change in 1 through 3 day lag average of PM_{10}. Chicago: 3.7% (t=3.17) per 50$\mu g/m^3$ change in 0 through 2 day lag average of PM_{10}.

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in µg/m^3.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
United States (cont'd)			
Neas et. al. (1999). Philadelphia. 1973-1980. TSP mean = 77.2.	Total, age over 65, cancer, and cardiovascular deaths analyzed for association with TSP. Conditional logistic regression analysis with case-crossover design conducted. Average values of current and previous days' TSP used. Case period is the 48-hr period ending at midnight on day of death. Control periods are 7, 14, and 21 days before and after the case period. Other covariates included temperature on the previous day, dewpoint on the same day, an indicator for hot days (> 80°F), an indicator for humid days (dewpoint > 66°F), and interaction of same-day temp. and winter season.	In each set of the six control periods, TSP was associated with total mortality. A model with four symmetric reference periods 7 and 14 days around the case period produced a similar result. A model with only two symmetric reference periods of 7 days around the case produced a larger estimate. A larger effect was seen for deaths in persons 65 years of age and for deaths due to pneumonia and to cardiovascular disease. Cancer mortality was not associated with TSP.	Odds Ratio (OR) for all cause mortality per 100 µg/m^3 increase in 48-hr mean TSP was 1.056 (1.027, 1.086). The corresponding number for those aged 65 and over was 1.074 (1.037, 1.111), and 1.063 (1.021, 1.107) for cardiovascular disease.
Schwartz (2000d). +Philadelphia. 1974-1988. TSP. Mean = 70 µg/m^3 for warm season (April through August) and 64 µg/m^3 for cold season.	Total (non-accidental) deaths analyzed. GAM Poisson models adjusting for temperature, dewpoint, day-of-week, and season applied to each of 15 warm and cold seasons. Humidity-corrected extinction coefficient, derived from airport visual range, also considered as explanatory variable. In the second stage, resulting 30 coefficients were regressed on regression coefficients of TSP on SO_2. Results of first stage analysis combined using inverse variance weighting.	When TSP controlled for, no significant association between SO_2 and daily deaths. SO_2 had no association with daily mortality when it was poorly correlated with TSP. In contrast, when SO_2 was controlled for, TSP was more strongly associated with mortality than when it was less correlated with SO_2. However, all of the association between TSP and mortality was explained by its correlation with extinction coefficient.	Total mortality excess risk estimates combined across seasons/years: 9.0 (5.7, 12.5) per 100 µg/m^3 TSP.
Levy et al. (2000). Years vary from study to study ranging between 1973 to 1994. 21 published studies included U.S., Canadian, Mexican, European, Australian, and Chilean cities. PM_{10} levels in the 19 U.S. cities (in some cases TSP were converted to PM_{10} using factor of 0.55) ranged from ~20 to ~60 uµg/m^3.	To determine whether across-study heterogeneity of PM effects could be explained by regional parameters, Levy et al. applied an empirical Bayes meta-analysis to 29 PM estimates from 21 published studies. They considered such city-specific variables as mortality rate, gaseous pollutants regression coefficients, PM_{10} levels, central air conditioning prevalence, heating and cooling degreedays. Several of the studies included were those that used GAM with multiple non-parametric smoothing terms.	Among the city-specific variables, $PM_{2.5}/PM_{10}$ ratio was a significant predictor (larger PM estimates for higher $PM_{2.5}/PM_{10}$ ratios) in the 19 U.S. cities data subsets. While the sulfate data were not available for all the 19 cities, the investigators noted that, based on their analysis of the limited data with sulfate for 10 estimates, the sulfate/PM10 ratio was highly correlated with both the mortality (r = 0.84) and with the $PM_{2.5}/PM_{10}$ ratio (r = 0.70). This indicates that the sulfate/PM_{10} ratio may be even better predictor of regional heterogeneity of PM RR estimates.	The pooled estimate from 19 U.S. cities was 0.70% (0.54, 0.84) per 10 µg/m^3 increase in PM_{10}.

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Canada			
Burnett et al. (1998a).+ 11 Canadian cities. 1980-1991. No PM index data available on consistent daily basis.	Total non-accidental deaths were linked to gaseous air pollutants (NO_2, O_3, SO_2, and CO) using GAM Poisson models adjusting for seasonal cycles, day-of-week, and weather (selected from spline-smoothed functions of temperature, dewpoint, relative humidity with 0, 1, and 2 day lags using forward stepwise procedure). Pollution variables evaluated at 0, 1, 2, and up to 3-day lag averages thereof. No PM index included in analyses because daily PM measurements not available. City-specific models containing all four gaseous pollutants examined. Overall risks computed by averaging risks across cities.	NO_2 had 4.1% increased risk per mean concentration; O_3 had 1.8%; SO_2 had 1.4%, and CO had 0.9% in multiple pollutant regression models. A 0.4% reduction in excess mortality was attributed to achieving a sulfur content of gasoline of 30 ppm in five Canadian cities. Daily PM data for fine and coarse mass and sulfates available on varying (not daily) schedules allowed ecologic comparison of gaseous pollutant risks by mean fine particle indicators mass concentrations.	Found suggestion of weak negative confounding of NO_2 and SO_2 effects with fine particles and weak positive confounding of particle effects with O_3. No quantitative RR or ER estimates reported for PM indicators.
Burnett et al. (2000).* 8 largest Canadian cities. 1986-1996. All city mean PM_{10} 25.9; $PM_{2.5}$ 13.3; $PM_{10\text{-}2.5}$ 12.6; sulfate 2.6.	Total non-accidental deaths linked to PM indices (PM_{10}, $PM_{2.5}$, $PM_{10\text{-}2.5}$, sulfate, 47 elemental component concentrations for fine and coarse fractions) and gaseous air pollutants (NO_2, O_3, SO_2, and CO). Each city's mortality, pollution, and weather variables separately filtered for seasonal trends and day-of-week patterns. The residual series from all the cities then analyzed in a GAM Poisson model. The weather model was selected from spline-smoothed functions of temperature, relative humidity, and maximum change in barometric pressure within a day, with 0 and 1 day lags using forward stepwise procedure. Pollution effects were examined at lags 0 through 5 days. To avoid unstable parameter estimates in multi-pollutant models, principal components were also used as predictors in the regression models.	O_3 was weakly correlated with other pollutants and other pollutants were "moderately" correlated with each other (the highest was r = 0.65 for NO_2 and CO). The strongest association with mortality for all pollutants considered were for 0 or 1 day lags. $PM_{2.5}$ was a stronger predictor of mortality than $PM_{10\text{-}2.5}$. The estimated gaseous pollutant effects were generally reduced by inclusion of $PM_{2.5}$ or PM_{10}, but not $PM_{10\text{-}2.5}$. Sulfate, Fe, Ni, and Zn were most strongly associated with mortality. Total effect of these four components was greater than that for $PM_{2.5}$ mass alone.	Percentage increase in daily filtered non-accidental deaths associated with increases of 50 $\mu g/m^3$ PM_{10} and 25 $\mu g/m^3$ $PM_{2.5}$ or $PM_{10\text{-}2.5}$ at lag 1 day: 3.5 (1.0, 6.0) for PM_{10}; 3.0 (1.1, 5.0) for $PM_{2.5}$; and 1.8 (-0.7, 4.4) for $PM_{10\text{-}2.5}$. In the multiple pollutant model with $PM_{2.5}$, $PM_{10\text{-}2.5}$, and the 4 gaseous pollutants, 1.9 (0.6, 3.2) for $PM_{2.5}$; and 1.2 (-1.3, 3.8) for $PM_{10\text{-}2.5}$.
Burnett and Goldberg (2003). Re-analysis of above study.	Re-analysis of above study using stringent convergence criteria as well as natural splines. In the main model of the original analysis, both dependent and independent variables were pre-filtered, but in the re-analysis, co-adjustment (i.e., more common simultaneous regression) approach was used. Additional sensitivity analysis included alternative fitting criteria and changing the extent of smoothing for temporal trends. Only PM_{10}, $PM_{2.5}$ and $PM_{10\text{-}2.5}$ were analyzed. No multiple pollutant models.	In the GAM model (stringent convergence criteria), inclusion of day-of-week variable made moderate increase in PM coefficients (up to 30%). Alternative fitting criteria and degrees of freedom for temporal trends also changed PM coefficients. Generally, larger the degrees of freedom for temporal trends, smaller the PM coefficients. $PM_{10\text{-}2.5}$ were more sensitive to alternative models than $PM_{2.5}$.	Excess total mortality in the GLM/natural splines with knot/2months, and using AIC and White-noise test fitting criteria at 1-day lag: PM_{10}: 2.7(-0.1, 5.5) per 50 $\mu g/m^3$ $PM_{2.5}$: 2.2(0.1, 4.2) per 25 $\mu g/m^3$ $PM_{10\text{-}2.5}$: 1.8(-0.6, 4.4) per 25 $\mu g/m^3$

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Canada (cont'd)			
Burnett et al. (1998b). + Toronto, 1980-1994. TSP (60); COH (0.42); SO4= (9.2 $\mu g/m^3$); PM_{10} (30, estimated); $PM_{2.5}$ (18, estimated)	Total, cardiac, and other nonaccidental deaths (and by age groups) were regressed on TSP, COH, SO_4=, CO, NO_2, SO_2, O_3, estimated PM_{10} and $PM_{2.5}$ (based on the relationship between the existing every-6th-day data and SO_4=, TSP and COH), adjusting for seasonal cycles, day-of-week, temperature, and dewpoint using Poisson GAM model.	Essentially all pollutants were significant predictors of total deaths in single pollutant models, but in two pollutant models with CO, most pollutants' estimated RRs reduced (all PM indices remained significant). Based on results from the co-pollutant models and various stepwise regressions, authors noted that effects of the complex mixture of air pollutants could be almost completely explained by the levels of CO and TSP.	Total mortality percent excess: 2.3% (0.8, 3.8) per 100 $\mu g/m^3$ TSP; 3.5% (1..8, 5.3) per 50 $\mu g/m^3$ PM_{10}; 4.8% (3.3, 6.4) per 25 $\mu g/m^3$ $PM_{2.5}$. 0 day lag for TSP and PM_{10}; Avg. of 0 and 1 day for $PM_{2.5}$.
Goldberg et al. (2000)* Montreal, Quebec 1984-95 Mean TSP = 53.1 (14.6 - 211.1) $\mu g/m^3$ PM_{10} = 32.2 (6.5 - 120.5) $\mu g/m^3$ $PM_{2.5}$ = 3.3 (0.0 - 30.0) $\mu g/m^3$	Study aimed to shed light on population subgroups that my be susceptible to PM effects. Linked data on daily deaths with other health data from the Quebec Health Insurance Plan (QHIP) (physician visits, pharmaceutical R_x, etc.) to identify individuals with presenting health conditions. PM_{10} and $PM_{2.5}$ measured by dichotomous sampler 1 in 6 days until 1992 (2 stations), then daily through 1993. PM missing days interpolated from COH, ext. coefficient, sulfates. Used quasi likelihood estimation in GAM's to assess PM associations with total and cause-specific mortality; and, also, in subgroups by age and/or preexisting health conditions. Adjusted for CO, NO_2, NO, O_3 and SO_2 in 2-pollutant and all-pollutant models.	Significant associations found for all-cause (total non-accidental) and cause-specific (cancer, CAD, respiratory disease, diabetes) with PM measures. Results reported for $PM_{2.5}$, COH and sulfates. All three PM measures associated with increases in total, resp., and "other nonaccidental", and diabetes-related mortality. No PM associations found with digestive, accidental, renal or neurologic causes of death. Also, mainly in 65+ yr group, found consistent associations with increased total mortality among persons who had cancer, acute lower resp. diseases, any cardiovascular disease, chronic CAD and congestive heart failure (CHF).	Percent excess mortality per 25 $\mu g/m^3$ estimated $PM_{2.5}$: Total deaths (3 d ave.) = 4.4% (2.5, 6.3) CV deaths (3 d ave.) = 2.6% (-0.1, 5.5) Resp deaths (3 d ave.) = 16.0% (9.7, 22.8) Coronary artery (3 d ave.) = 3.4% (-0.2, 7.1) Diabetes (3 d ave.) = 15.7% (4.8, 27.9) Lower Resp Disease (3 d ave.) = 9.7% (4.5, 15.1) Airways disease (3 d ave.) = 2.7% (-0.9, 6.4) CHF (3 d ave.) = 8.2% (3.3, 13.4)
Goldberg et al. (2001b)* Montreal, Quebec. 1984-1993. Predicted $PM_{2.5}$ mean = 17.6. CoH (1000ft) mean = 0.24, sulfate mean = 3.3.	The investigators used the universal Quebec medicare system to obtain disease conditions prior to deaths, and the roles of these respiratory and cardiovascular conditions in the PM-mortality associations were examined. GAM Poisson model adjusting for temporal pattern and weather was used.	The PM-mortality associations were found for those who had acute lower respiratory diseases, chronic coronary diseases, and congestive heart failure. They did not find PM-mortality associations for those chronic upper respiratory diseases, airways disease, cerebrovascular diseases, acute coronary artery diseases, and hypertension. Adjusting for gaseous pollutants generally attenuated PM RR estimates, but the general pattern remained. Effects were larger in summer.	The percent excess deaths estimates for non-accidental deaths per IQR (average of 0-2 day lags) for CoH, predicted $PM_{2.5}$, and sulfate were: 1.98% (1.07, 2.90), 2.17% (1.26, 3.08), and 1.29% (0.68, 1.90), respectively.
Goldberg et al. (2001d). Data same as above.	Cause-specific mortality (non-accidental, neoplasm, lung cancer, cardiovascular, coronary artery disease, diabetes, renal disease, and respiratory) series were examined for their associations with O_3, using GAM Poisson model adjusting for temporal pattern and weather. Results were also reported for models with adjustments for other pollutants (SO_2, CO, NO_2, CoH, etc.).	The effect of O_3 was generally higher in the warm season and among persons aged 65 years and over. O_3 showed positive and statistically significant associations with non-accidental cause, neoplasms, cardiovascular disease, and coronary artery disease. These associations were not reduced when the model adjusted for SO_2, CO, NO_2, CoH simultaneously (or when CoH was replaced with $PM_{2.5}$ or total sulfates).	PM RRs not reported.

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in µg/m^3.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Canada (cont'd)			
Goldberg and Burnett (2003). Re-analysis of above studies by Goldberg et al.	Re-analysis of above study using stringent convergence criteria as well as natural splines. Cause-specific mortality was not re-analyzed; re-analysis was focused only on the sub-groups defined using the QHIP data that showed associations with particles in the original study. Sensitivity analyses included alternative weather models and using different degrees of freedom for temporal trends.	The PM coefficients were not very sensitive to the extent of temporal smoothing but were sensitive to the functional form of weather models. Most of the originally reported associations except for congestive heart failure were highly attenuated when natural splines were used for weather model.	The percent excess deaths estimates for non-accidental deaths per IQR (average of 0-2 day lags) for CoH, predicted $PM_{2.5}$, and sulfate for GAM(stringent convergence criteria) and GLM/natural splines, respectively, were: CoH: 1.38, 0.85; Predicted $PM_{2.5}$: 1.57, 0.55; sulfate: 1.03, 0.27. Confidence bands were not given but the GAM results for predicted $PM_{2.5}$ and sulfate were indicated as significant at 0.05 level.
Özkaynak et al. (1996). Toronto, 1970-1991. TSP (80); COH (0.42 /1000ft).	Total, cardiovascular, COPD, pneumonia, respiratory, cancer, and the remaining mortality series were related to TSP, SO_2, COH, NO_2, O_3, and CO, adjusting for seasonal cycles (by high-pass filtering each series) temperature, humidity, day-of-week, using OLS regression. Factor analysis of multiple pollutants was also conducted to extract automobile related pollution, and mortality series were regressed on the resulting automobile factor scores.	TSP (0 day lag) was significantly associated with total and cardiovascular deaths. NO_2 (0-day lag) was a significant predictor for respiratory and COPD deaths. 2-day lagged O_3 was associated with total, respiratory, and pneumonia deaths. Factor analysis showed factor with high loadings for NO_2, COH, and CO (apparently representing automobile factor) as significant predictor for total, cancer, cardiovascular, respiratory, and pneumonia deaths.	Total mortality excess risk: 2.8% per 100 µg/m^3 TSP at 0 day lag.

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in µg/m^3.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Europe			
Katsouyanni et al. (1997). 12 European (APHEA) cities. 1975-1992 (study years different from city to city). Median Black Smoke (BS) levels ranged from 13 in London to 73 in Athens and Kracow.	Total daily deaths regressed on BS or SO_2 using Poisson GLM models, adjusting for seasonal cycles, day-of-week, influenza epidemic, holidays, temp., humidity. Final analysis done with autoregressive Poisson models to allow for overdispersion and autocorrelation. Pollution effects examined at 0 through 3 day lags and multi-day averages thereof. When city-specific coefficients tested to be homogeneous, overall estimates obtained by computing variance-weighted means of city-specific estimates (fixed effects model). When significant heterogeneity present, source of heterogeneity sought by examining a predefined list of city-specific variables, including annual and seasonal means of pollution and weather variables, number of monitoring sites, correlation between measurements from different sites, age-standardized mortality, proportion of elderly people, smoking prevalence, and geographic difference (north-south, east-west). A random effects model was fit when heterogeneity could not be explained.	Substantial variation in pollution levels (winter mean SO_2 ranged from 30 to 330 µg/m^3), climate, and seasonal patterns were observed across cities. Significant heterogeneity was found for the effects of BS and SO_2, but only the separation between western and central eastern European cities resulted in more homogeneous subgroups. Significant heterogeneity for SO_2 remained in western cities. Cumulative effects of prolonged (two to four days) exposure to air pollutants resulted in estimates comparable with the one day effects. The effects of both SO_2 and BS were stronger during the summer and were independent.	Total mortality excess deaths per 25 µg/m^3 increase in single day BS for western European cities: 1.4 (1.0, 1.8); and 2 (1, 3) per 50 µg/m^3 PM_{10} increase. In central/eastern Europe cities, corresponding figure was 0.3 (0.05, 0.5) per 25 µg/m^3 BS.
Samoli et al. (2001). * APHEA 1 cities (see Katsouyanni (1997). At least five years between 1980-1992. The PM levels are the same as those in Katsouyanni et al. (1997).	In order to further investigate the source of the regional heterogeneity of PM effects, and to examine the sensitivity of the RRs, the APHEA data were re-analyzed by the APHEA investigators themselves (Samoli et al., 2001). Unlike previous model in which sinusoidal terms for seasonal control and polynomial terms for weather, the investigators this time used a GAM model with smoothing terms for seasonal trend and weather, which is more commonly used approach in recent years.	T he estimated relative risks for central-eastern cities were larger than those obtained from the previous model. Also, restricting the analysis to days with concentration < 150 µg/m^3 further reduced the differences between the western and central-eastern European cities. The authors concluded that part of the heterogeneity in the estimated air pollution effects between western and central eastern cities in previous publications was caused by the statistical approach and the data range.	Total mortality RRs per 50 µg/m^3 BS for all cities, western cities, and central-eastern cities using the GAM approach were: 2.5% (2.1, 2.9); 3.1% (2.3, 3.8); and, 2.3% (1.7, 2.9), respectively. In contrast, those with old method were: 1.3% (0.9, 1.7); 2.9% (2.1, 3.7); and, 0.6% (0.1, 1.1), respectively.
Samoli et al. (2003). Re-analysis of above study.	Re-analysis of above study using stringent convergence criteria as well as natural splines.	BS risk estimates using GAM were reduced by ~ 10% when stringent convergence criteria were applied. Use of GLM/natural splines resulted in further and greater reductions.	Results corresponding to above using the GAM with stringent convergence criteria were: 2.3%(1.9, 2.7); 2.7% (2.0, 3.4); and, 2.1% (1.5, 2.7), respectively. Corresponding GLM/natural splines results were: 1.2%(0.7, 1.7); 1.6%(0.8, 2.4); and, 1.0%(0.3, 1.7).

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in µg/m^3.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Europe (cont'd)			
Katsouyanni et al. (2001).* 1990-1997 (variable from city to city). 29 European cities. Median PM_{10} ranged from 14 (Stockholm) to 66 (Prague). Median BS ranged from 10 (Dublin) to 64 (Athens).	The 2nd phase of APHEA (APHEA 2) put emphasis on the effect modification by city-specific factors. The first stage of city specific regressions used GAM Poisson model. The second stage regression analysis was conducted to explain any heterogeneity of air pollution effects using city-specific variables. These city-specific variables included average air pollution levels, average temperature/humidity, age-standardize mortality rate, region indicators, etc.	The authors found several effect modifiers. The cities with higher NO_2 levels showed larger PM effects. The cities with warmer climate showed larger PM effects. The cities with low standardized mortality rate showed larger PM effects.	Total mortality excess risk per 50µg/m3 increase in PM_{10}: Fixed effects model: 3.5(2.9, 4.1) Random effects model: 3.1(2.1, 4.2)
Katsouyanni et al. (2003). Re-analysis of above study.	Re-analysis of above study using stringent convergence criteria as well as natural splines and penalized splines.	The pooled estimate (random effects estimate) was reduced by 4% when stringent convergence criteria in GAM were used, by 34% when natural splines were used, and by 11% when penalized splines were used. The pattern of effect modification originally reported remained the same. The original findings were unchanged.	Total mortality excess risk per 50µg/m3 increase in PM_{10} using GAM (stringent convergence criteria): 3.3(2.7, 3.9) and 3.0(2.0, 4.1) for fixed effects and random effects models, respectively. Corresponding estimates for GLM/natural splines are: 2.1(1.5, 2.8) and 2.1(1.2, 3.0). Using penalized splines, the estimates are 2.9(2.3, 3.6) and 2.8(1.8, 3.8).
Touloumi et al. (1997). 6 European (APHEA) cities. 1977-1992 (study years different from city to city). Median Black Smoke (BS) levels ranged from 14.6 in London to 84.4 in Athens.	Results of the short-term effects of ambient NO_2 and/or O_3 on daily deaths from all causes (excluding accidents) were discussed to provide a basis for comparison with estimated SO_2 or BS effects in APHEA cities. Poisson GLM models, lag/averaging of pollution, and the computation of combined effects across the cities were done in the same way as done by Katsouyanni et al. (1997), as above.	Significant positive associations found between daily deaths and both NO_2 and O_3. Tendency for larger effects of NO_2 in cities with higher levels of BS. When BS included in the model, pooled estimate for O_3 effect only slightly reduced, but coefficient for NO_2 reduced by half. Authors speculated that short-term effects of NO_2 on mortality confounded by other vehicle-derived pollutants.	NO_2 and/or O_3 estimates only.
Zanobetti and Schwartz (2003b). Re-analysis of above study.	Re-analysis of above study using stringent convergence criteria as well as natural splines and penalized splines.	The pooled PM_{10} (average of 0 and 1 day) mortality risk estimate was reduced by 4% when stringent convergence criteria in GAM were used, by 18% when penalized splines were used. For the 4th degree polynomial distributed lag model, corresponding reductions were 10% and 26%.	Combined total mortality excess risk per 50µg/m^3 increase in the average of 0 and 1 day lag PM_{10} was 3.4(2.0, 4.8) using GAM with stringent convergence criteria. For 4th degree polynomial distributed lag model, it was 7.5(4.4, 10.7). Corresponding reductions using penalized splines were 2.9(1.4, 4.4) and 5.6(1.5, 9.8)

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Europe (cont'd)			
Zmirou et al. (1998). 10 European (APHEA) cities. 1977-1992 (study years different from city to city). Median Black Smoke (BS) levels ranged from 13 in London to 73 in Kracow.	Cardiovascular, respiratory, and digestive mortality series in10 European cities analyzed to examine cause-specificity of air pollution. The mortality series were analyzed for associations with PM (BS, except TSP in Milan and Bratislava; PM_{13} in Lyon), NO_2, O_3, and SO_2. Poisson GLM models, lag/averaging of pollution, and computation of combined effects across the cities done in the same way as by Katsouyanni et al. (1997), above.	The cardiovascular and respiratory mortality series were associated with BS and SO_2 in western European cities, but not in the five central European cities. NO_2 did not show consistent mortality associations. RRs for respiratory causes were at least equal to, or greater than those for cardiovascular causes. No pollutant exhibited any association with digestive mortality.	Pooled cardiovascular mortality percent excess deaths per 25 $\mu g/m^3$ increase in BS for western European cities: 1.0 (0.3, 1.7); for respiratory mortality, it was 2.0 (0.8, 3.2) in single lag day models (the lags apparently varied across cities).
Bremner et al. (1999). London, UK, 1992-1994. BS (13), PM_{10} (29).	Total, cardiovascular, and respiratory (by age) mortality series were regressed on PM_{10}, BS, O_3, NO_2, CO, and SO_2, adjusting for seasonal cycles, day-of-week, influenza, holidays, temperature, humidity, and autocorrelation using Poisson GLM model.	All effect size estimates (except O_3) were positive for total deaths (though not significant for single lag models). The effects of O_3 found in 1987-1992 were not replicated, except in cardiovascular deaths. Multiple day averaging (e.g., 0-1, 0-2 days) tend to give more significant effect size estimates. The effect size for PM_{10} and BS were similar for the same distributional increment.	1.9% (0.0, 3.8) per 25 $\mu g/m^3$ BS at lag 1 day; 1.3% (-1.0, 3.6) per 50 $\mu g/m^3$ PM_{10} at lag 1 d for total deaths. Resp. deaths (3 d) = 4.9% (0.5, 9.4). CVD deaths (1 d) = 3.0% (0.3, 5.7).
Prescott et al. (1998). Edinburgh, UK, 1981-1995. PM_{10} (21, by TEOM only for 1992-1995); BS (8.7).	Both mortality (total, cardiovascular, and respiratory) and emergency hospital admissions (cardiovascular and respiratory), in two age groups (<65 and >= 65), were analyzed for their associations with PM_{10}, BS, SO_2, NO_2, O_3, and CO, using Poisson GLM regression adjusting for seasonal cycles, day-of-week, temperature, and wind speed.	Among all the pollutants, BS was most significantly associated with all cause, cardiovascular, and respiratory mortality series. In the subset in which PM_{10} data were available, the RR estimates for BS and PM_{10} for all cause elderly mortality were comparable. Other pollutants' mortality associations were generally inconsistent.	3.8 (1.3, 6.4) per 25 $\mu g/m^3$ increase in BS for all cause mortality in age 65+ group, avg. of 1-3 day lags.
Rooney et al. (1998). England and Wales, and Greater London, UK PM_{10} (56, during the worst heat wave; 39, July-August mean)	Excess deaths, by age, sex , and cause, during the 1995 heat wave were estimated by taking the difference between the deaths during heat wave and the 31-day moving averages (for 1995 and 1993-94 separately). The pollution effects, additively for O_3, PM_{10}, and NO_2, were estimated based on the published season-specific coefficients from the 1987-1992 study (Anderson et al., 1996).	Air pollution levels at all the locations rose during the heat wave. 8.9% and 16.1% excess deaths were estimated for England and Wales, and Greater London, respectively. Of these excess deaths, up to 62% and 38%, respectively for these locations, may be attributable to combined pollution effects.	2.6% increase for PM_{10} in Greater London during heat wave.

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Europe (cont'd)			
Wordley et al. (1997). Birmingham, UK, 1992-1994. PM_{10} (apparently beta-attenuation, 26)	Mortality data were analyzed for COPD, pneumonia, all respiratory diseases, all circulatory diseases, and all causes. Mortality associations with PM_{10} , NO_2, SO_2, and O_3 were examined using OLS (with some health outcomes log- or square-root transformed), adjusting for day-of-week, month, linear trend, temperature and relative humidity. The study also analyzed hospital admission data.	Total, circulatory, and COPD deaths were significantly associated with 1-day lag PM_{10}. The gaseous pollutants "did not have significant associations independent from that of PM_{10}", and the results for gaseous pollutants were not presented. The impact of reducing PM_{10} to below 70 $\mu g/m^3$ was estimated to be "small" (0.2% for total deaths), but the PM_{10} level above 70 $\mu g/m^3$ occurred only once during the study period.	5.6% (0.5, 11.0) per 50 $\mu g/m^3$ PM_{10} at 1 d lag for total deaths. COPD (1 d lag) deaths = 27.6 (5.1, 54.9). Circulatory (1 d) deaths = 8.8 (1.9, 17.1)
Hoek et al. (2000). * The Netherlands, 1986-1994. PM_{10} (median 34); BS (median 10).	Total, cardiovascular, COPD, and pneumonia mortality series were regressed on PM_{10}, BS, sulfate, nitrate, O_3, SO_2, CO, adjusting for seasonal cycles, day-of-week, influenza, temperature, and humidity using Poisson GAM model. Deaths occurring inside and outside hospitals were also examined.	Particulate air pollution was not more consistently associated with mortality than were the gaseous pollutants SO_2 and NO_2. Sulfate, nitrate, and BS were more consistently associated with total mortality than was PM_{10}. The RRs for all pollutants were larger in the summer months than in the winter months.	Total mortality excess risk estimate per 50 $\mu g/m^3$ PM_{10} (average of 0-6 days): 1.2(0.2, 2.2); 0.9(-0.8, 2.7) for CVD; 5.9(0.9, 11.2) for COPD; and 10.1(3.6, 17.1) for pneumonia.
Hoek (2003). Re-analysis of above study.	Re-analysis of above study using stringent convergence criteria and natural splines.	Very little change in PM risk coefficients (often slightly increased) whether GAM with stringent convergence criteria or GLM./natural splines were used.	Total mortality excess risk estimate per 50 $\mu g/m^3$ PM_{10} (average of 0-6 days) using GAM with stringent convergence criteria: 1.4(0.3, 2.6); 0.9(-0.8, 2.7) for CVD; 6.1(1.0, 11.4) for COPD; and 10.3(3.7, 17.2) for pneumonia. Corresponding numbers using GLM/natural splines are: 1.2(-0.1, 2.5); 1.6(-0.3, 3.5); 6.0(0.4, 11.8); 10.7 (3.5, 18.3).
Hoek et al. (2001).* The Netherlands. 1986-1994. PM_{10} (median 34); BS (median 10).	This study of the whole population of the Netherlands, with its large sample size (mean daily total deaths ~ 330, allowed examination of specific cardiovascular cause of deaths. GAM Poisson regression models, adjusting for seasonal cycles, temperature, humidity, day-of-week was used.	Deaths due to heart failure, arrhythmia, cerebrovascular causes, and thrombocytic causes were more strongly (~ 2.5 to 4 times larger relative risks) associated with air pollution than the overall cardiovascular deaths (CVD) or myocardial infarction (MI) and other ischemic heart disease (IHD).	For PM_{10} (7-day mean), RRs for total CVD, MI/IHD, arrhythmia, heart failure, cerebrovascular, and thrombocytic mortality per 50 $\mu g/m^3$ increase were:0.9(-0.8, 2.7), 0.3(-2.3, 3.0), 2.5(-4.3, 9.9), 2.2(-2.5, 7.2), 1.9(-1.8, 5.8), and 0.6(-6.8, 8.7) , respectively. The RRs for BS were larger and more significant than those for PM_{10}.

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Europe (cont'd)			
Hoek (2003). Re-analysis of above study.	Re-analysis of above study using stringent convergence criteria and natural splines.	Very little change in PM risk coefficients (often slightly increased) whether GAM with stringent convergence criteria or GLM./natural splines were used.	For PM_{10} (7-day mean), RRs for total CVD, MI/IHD, arrhythmia, heart failure, cerebrovascular, and thrombocytic mortality per 50 $\mu g/m^3$ increase using GAM with stringent convergence criteria were:0.9(-0.8, 2.7), 0.4(-2.2, 3.0), 2.7(-4.2, 10.1), 2.4(-2.3, 7.4), 2.0(-1.7, 5.9), and 0.7(-6.8, 8.8) , respectively. The RRs for BS were larger and more significant than those for PM_{10}.
Pönkä et al. (1998). Helsinki, Finland, 1987-1993. TSP (median 64); PM_{10} (median 28)	Total and cardiovascular deaths, for age groups < 65 and 65 +, were related to PM_{10}, TSP, SO_2, NO_2, and O_3, using Poisson GLM model adjusting for temperature, relative humidity, day-of-week, temporal patterns, holiday and influenza epidemics.	No pollutant significantly associated with mortality from all cardiovascular or CVD causes in 65+ year age group. Only in age <65 year group, PM_{10} associated with total and CVD deaths with 4 and 5 d lags, respectively. The "significant" lags were rather "spiky". O_3 was also associated with CVD mortality <65 yr. group with inconsistent signs and late and spiky lags (neg. on d 5 and pos. on d 6).	18.8% (5.6, 33.2) per 50 $\mu g/m^3$ PM_{10} 4 day lag (other lags negative or zero).
Peters et al. (2000b). A highly polluted coal basin area in the Czech Republic and a rural area in Germany, northeast Bavaria districts. 1982-1994. TSP: mean = 121.1 and 51.6, respectively, for these two regions. PM_{10} and $PM_{2.5}$ were also measured in the coal basin during 1993-1994 (mean = 65.9 and 51.0, respectively).	Non-accidental total and cardiovascular deaths (mean = 18.2 and 12.0 per day, for the Czech and Bavaria areas, respectively). The APHEA approach (Poisson GLM model with sine/cosine, temperature as a quadratic function, relative humidity, influenza, day-of-week as covariates), as well as GLM with natural splines for temporal trends and weather terms were considered. Logarithm of TSP, SO_2, NO_2, O_3, and CO (and PM_{10} and $PM_{2.5}$ for 1993-1994) were examined at lags 0 through 3 days.	In the coal basin (i.e., the Czech Republic polluted area), on the average, 68% of the TSP was PM_{10}, and most of PM_{10} was $PM_{2.5}$ (75%). For the coal basin, associations were found between the logarithm of TSP and all-cause mortality at lag 1 or 2 days. SO_2 was also associated with all-cause mortality with slightly lower significance. PM_{10} and $PM_{2.5}$ were both associated with all-cause mortality in 1993-1994 with a lag of 1-day. NO_2, O_3 and CO were positively but more weakly associated with mortality than PM indices or SO_2. In the Bavarian region, neither TSP nor SO_2 was associated with mortality, but CO (at lag 1-day) and O_3 (at lag 0-day) were associated with all-cause mortality.	Total mortality excess deaths per 100 $\mu g/m^3$ increase in TSP for the Czech region: 3.8 (0.8, 6.9) at lag 2-day for 1982-1994 period. For period 1993-1994, 9.5 (1.2, 18.5) per 100 $\mu g/m^3$ increase in TSP at lag 1-day, and 4.8 (0.7, 9.0) per 50 $\mu g/m^3$ increase in PM_{10}; and 1.4 (-0.5, 3.4) per 25 $\mu g/m^3$ $PM_{2.5}$.

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Europe (cont'd)			
Hoek et al. (1997). +Rotterdam, the Netherlands, 1983-1991. TSP (median 42); BS (median 13).	Total mortality (also by age group) was regressed on TSP, Fe (from TSP filter), BS, O_3, SO_2, CO, adjusting for seasonal cycles, day-of-week, influenza, temperature, and humidity using Poisson GAM model.	Daily deaths were most consistently associated with TSP. TSP and O_3 effects were "independent" of SO_2 and CO. Total iron (from TSP filter) was associated "less consistently" with mortality than TSP was. The estimated RRs for PM indices were higher in warm season than in cold season.	5.5 (1.1, 9.9) per 100 $\mu g/m^3$ TSP at 1 day lag.
Kotěšovec et al. (2000). Northern Bohemia, Czech Republic, 1982-1994. TSP (121.3).	Total (excluding accidents and children younger than 1 yr), cause specific (cardiovascular and cancer), age (65 and less vs. otherwise), and gender specific mortality series were examined for their associations with TSP and SO_2 using logistic model, adjusting for seasonal cycles, influenza epidemics, linear and quadratic temperature terms. Lags 0 through 6 days, as well as a 7 day mean values were examined.	For the total mortality, TSP, but not SO_2, was associated. There were apparent differences in associations were found between men and women. For example, for age below 65 cardiovascular mortality was associated with TSP for men but not for women.	Total mortality percent excess deaths per 100 $\mu g/m^3$ increase in TSP at 2 day lag was 3.4 (0.5, 6.4).
Zanobetti et al. (2000a). Milan, Italy. 1980-1989. TSP mean = 142.	The focus of this study was to quantify mortality displacement using what they termed "GAM distributed lag models". (smoothing term was fited with Penalized Plines) Non-accidental total deaths were regressed on smooth function of TSP distributed over the same day and the previous 45 days using penalized splines for the smooth terms and seasonal cycles, temperature, humidity, day-of-week, holidays, and influenza epidemics. The mortality displacement was modeled as the initial positive increase, negative rebound (due to depletion), followed by another positive coefficients period, and the sum of the three phases were considered as the total cumulative effect.	TSP was positively associated with mortality up to 13 days, followed by nearly zero coefficients between 14 and 20 days, and then followed by smaller but positive coefficients up to the 45^{th} day (maximum examined). The sum of these coefficients was over three times larger than that for the single-day estimate.	Total mortality percent increase estimates per IQR increase in TSP: 2.2 (1.4, 3.1) for single-day model; 6.7 (3.8, 9.6) for distributed lag model.
Anderson et al. (1996). London, UK, 1987-1992. BS (15)	Total, cardiovascular, and respiratory mortality series were regressed on BS, O_3, NO_2, and SO_2, adjusting for seasonal cycles, day-of-week, influenza, holidays, temperature, humidity, and autocorrelation using Poisson GLM model.	Both O_3 (0 day lag) and BS (1 day lag) were significant predictors of total deaths. O_3 was also positively significantly associated with respiratory and cardiovascular deaths. The effect size estimates per the same distributional increment (10% to 90%) were larger for O_3 than for BS. These effects were larger in warm season. SO_2 and NO_2 were not consistently associated with mortality.	2.8% (1.4, 4.3) per 25 $\mu g/m^3$ BS at 1-d lag for total deaths. CVD (1 d) = 1.0 (-1.1, 3.1). Resp. (1 d) = 1.1 (-2.7, 5.0).

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Europe (cont'd)			
Michelozzi et al. (1998) +Rome, Italy, 1992-1995. TSP ("PM_{13}" beta attenuation, 84).	Total mortality was related to PM_{13}, SO_2, NO_2, CO, and O_3, using Poisson GAM model , adjusting for seasonal cycles, temperature, humidity, day-of-week, and holiday. Analysis of mortality by place of residence, by season, age, place of death (in or out of hospital), and cause was also conducted.	PM_{13} and NO_2 were most consistently associated with mortality. CO and O_3 coefficients were positive, SO_2 coefficients negative. RR estimates higher in the warmer season. RRs similar for in- and out-of hospital deaths.	1.9% (0.5, 3.4) per 50 $\mu g/m^3$ PM_{13} at 0 day lag.
Garcia-Aymerich et al. (2000). Barcelona, Spain. 1985-1989. Black Smoke no data distribution was reported).	Daily total (mean = 1.8/day), respiratory, and cardiovascular mortality counts of a cohort (9,987 people) with COPD or asthma were associated with black smoke (24-hr), SO_2 (24-hr and 1-hr max), NO_2 (24-hr and 1-hr max), O_3 (1-hr max), temperature, and relative humidity. Poisson GLM regression models using APHEA protocol were used. The resulting RRs were compared with those of the general population.	Daily mortality in COPD patients was associated with all six pollution indices. This association was stronger than in the general population only for daily 1-hr max of SO_2, daily 1-hr max and daily means of NO_2. BS and daily means of SO_2 showed similar or weaker associations for COPD patients than for the general population.	Total mortality percent increase per 25 $\mu g/m^3$ increase in avg. of 0-3 day lags of BS: 2.76 (1.31, 4.23) in general population, and 1.14 (-4.4, 6.98) in the COPD cohort.
Rahlenbeck and Kahl (1996). East Berlin, 1981-1989. "SP" (beta attenuation, 97)	Total mortality (as well as deviations from long-wave cycles) was regressed (OLS) on SP and SO_2, adjusting for day-of-week, month, year, temperature, and relative humidity, using OLS, with options to log-transform pollution, and w/ and w/o days with pollution above 150 $\mu g/m^3$.	Both SP and SO_2 were significantly associated with total mortality with 2 day lag in single pollutant model. When both pollutants were included, their coefficients were reduced by 33% and 46% for SP and SO_2, respectively.	6.1% per 100 $\mu g/m^3$ "SP" at 2 day lag.
Rossi et al. (1999) + Milan, Italy, 1980-1989 TSP ("PM_{13}" beta attenuation, 142)	Specific causes of death (respiratory, respiratory infections, COPD, circulatory, cardiac, heart failure, and myocardial infarction) were related to TSP, SO_2, and NO_2, adjusting for seasonal cycles, temperature, and humidity, using Poisson GAM model.	All three pollutants were associated with all cause mortality. Cause-specific analysis was conducted for TSP only. Respiratory infection and heart failure deaths were both associated with TSP on the concurrent day, whereas the associations for myocardial infarction and COPD deaths were found for the average of 3 to 4 day prior TSP.	3.3% (2.4, 4.3) per 100 $\mu g/m^3$ TSP at 0 day lag.
Sunyer et al. (2000). Barcelona, Spain. 1990-1995. BS means: 43.9 for case period, and 43.1 for control period.	Those over age 35 who sought emergency room services for COPD exacerbation during 1985-1989 and died during 1990-1995 were included in analysis. Total, respiratory, and cardiovascular deaths were analyzed using a conditional logistic regression analysis with a case-crossover design, adjusting for temperature, relative humidity, and influenza epidemics. Bi-directional control period at 7 days was used. Average of the same and previous 2 days used for pollution exposure period. Data also stratified by potential effect modifiers (e.g., age, gender, severity and number of ER visits, etc.).	BS levels were associated with all cause deaths. The association was stronger for respiratory causes. Older women, patients admitted to intensive care units, and patients with a higher rate of ER visits were at greater risk of deaths associated with BS.	Percent increase per 25 $\mu g/m^3$ increase in 3-day average BS: 14.2 (1.6, 28.4) for all causes; 9.7 (-10.2, 34.1) for cardiovascular deaths; 23.2 (3.0, 47.4) for respiratory deaths.

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in µg/m^3.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Europe (cont'd)			
Sunyer and Basagana (2001). Barcelona, Spain. 1990-1995. See Sunyer et al. (2000) for PM levels.	The analysis assessed any "independent" particle effects, after controlling for gaseous pollutants, on a cohort of patients with COPD (see the summary description for Sunyer et al. (2000) for analytical approach). PM_{10}, NO_2, O_3, and CO were analyzed.	PM_{10}, but not gaseous pollutants were associated with mortality for all causes. In the two-pollutant models, the PM_{10}-mortality associations were not diminished, whereas those with gaseous pollutants were.	Odds ratio for all cause mortality per IQR PM_{10} on the same-day (27 µg/m^3) was 11% (0, 24). In two pollutant models, the PM_{10} RRs were 10.5%, 12.9%, and 10.8% with NO_2, O_3, and CO, respectively.
Tobias and Campbell (1999). Barcelona, Spain. 1991-1995. Black Smoke (BS) (no data distribution was reported).	Study examined the sensitivity of estimated total mortality effects of BS to different approaches to modeling influenza epidemics: (1) with a single dummy variable; (2) with three dummy variables; (3) using daily number of cases of influenza. Poisson GLM regression used to model total daily mortality, adjusting for weather, long-term trend, and season, apparently following APHEA protocol.	Using the reported daily number of influenza cases resulted in a better fit (i.e., a lower AIC) than those using dummy variables. In the "better" model, the black smoke coefficient was about 10% smaller than those in the models with dummy influenza variables, but remained significant. Lags not reported.	Total mortality excess deaths per 25 µg/m^3 increase in BS: 1.37 (0.20, 2.56) for model using the daily case of influenza; 1.71 (0.53, 2.91) for model with three influenza dummy variables.
Alberdi Odriozola et al. (1998). Madrid, Spain, 1986-1992. "TSP" (beta attenuation, 47 for average of 2 stations)	Total, respiratory, and cardiovascular deaths were related to TSP and SO_2. Multivariate autoregressive integrated moving average models used to adjust for season, temperature, relative humidity, and influenza epidemics.	TSP (1-day lag) and SO_2 (3-day lagged) were independently associated with mortality.	4.8% (1.8, 7.7) per 100 µg/m^3 TSP at lag 1 day.
Díaz et al. (1999). Madrid, Spain. 1990-1992. TSP (no data distribution was reported).	Non-accidental, respiratory, and cardiovascular deaths (mean = 62.4, 6.3, and 23.8 per day, respectively). Auto-regressive Integrated Moving Average (ARIMA) models fit to both depend and independ. variables first to remove auto-correlation and seasonality (i.e., pre-whitening"), followed by examining cross-correlation to find optimal lags. Multivariate OLS models thus included ARIMA components, seasonal cycles (sine/cosine), V-shaped temp., and optimal lags found for pollution and weather variables. TSP, SO_2, NO_2, and O_3 examined. Season-specific analyses also conducted.	TSP was significantly associated with non-accidental mortality at lag 0 for year around and winter, but with a 1-day lag in summer. A similar pattern was seen for circulatory deaths. For respiratory mortality, a significant association with TSP was found only in summer (0-day lag). SO_2, NOx, and NO_2 showed similar associations with non-accidental deaths at lag 0 day. O_3' associations with non-accidental mortality was U-shaped, with inconsistent lags (1, 4, and 10).	For non-accidental mortality, excess deaths was 7.4% (confidence bands not reported; $p < 0.05$) per 100 µg/m^3 TSP at 0 day lag.

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in µg/m^3.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Europe (cont'd)			
Wichmann et al., (2000) *Erfurt, Germany. 1995-1998. Number counts (NC) & mass concentrations (MC) of ultrafine particles in three size classes, 0.01 to 0.1 m, and fine particles in three size classes from 0.1 to 2.5 m diameter, using Spectrometryll Mobile Aerosol Spectrometry (MAS). MAS MC PM2.5-0.01 (mean 25.8, median 18.8, IQR 19.9). Filter measurements of PM_{10} (mean 38.2, median 31.0, IQR 27.7) and $PM_{2.5}$ (mean 26.3, median 20.2, IQR 18.5). MAS NC2.5-0.01 (mean 17,966 per cu.cm, median 14,769, IQR 13,269).	Total non-accidental, cardiovascular, and respiratory deaths (mean 4.88, 2.87, 1.08 per day, respectively) were related to particle mass concentration and number counts in each size class, and to mass concentrations of gaseous co-pollutants NO_2, CO, SO_2, using GAM regression models adjusted for temporal trends, day of week, weekly national influenza rates, temperature and relative humidity. Data analyzed by season, age group, and cause of death separately. Single-day lags and polynomial distributed lag models (PDL) used. Particle indices and pollutants fitted using linear, log-transformed, and LOESS transformations. Two-pollutant models with a particle index and a gaseous pollutant were fitted. The "best" model as used by Wichmann et al. (2000) was that having the highest t-statistic, since other criteria (e.g., log-likelihood for nested models) and AIC for non-nested models could not be applied due to different numbers of observations in each model. There should be little difference between these approaches and resulting differences in results should be small in practice. Sensitivity analyses included stratifying data by season, winter year, age, cause of death, or transformation of the pollution variable (none, logarithmic, non-parametric smooth).	Loss of stat. power by using a small city with a small number of deaths was offset by advantage of having good exposure representation from single monitoring site. Since ultrafine particles can coagulate into larger aggregates in a few hours, ultrafine particle size and numbers can increase into the fine particle category, resulting in some ambiguity. Significant associations were found between mortality and ultrafine particle number concentration (NC), ultrafine particle mass concentration (MC), fine particle mass concentration, or SO_2 concentration. The correlation between MC0.01-2.5 and NC0.01-0.1 is only moderate, suggesting it may be possible to partially separate effects of ultrafine and fine particles. The most predictive single-day effects are either immediate (lag 0 or 1) or delayed (lag 4 or 5 days), but cumulative effects characterized by PDL are larger than single-day effects. The significance of SO_2 is robust, but hard to explain as a true causal factor since its concentrations are very low. Age is an important modifying factor, with larger effects at ages < 70 than ≥ 70 years. Respiratory mortality has a higher RR than cardio-vascular mortality. A large number of models were fitted, with some significant findings of association between mortality and particle mass or number indices.	Total mortality excess deaths: Filter PM_{10} (0-4 d lag) = 6.6 (0.7, 12.8) per 50 µg/m^3. Filter $PM_{2.5}$ (0-1 d) = 3.0 (-1.7, 7.9). MC for $PM_{0.01-2.5}$ 6.2% (1.4, 11.2) for all year; by season, Winter = 9.2% (3.0, 15.7) Spring = 5.2% (-2.0, 12.8) Summer = -4.7% (-18.7, 11.7) Fall = 9.7% (1.9, 18.1) For ultrafine PM, NC 0.01-0.1 (0-4 d lag): All Year = 8.2% (0.3, 16.9) Winter = 9.7% (0.3, 19.9) Spring = 10.5% (-1.4, 23.9) Summer = -13.9% (-29.8, 5.7) Fall = 12.0% (2.1, 22.7) Best single-day lag: $PM_{0.01-0.1}$ per 25 µg/m^3: 3.6(-0.4, 7.7) $PM_{0.01-2.5}$ per 25 µg/m^3: 3.9(0.0, 8.0) $PM_{2.5}$ per 25 µg/m^3: -4.0(-7.9, 0) PM_{10} per 25 µg/m^3: 6.4(0.3, 12.9)
Stolzel et al. (2003). Re-analysis of above study.	Re-analysis of above study using GAM with stringent convergence criteria as well as GLM/natural splines. The polynomial distributed lag model was not re-analyzed.	Very little change in PM risk coefficients when GAM models with stringent convergence criteria were used. When GLM./natural splines were used, many of the coefficients for number concentrations slightly increased, but the coefficients for mass concentrations decreased slightly.	Best single-day lag using GAM (stringent): $PM_{0.01-0.1}$ per 25 µg/m^3: 3.6(-0.4, 7.7) $PM_{0.01-2.5}$ per 25 µg/m^3: 3.8(-0.1, 7.8) $PM_{2.5}$ per 25 µg/m^3: -4.0(-7.8, -0.1) PM_{10} per 25 µg/m^3: 6.2(0.1, 12.7) Best single-day lag using GLM/natural splines: $PM_{0.01-0.1}$ per 25 µg/m^3: 3.1(-1.6, 7.9) $PM_{0.01-2.5}$ per 25 µg/m^3: 3.7(-0.9, 8.4) $PM_{2.5}$ per 25 µg/m^3: -3.4(-7.9, 1.4) PM_{10} per 25 µg/m^3: 5.3(-1.8, 12.9)

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in µg/m^3.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Europe (cont'd)			
Zeghnoun et al. (2001). +Rouen and Le Havre, France. 1990-1995. PM_{13} mean = 32.9 for Rouen, 36.4 for Le Havre. BS mean = 18.7 for Rouen, 16.3 for Le Havre.	Total, cardiovascular, and respiratory mortality series were regressed on BS, PM_{13}, SO_2, NO_2, and O_3 in 1- and 2-pollutant models using GAM Poisson models adjusting for seasonal trends, day-of-week, and weather.	In Rouen, O_3, SO_2, and NO_2 were each significantly associated with total, respiratory, and cardiovascular mortality, respectively. In Le Havre, SO_2 and PM_{13} were associated with cardiovascular mortality. However, the lack of statistical significance reported for most of these results may be in part due to the relatively small population size of these cities (430,000 and 260,000, respectively).	PM_{13} total mortality RRs per IQR were 0.5% (-1.1, 2.1) in Rouen (IQR=20.6, 1-day lag) and 1.9% (-0.8, 7.4) in Le Havre (IQR=23.9, 1-day lag). BS total mortality RRs per IQR were 0.5% (-1.8, 2.9) in Rouen (IQR=14.2, 1-day lag) and 0.3% (-1.6, 2.2) in Le Havre (IQR=11.5, 0-1 day lag avg.).
Roemer and Van Wijnen (2001). + Amsterdam. 1987-1998. BS and PM_{10} means in "background" = 10 and 39; BS mean in "traffic" area = 21. (No PM_{10} measurements available at traffic sites)	Daily deaths for those who lived along roads with more than 10,000 motor vehicle, as well as deaths for total population, were analyzed using data from background and traffic monitors. Poisson GAM model was used adjusting for season, day-of-week, and weather. BS, PM_{10}, SO_2, NO_2, CO, and O3 were analyzed.	Correlations between the background monitors and traffic monitors were moderate for BS (r = 0.55) but higher for NO_2 (r = 0.79) and O_3 (r = 0.80). BS and NO_2 were associated with mortality in both total and traffic population. Estimated RR for traffic population using background sites was larger than the RR for total population using background sites. The RR for total pop. using traffic sites was smaller that RRs for total population using background sites. This is not surprising since the mean BS for traffic sites were larger that for background sites.	The RRs per 100 µg/m^3 BS (at lag 1-day) were 1.383 (1.153, 1.659), 1.887 (1.207, 2.949), and 1.122 (1.023, 1.231) for total population using background sites, traffic population using background sites, and total population using traffic sites, respectively. Results for traffic pop. using traffic sites not reported)
Anderson et al. (2001). +The west Midlands conurbation, UK. 1994-1996. PM means: PM_{10} = 23, $PM_{2.5}$ = 15, $PM_{10\text{-}2.5}$ = 9, BS = 13.2, sulfate = 3.7.	Non-accidental cause, cardiovascular, and respiratory mortality (as well as hospital admissions) were analyzed for their associations with PM indices and gaseous pollutants using GAM Poisson models adjusting for seasonal cycles, day-of-week, and weather.	Daily non-accidental mortality was not associated with PM indices or gaseous pollutants in the all-year analysis. However, all the PM indices (except coarse particles) were positively and significantly associated with non-accidental mortality (age over 65) in the warm season. Of gaseous pollutants, NO_2 and O_3 were positively and significantly associated with non-accidental mortality in warm season. Two pollutant models were not considered because "so few associations were found".	Percent excess mortality for PM_{10}, $PM_{2.5}$, and $PM_{10\text{-}2.5}$ (avg. lag 0 and 1 days) were 0.2% (-1.8, 2.2) per 24.4 uµg/m^3 PM_{10}, 0.6% (-1.5, 2.7) per 17.7 uµg/m^3 $PM_{2.5}$, and –0.6% (-4.2, 2.3) per 11.3 uµg/m^3 $PM_{10\text{-}2.5}$ in all-year analysis. The results for season specific analysis were given only as figures.
Keatinge and Donaldson (2001). Greater London, England, 1976-1995. BS mean = 17.7.	The study examined potential confounding effects of atypical cold weather on air pollution/mortality relationships. First, air pollution variables (SO_2, CO and BS) were modeled as a function of lagged weather variables These variables were deseasonalized by regressing on seine and cosine variables. Mortality regression (OLS) included various lagged and averaged weather and pollution variables. Analyses were conducted in the linear range of mortality/temperature relationship (15 to 0 degrees C).	Polluted days were found to be colder and less windy and rainy than usual. In the regression of mortality on the multiple-lagged temperature, wind, rain, humidity, sumshine, SO_2, CO, and BS, cold temperature was associated with mortality increase, but not SO_2 or CO. BS suggestive evidence, though not statistically significant, of association at 0- and 1-day lag.	3% (95% CI not reported) increase in daily mortality per 17.7 µg/m^3 of BS (lag 0 and 1).

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Latin America			
Cifuentes et al. (2000).+ Santiago, Chile. 1988-1996. $PM_{2.5}$ (64.0), and $PM_{10\text{-}2.5}$ (47.3).	Non-accidental total deaths (56.6 per day) were examined for associations with $PM_{2.5}$, $PM_{10\text{-}2.5}$, O_3, CO, SO_2, and NO_2. Data analyzed using GAM Poisson regression models, adjusting for temperature, seasonal cycles. Single and two pollutant models with lag days from 0 to 5, as well as the 2- to 5-day average concentrations evaluated. They also reported results for comparable GLM model.	Both PM size fractions associated with mortality, but different effects found for warmer and colder months. $PM_{2.5}$ and $PM_{10\text{-}2.5}$ both important in whole year, winter, and summer. In summer, $PM_{10\text{-}2.5}$ had largest effect size estimate. NO_2 and CO also associated with mortality, as was O_3 in warmer months. No consistent SO_2-mortality associations.	Percent excess total deaths per 25 $\mu g/m^3$ increase in the average of previous two days for the whole year: 1.8 (1.3, 2.4) for $PM_{2.5}$ and 2.3 (1.4, 3.2) for $PM_{10\text{-}2.5}$ in single pollutant GAM models. In GLM models (whole year only), 1.4 (0.6, 2.1) for $PM_{2.5}$ and 1.6 (0.2, 3.0) for $PM_{10\text{-}2.5}$
Castillejos et al. (2000). Mexico City. 1992-1995. PM_{10} (44.6), $PM_{2.5}$ (27.4), and $PM_{10\text{-}2.5}$ (17.2).	Non-accidental total deaths, deaths for age 65 and over, and cause-specific (cardiac, respiratory, and the other remaining) deaths were examined for their associations with PM_{10}, $PM_{2.5}$, $PM_{10\text{-}2.5}$, O_3, and NO_2. Data were analyzed using GAM Poisson regression model (only one non-parametric smoothing term), adjusting for temperature (average of 1-3 day lags) and seasonal cycles. Individual pollution lag days from 0 to 5, and average concentrations of previous 5 days were considered.	All three particle size fractions were associated individually with mortality. The effect size estimate was largest for $PM_{10\text{-}2.5}$. The effect size estimate was stronger for respiratory causes than for total, cardiovascular, or other causes of death. The results were not sensitive to additions of O_3 and NO_2. In the model with simultaneous inclusion of $PM_{2.5}$ and $PM_{10\text{-}2.5}$, the effect size for $PM_{10\text{-}2.5}$ remained about the same, but the effect size for $PM_{2.5}$ became negligible.	Total mortality percent increase estimates per increase for average of previous 5 days: 9.5 (5.0, 14.2) for 50 $\mu g/m^3$ PM_{10}; 3.7 (0, 7.6) for 25 $\mu g/m^3$ $PM_{2.5}$; and 10.5 (6.4, 14.8) for 25 $\mu g/m^3$ $PM_{10\text{-}2.5}$.
Loomis et al. (1999). Mexico-City, 1993-1995. $PM_{2.5}$ (mean: 27.4 $\mu g/m^3$)	Infant mortality (avg. 3/day) related to $PM_{2.5}$, O_3, and NO_2, adjusting for temperature and smoothed time, using Poisson GAM model (same model as above, with only one non-parametric smoothing term)	Excess infant mortality associated with $PM_{2.5}$, NO_2, and O_3 in the same average/lags. NO_2 and O_3 associations less consistent in multi-pollutant models.	Infant mortality excess risk: 18.2% (6.4, 30.7) per 25 $\mu g/m^3$ $PM_{2.5}$ at avg. 3-5 lag days.
Borja-Aburto et al. (1998). Mexico-City, 1993-1995. $PM_{2.5}$ (mean: 27)	Total, respiratory, cardiovascular, other deaths, and age-specific (age >= 65) deaths were related to $PM_{2.5}$, O_3, and NO_2, adjusting for 3-day lagged temperature and smoothing splines for temporal trend, using Poisson GAM model (only one non-parametric smoothing term).	$PM_{2.5}$, O_3, and NO_2 were associated with mortality with different lag/averaging periods (1 and 4 day lags; 1-2 avg.; 1-5 avg., respectively). $PM_{2.5}$ associations were most consistently significant. SO_2 was available, but not analyzed because of its "low" levels.	For total excess deaths, 3.4% (0.4, 6.4) per 25 $\mu g/m^3$ $PM_{2.5}$ for both 0 and 4 d lags. For respiratory (4 d) = 6.4 (-2.6, 16.2); for CVD (4 d) = 5.6 (-0.1, 11.5)
Borja-Aburto et al. (1997). Mexico-City, 1990-1992. TSP (median: 204)	Total, respiratory, cardiovascular, and age-specific (age > = 65) deaths were related to O_3, TSP, and CO, adjusting for minimum temperature (temperature also fitted seasonal cycles) using Poisson GLM models. The final models were estimated using the iteratively weighted and filtered least squares method to account for overdispersion and autocorrelation.	O_3, SO_2, and TSP were all associated with total mortality in separate models, but in multiple pollutant model, only TSP remained associated with mortality. CO association weak.	Total deaths: 6% (3.3, 8.3) per 100 $\mu g/m^3$ TSP at 0 d lag. CVD deaths: 5.2% (0.9, 9.9). Resp. deaths: 9.5% (1.3, 18.4).

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in µg/m^3.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Latin America (cont'd)			
Tellez-Rojo et al. (2000). Mexico City. 1994. PM10 mean = 75.1.	One year of daily total respiratory and COPD mortality series were analyzed for their associations with PM_{10} and O3 using Poisson GLM model adjusting for cold or warm months, and 1-day lagged minimum temperature. The data were stratified by the place of deaths.	The average number of daily respiratory deaths, as well as that of COPD deaths, was similar for in and out of hospital. They found that the estimated PM_{10} relative risks were consistently larger for the deaths that occurred outside medical units. The results are apparently consistent with the assumption that the extent of exposure misclassification may be smaller for those who died outside medical units.	Percent excess for total respiratory and COPD mortality were 2.9% (0.9, 4.9) and 4.1% (1.3, 6.9) per 10 uµg/m^3 increase in 3-day lag PM_{10},
Pereira et al. (1998). Sao Paulo, Brazil, 1991-1992. PM_{10} (beta-attenuation, 65)	Intrauterine mortality associations with PM_{10}, NO_2, SO_2, CO, and O_3 investigated using Poisson GLM regression adjusting for season and weather. Ambient CO association with blood carboxyhemoglobin sampled from umbilical cords of non-smoking pregnant mothers studied in separate time period.	NO_2, SO_2, and CO were all individually significant predictor of the intrauterine mortality. NO_2 was most significant in multi-pollutant model. PM_{10} and O_3 were not significantly associated with the mortality. Ambient CO levels were associated with and carboxyhemoglobin of blood sampled from the umbilical cords.	Intrauterine mortality excess risk: 4.1% (-1.8, 10.4) per 50 µg/m^3 PM_{10} at 0 day lag.
Gouveia and Fletcher (2000). Sao Paulo, Brazil. 1991-1993. PM_{10} mean = 64.3.	All non-accidental causes, cardiovascular, and respiratory mortality were analyzed for their associations with air pollution (PM_{10}, SO_2, NO_2, O_3, and CO) using Poisson GLM model adjusting for trend, seasonal cycles, and weather. Potential roles of age and socio-economic status were examined by stratifying data by these factors.	There was an apparent effect modification by age categories. Estimated PM_{10} effects were higher for deaths above age 65 (highest for the age 85+ category), and no associations were found in age group < 65 years. Respiratory excess deaths were larger than those for cardiovascular or non-accidental deaths. Other pollutants were also associated with the elderly mortality.	Percent excess for total non-accidental, cardiovascular, and respiratory mortality for those with age > 65 were 3.3% (0.6, 6.0), 3.8% (0.1, 7.6), and 6.0 (0.5, 11.8), respectively, per 64.2 uµg/m^3 increase in PM_{10} (0-, 0-, and 1-day lag, respectively).
Conceição et al. (2001) +Sao Paulo, Brazil. 1994-1997. PM_{10} mean = 66.2	Daily respiratory deaths for children under 5 years of age were analyzed for their associations with air pollution (PM_{10}, SO_2, O_3, and CO) using GAM Poisson model adjusting for seasonal cycles and weather.	Significant mortality associations were found for CO, SO_2, and PM_{10} in single pollutant models. When all the pollutants were included, PM_{10} coefficient became negative and non-significant.	Percent excess for child (age < 5) respiratory deaths: 9.7% (1.5, 18.6) per 66.2 µg/m^3 PM_{10} (2-day lag) in single pollutant model.

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Australia			
Morgan et al. (1998). Sydney, 1989-1993. Nephelometer (0.30 bscat/104m). Site-specific conversion: $PM_{2.5}$ 9; PM_{10} 18	Total, cardiovascular, and respiratory deaths were related to PM (nephelometer), O_3, and NO_2, adjusting for seasonal cycles, day-of-week, temperature, dewpoint, holidays, and influenza, using Poisson GEE model to adjust for autocorrelation.	PM, O_3, and NO_2 all showed significant associations with total mortality in single pollutant models. In multiple pollutant models, the PM and O_3 effect estimates for total and cardiovascular deaths were marginally reduced, but the PM effect estimate for respiratory deaths was substantially reduced.	4.7% (1.6, 8.0) per 25 $\mu g/m^3$ estimated $PM_{2.5}$ or 50 $\mu g/m^3$ estimated PM_{10} at avg. of 0 and 1 day lags. (Note: converted from nephelometry data)
Simpson et al. (1997). Brisbane, 1987-1993. PM_{10} (27, not used in analysis). Nephelometer (0.26 bscat/104m, size range: 0.01-2 m).	Total, cardiovascular, and respiratory deaths (also by age group) were related to PM (nephelometer), O_3, SO_2, and NO_2, adjusting for seasonal cycles, day-of-week, temperature, dewpoint, holidays, and influenza, using Poisson GEE model to adjust for autocorrelation. Season-specific (warm and cold) analyses were also conducted.	Same-day PM and O_3 were associated most significantly with total deaths. The O_3 effect size estimates for cardiovascular and respiratory deaths were consistently positive (though not significant), and larger in summer. PM's effect size estimates were comparable for warm and cold season for cardiovascular deaths, but larger in warm season for respiratory deaths. NO_2 and SO_2 were not associated with mortality.	3.4% (0.4, 6.4) per 25 $\mu g/m^3$ 1-h $PM_{2.5}$ increment at 0 d lag; and 7.8% (2.5, 13.2) per 25 $\mu g/m^3$ 24-h $PM_{2.5}$ increment.
Asia			
Hong et al. (1999) +Inchon, South Korea, 1995-1996 (20 months). PM_{10} mean = 71.2.	Non-accidental total deaths, cardiovascular, and respiratory deaths were examined for their associations with PM_{10}, O_3, SO_2, CO, and NO_2. Data were analyzed using GAM Poisson regression models, adjusting for temperature, relative humidity, and seasonal cycles. Individual pollution lag days from 0 to 5, as well as the average concentrations of previous 5 days were considered.	A greater association with mortality was seen with the 5-day moving average and the previous day's exposure than other lag/averaging time. In the models that included a 5-day moving average of one or multiple pollutants, PM_{10} was a significant predictor of total mortality, but gaseous pollutants were not significant. PM_{10} was also a significant predictor of cardiovascular and respiratory mortality.	Percent excess deaths (t-ratio) per 50 $\mu g/m^3$ increase in the 5-day moving average of PM_{10}: 4.1 (0.1, 8.2) for total deaths; 5.1 (0.1, 10.4) for cardiovascular deaths; 14.4 (-3.2, 35.2) for respiratory deaths.
Lee et al. (1999). Seoul and Ulsan, Korea, 1991-1995. TSP (beta attenuation, 93 for Seoul and 72 for Ulsan)	Total mortality series was examined for its association with TSP, SO_2, and O_3, in Poisson GEE (exchangeable correlation for days in the same year), adjusting for season, temperature, and humidity.	All the pollutants were significant predictors of mortality in single pollutant models. TSP was not significant in multiple pollutant models, but SO_2 and O_3 remained significant.	5.1% (3.1, 7.2) for Seoul, and -0.1% (-3.9, 3.9) for Ulsan, per 100 $\mu g/m^3$ TSP at avg. of 0, 1, and 2 day lags.
Lee and Schwartz (1999). Seoul, Korea. 1991-1995. TSP mean = $9_{2.5}$.	Total deaths were analyzed for their association with TSP, SO_2, and O_3. A conditional logistic regression analysis with a case-crossover design was conducted. Three-day moving average values (current and two past days) of TSP and SO_2, and 1-hr max O_3 were analyzed separately. The control periods are 7 and 14 days before and/or after the case period. Both unidirectional and bi-directional controls (7 or 7 and 14 days) were examined, resulting in six sets of control selection schemes. Other covariates included temperature and relative humidity.	Among the six control periods, the two unidirectional retrospective control schemes resulted in odds ratios less than 1; the two unidirectional prospective control schemes resulted in larger odds ratios (e.g., 1.4 for 50 ppb increase in SO_2); and bi-directional control schemes resulted in odds ratios between those for uni-directional schemes. SO_2 was more significantly associated with mortality than TSP.	OR for non-accidental mortality per 100 $\mu g/m^3$ increase in 3-day average TSP was 1.010 (0.988, 1.032).

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in μg/m^3.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Asia (cont'd)			
Xu et al. (2000). Shenyang, China, 1992. TSP (430).	Total (non-accidental), CVD, COPD, cancer and other deaths examined for their associations with TSP and SO_2,using Poisson (GAM, and Markov approach to adjust for mortality serial dependence) models, adjusting for seasonal cycles, Sunday indicator, quintiles of temp. and humidity. Ave. pollution values of concurrent and 3 preceding days used. While GAM models were used in the process, the risk estimates presented were for a fully parametric model (i.e., GLM).	Total deaths were associated with TSP and SO_2 in both single and two pollutant models. TSP was significantly associated with CVD deaths, but not with COPD. SO_2 significantly associated with COPD, but not with CVD deaths. Cancer deaths not associated with TSP or SO_2.	Percent total excess deaths per 100 μg/m^3 increase in 0-3 day ave. of TSP = 1.75 (0.65, 2.85); with SO_2 = 1.31 (0.14, 2.49) COPD TSP = 2.6 (-0.58, 5.89); with SO_2 = 0.76 (-2.46, 4.10). CVD TSP = 2.15 (0.56, 3.71); with SO_2 = 1.95 (1.19, 3.74). Cancer TSP = 0.87 (-1.14, 2.53); with SO_2 = 1.07 (-1.05, 3.23). Other deaths TSP = 3.52 (0.82, 6.30); with SO_2 = 2.40 (-0.51, 5.89).
Ostro et al. (1998). Bangkok, Thailand, 1992-1995 PM_{10} (beta attenuation, 65)	Total (non-accidental), cardiovascular, respiratory deaths examined for associations with PM_{10} (separate measurements showed 50% of PM_{10} was $PM_{2.5}$),using Poisson GAM model (only one non-parametric smoothing term in the model) adjusting for seasonal cycles, day-of-week, temp., humidity.	All the mortality series were associated with PM_{10} at various lags. The effects appear across all age groups. No other pollutants were examined.	Total mortality excess risk: 5.1% (2.1, 8.3) per 50 μg/m^3 PM_{10} at 3 d lag (0 and 2 d lags also significant). CVD (3 d ave.) = 8.3 (3.1, 13.8) Resp. (3 d ave.) = 3.0 (-8.4, 15.9)
Cropper et al. (1997). Delhi, India, 1991-1994 TSP (375)	Total (by age group), respiratory and CVD deaths related to TSP, SO_2, and NOx, using GEE Poisson model (to control for autocorrelation), adjusting for seasonal cycles (trigonometric terms), temperature, and humidity. 70% deaths occur before age 65 (in U.S., 70% occur after age 65).	TSP was significantly associated with all mortality series except with the very young (age 0-4) and the "very old" (age >= 65). The results were reported to be unaffected by addition of SO_2 to the model. The authors note that, because those who are affected are younger (than Western cities), more life-years are likely to be lost per person from air pollution impacts.	2.3% (significant at 0.05, but SE of estimate not reported) per 100 μg/m^3 TSP at 2 day lag.
Kwon et al. (2001) +Seoul, South Korea, 1994-1998. PM10 mean = 68.7.	The study was planned to test the hypothesis that patients with congestive heart failure are more susceptible to the harmful effects of ambient air pollution than the general population. GAM Poisson regression models, adjusting for seasonal cycles, temperature, humidity, day-of-week, as well as the case-crossover design, with 7 and 14 days before and after the case period, were applied	The estimated effects were larger among the congestive heart failure patients than among the general population (2.5 ~ 4.1 times larger depending on the pollutants). The case-crossover analysis showed similar results. In two pollutant models, the PM_{10} effects were much lower when CO, NO_2, or SO_2 were included. O_3 had little impact on the effects of the other pollutants.	The RRs for PM_{10} (same-day) using the GAM approach for the general population and for the cohort with congestive heart failure were 1.4% (0.6, 2.2) and 5.8 (-1.1, 13.1), respectively, per 42.1 μg/m^3. Corresponding ORs using the case-crossover approach were 0.1% (-0.9, 1.2) and 7.4% (−2.2, 17.9), respectively.

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

TABLE 8A-1 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE MORTALITY EFFECTS STUDIES

Reference, Location, Years, PM Index, Mean or Median, IQR in $\mu g/m^3$.	Study Description: Outcomes, Mean outcome rate, and ages. Concentration measures or estimates. Modeling methods: lags, smoothing, and covariates.	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes.	PM Index, lag, Excess Risk% (95% LCL, UCL), Co-pollutants.
Asia (cont'd)			
Lee et al. (2000) +Seven major cities, Korea. 1991-1997. TSP mean = 77.9.	All non-accidental deaths were analyzed for their associations with TSP, SO_2, NO_2, O_3, and CO using GAM Poisson model adjusting for trend, seasonal cycles, and weather. Pollution relative risk estimates were obtained for each city, and then pooled.	In the results of pooled estimates for multiple pollutant models, the SO_2 relative risks were not affected by addition of other pollutants, whereas the relative risks for other pollutants, including TSP, were. The SO_2 levels in these Korean cities were much higher than the levels observed in the current U.S. For example, the 24-hr mean SO_2 levels in the Korean cities ranged from 12.1 to 31.4 ppb, whereas, in Samet et al.'s 20 largest U.S. cities, the range of 24-hr mean SO_2 levels were 0.7 to 12.8 ppb.	Percent excess deaths for all non-accidental deaths was 1.7% (0.8, 2.6) per 100 $\mu g/m^3$ 2-day moving average TSP.

+ = Used GAM with multiple non-parametric smooths, but have not yet re-analyzed. * = Used S-Plus Default GAM, and have re-analyzed results; GAM = Generalized Additive Model, GEE = Generalized Estimation Equations, GLM = Generalized Linear Model.

APPENDIX 8B

PARTICULATE MATTER-MORBIDITY STUDIES: SUMMARY TABLES

Appendix 8B.1

PM-Cardiovascular Admissions Studies

TABLE 8B-1. ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes. Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
United States			
Samet et al. (2000a,b) 14 US cities 1985-1994, but range of years varied by city PM_{10} ($\mu g/m^3$) mean, median, IQR: Birmingham, AL: 34.8, 30.6, 26.3 Boulder, CO: 24.4, 22.0, 14.0 Canton, OH: 28.4, 25.6, 15.3 Chicago, Il: 36.4, 32.6, 22.4 Colorado Springs, CO: 26.9, 22.9, 11.9 Detroit, MI: 36.8, 32.0, 28.2 Minneapolis/St. Paul, MN: 27.4, 24.1, 17.9 Nashville, TN: 31.6, 29.2, 17.9 New Haven, CT: 29.3h, 26.0, 20.2 Pittsburgh, PA: 36.0, 30.5, 27.4 Provo/Orem, UT: 38.9, 30.3, 22.8 Seattle, WA: 31.0, 26.7, 20.0 Spokane, WA: 45.3, 36.2, 33.5 Youngstown, OH: 33.1, 29.4, 18.6	Daily medicare hospital admissions for total cardiovascular disease, CVD (ICD9 codes 390-429), in persons 65 or greater. Mean CVD counts ranged from 3 to 102/day in the 14 cities. Covariates: SO_2, NO_2, O_3, CO, temperature, relative humidity, barometric pressure. Stats: In first stage, performed city-specific, PM10-ONLY, generalized additive robust Poisson regression with seasonal, weather, and day of week controls. Repeated analysis for days with PM_{10} less than 50 $\mu g/m^3$ to test for threshold. Lags of 0-5 considered, as well as the quadratic function of lags 0-5. Individual cities analyzed first. The 14 risk estimates were then analyzed in several second stage analyses: combining risks across cities using inverse variance weights, and regressing risk estimates on potential effect-modifiers and slopes of PM_{10} on co-pollutants.	City-specific risk estimates for a 10 $\mu g/m^3$ increase in PM_{10} ranged from -1.2% in Canton to 2.2% in Colorado Springs. Across-city weighted mean risk estimate was largest at lag 0, diminishing rapidly at other lags. Only the mean of lags 0 and 1 was significantly associated with CVD. There was no evidence of statistical heterogeniety in risk estimates across cities for CVD. City-specific risk estimates were not associated with the percent of the population that was non-white, living in poverty, college educated, nor unemployed. No evidence was observed that PM_{10} effects were modified by weather. No association was observed between the city-specific PM_{10} risk estimates and the city-specific correlation between PM_{10} and co-pollutants. However, due to the absence of multi-pollutant regression results, it is not clear whether this study demonstrates an independent effect of PM_{10}.	Percent Excess CVD Risk (95% CI), combined over cities per 50 $\mu g/m^3$ change in PM_{10}. PM_{10}: 0 d lag. 5.5% (4.7, 6.2) PM_{10}: 0–1d lag. 6.0% (5.1, 6.8) $PM_{10} < 50$ $\mu g/m^3$: 0–1 d lag. 7.6% (6.0, 9.1)
Zanobetti and Schwartz (2003b)	Statistical reanalysis using GAM with improved convergence criterion (New GAM), GLM with natural splines (GLM NS), and GLM with penalized splines (GLM PS). Lag structure: average of lags 0 and 1.		Default GAM: 5.9% (5.1-6.7) New GAM: 4.95% (3.95-5.95) GLM NS: 4.8% (3.55-6.0) GLM PS: 5.0% (4.0-5.95)

TABLE 8B-1 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
United States (cont'd)			
Janssen et al. (2002) 14 U.S. cities studied in Samet et al. (2000a,b) above PM_{10} ($\mu g/m^3$) — Mean Summer/Winter — Ratio Birmingham 40.0/27.4 0.69 Boulder* 26.8/36.3 1.35 Canton 36.6/25.8 0.70 Chicago 42.5/30.4 0.71 Colorado Springs* 21.3/37.3 1.75 Detroit 42.8/32.8 0.77 Minneapolis 30.5/23.0 0.75 Nashville 40.1/31.9 0.80 New Haven 30.3/31.6 1.04 Pittsburgh 46.6/29.4 0.63 Seattle* 23.8/43.3 1.82 Spokane* 32.7/42.2 1.29 Provo-Urem* 31.4/66.3 2.11 Youngstown 40.7/30.1 0.74	Examined same database as Samet et al. (2000a,b) to evaluate whether differences in prevalence in air conditioning (AC) and/or the contribution of different sources to total PM_{10} emissions could partially explain the observed variability in exposure effect relations. Variables included 24-hr means of temperature. Cities were characterized and analyzed as either winter or nonwinter peaking. Rations between mean concentrations during summer (June, July August) and winter (January, February, March) were calculated. (*Winter peaking PM_{10} concentration.)	Analysis of city groups of winter peaking, PM_{10} and nonwinter peaking PM_{10} yielded coefficients for CVD-related hospitalization admissions that decreased significantly with increasing percentage of central AC for both city groups. Four source related variables coefficients for hospital admissions for CVD increased significantly with increasing percentage of PM_{10} from highway vehicles, highway diesels, oil combustion, metal processing, increasing population, and vehicle miles traveled (VMT) per sq mile and with decreasing percentage of PM_{10} from fugitive dust. For COPD and pneumonia association were less significant but the pattern of association were similar to that for CVD.	**Homes with AC** β CVD % change (SE) All cities −15.2 (14.8) Nonwinter peak cities −50.3** (17.4) Winter peak cities −51.7** (13.8) **Source PM_{10} from highway vehicles** % change (SE) β CVD 58.0* (9.9) [**p <0.05]
Zanobetti and Schwartz (2003a)	Statistical reanalysis of Janssen et al., 2002 findings using GLM with natural splines (GLM NS), and GLM with penalized splines (GLM PS). Lag structure: average of lags 0 and 1.	Zanobetti and Schwartz (2003a) reanalyzed the main findings from this study using alternative methods for controlling time and weather covariates. While the main conclusions of the study were not significantly altered, some changes in results are worth noting. The effect of air conditioning use on PM10 effect estimates was less pronounced and no longer statistically significant for the winter PM10-peaking cities using natural splines or penalized splines in comparison to the original Janssen et al. GAM analysis. The effect of air conditioning remained significant for the non-winter PM10-peaking cities. The significance of highway vehicles and diesels on PM10 effect sizes remained significant, as did oil combustion.	**Homes with AC** β CVD % change (SE) All cities GLM NS: −13.55 (14.9) GLM PS: -12.0 (14.1) Nonwinter peaking cities GLM NS: −44.1** (20.15) GLM PS: -38.4** (17.8) Winter peaking cities GLM NS: −6.1 (40.3) GLM PS: -41.5 (39.6) **Source PM_{10} from highway vehicles** % change (SE) β CVD GLM NS: 51.1** (14.7) GLM PS: 35.1** (14.3) [**p <0.05]

TABLE 8B-1 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
United States (cont'd)			
Zanobetti et al. (2000b) 10 US cities 1986-1994 PM_{10} ($\mu g/m^3$) median, IQR: Canton, OH: 26, 15 Birmingham, AL: 31, 26 Chicago, Il: 33, 23 Colorado Springs, CO: 23, 13 Detroit, MI: 32, 28 Minneapolis/St. Paul, MN: 24, 18 New Haven, CT: 26, 21 Pittsburgh, PA: 30, 28 Seattle, WA: 27, 21 Spokane, WA: 36, 34	Derived from the Samet et al. (2000a,b) study, but for a subset of 10 cities. Daily hospital admissions for total cardiovascular disease, CVD (ICD9 codes 390-429), in persons 65 or greater. Median CVD counts ranged from 3 to 103/day in the 10 cities. Covariates: SO_2, O_3, CO, temperature, relative humidity, barommetric pressure. Stats: In first stage, performed single-pollutant generalized additive robust Poisson regression with seasonal, weather, and day of week controls. Repeated analysis for days with PM_{10} less than 50 $\mu g/m^3$ to test for threshold. Lags of 0-5 considered, as well as the quadratic function of lags 0-5. Individual cities analyzed first. The 10 risk estimates were then analyzed in several second stage analyses: combining risks across cities using inverse variance weights, and regressing risk estimates on potential effect-modifiers and pollutant confounders.	Same basic pattern of results as in Samet et al. (2000a,b). For distributed lag analysis, lag 0 had largest effect, lags 1 and 2 smaller effects, and none at larger lags. City-specific slopes were independent of percent poverty and percent non-white. Effect size increase when data were restricted to days with PM_{10} less than 50 $\mu g/m^3$. No multi-pollutant models reported; however, no evidence of effect modification by co-pollutants in second stage analysis. As with Samet et al. 2000., it is not clear whether this study demonstrates an independent effect of PM_{10}. This study used the old GAM model. Results have not been explicitly reanalyzed, but note that the 14 cities noted above in Zanobetti and Schwartz (2003a) include these 10 cities.	Percent Excess Risk (SE) combined over cities: Effects computed for 50 $\mu g/m^3$ change in PM_{10}. PM_{10}: 0 d. 5.6 (4.7, 6.4) PM_{10}: 0–1 d. 6.2 (5.4, 7.0) $PM_{10} < 50$ $\mu g/m^3$: 0–1 d. 7.8 (6.2, 9.4)
Schwartz (1999) 8 US metropolitan counties 1988-1990 median, IQR for PM_{10} ($\mu g/m^3$): Chicago, IL: 35, 23 Colorado Springs, CO: 23, 14 Minneapolis, MN: 28, 15 New Haven, CT: 37, 25 St. Paul, MN: 34, 23 Seattle, WA: 29, 20 Spokane, WA: 37, 33 Tacoma, WA: 37, 27	Daily hospital admissions for total cardiovascular diseases (ICD9 codes 390-429) among persons over 65 years. Median daily hospitalizations: 110, 3, 14, 18, 9, 22, 6, 7, alphabetically by city. Covariates: CO, temperature, dewpoint temp. Stats: robust Poisson regression after removing admission outliers; generalized additive models with LOESS smooths for control of trends, seasons, and weather. Day of week dummy variables. Lag 0 used for all covariates.	In single-pollutant models, similar PM_{10} effect sizes obtained for each county. Five of eight county-specific effects were statistically significant, as was the PM_{10} effect pooled across locations. CO effects significant in six of eight counties. The PM_{10} and CO effects were both significant in a two pollutant model that was run for five counties where the PM_{10}/CO correlation was less than 0.5. Results reinforce those of Schwartz, 1997. This study used the old GAM model. No reanalysis has been reported.	Percent Excess Risk (95% CI): Effects computed for 50 $\mu g/m^3$ change in PM_{10}. PM_{10}: 0d. Individual counties: Chicago: 4.7 (2.6, 6.8) CO Spng: 5.6 (−6.8, 19.0) Minneap: 4.1 (−3.6, 12.5) New Hav: 5.8 (2.1, 9.7) St. Paul: 8.6 (2.9, 14.5) Seattle: 3.6 (−0.1, 7.4) Spokane: 6.7 (0.9, 12.8) Tacoma: 5.3 (3.1, 7.6) Pooled: 5.0 (3.7, 6.4) 3.8 (2.0, 5.5) w. CO

TABLE 8B-1 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
United States (cont'd)			
Linn et al. (2000) Los Angeles 1992-1995 mean, SD: $PM_{10\ est}$ (μg/m^3): 45, 18	Hospital admissions for total cardiovascular diseases (CVD), congestive heart failure (CHF), myocardial infarction (MI), cardiac arrhythmia (CA) among all persons 30 years and older, and by sex, age, race, and season. Mean hospital admissions for CVD: 428. Covariates: CO, NO_2, O_3, temperature, rainfall. Daily gravimetric PM_{10} estimated by regression of every sixth day PM_{10} on daily real-time PM_{10} data collected by TEOM. Poisson regression with controls for seasons and day of week. Reported results for lag 0 only. Results reported as Poisson regression coefficients and their standard errors. The number of daily CVD admissions associated with the mean PM_{10} concentration can be computed by multiplying the PM_{10} coefficient by the PM_{10} mean and then exponentiating. Percent effects are calculated by dividing this result by the mean daily admission count for CVD.	In year-round, single-pollutant models, significant effects of CO, NO_2, and PM_{10} on CVD were reported. PM_{10} effects appeared larger in winter and fall than in spring and summer. No consistent differences in PM_{10} effects across sex, age, and race. CO risk was robust to including PM_{10} in the model; no results presented on PM_{10} robustness to co-pollutants. This study did not use the GAM model in developing its main findings.	% increase with PM_{10} change of 50 μg/m^3: $PM_{10\ est}$: 0 d. CVD ages 30+ 3.25% (2.04, 4.47) MI ages 30+ 3.04% (0.06, 6.12) CHF ages 30+ 2.02% (−0.94, 5.06) CA ages 30+ 1.01% (−1.93, 4.02)
Morris and Naumova (1998) Chicago, IL 1986-1989 mean, median, IQR, 75th percentile: PM_{10} (μg/m^3): 41, 38, 23, 51	Daily hospital admissions for congestive heart failure, CHF (ICD9 428), among persons over 65 years. Mean hospitalizations: 34/day. Covariates: O_3, NO_2, SO_2, CO, temperature, relative humidity. Gases measured at up to eight sites; daily PM_{10} measured at one site. Stats: GLM for time series data. Controlled for trends and cycles using dummy variables for day of week, month, and year. Residuals were modeled as negative binomial distribution. Lags of 0-3 days examined.	CO was only pollutant statistically significant in both single- and multi-pollutant models. Exposure misclassification may have been larger for PM_{10} due to single site. Results suggest effects of both CO and PM_{10} on congestive heart failure hospitalizations among elderly, but CO effects appear more robust. This study did not use the GAM model.	Percent Excess Risk (95% CI) per 50 μg/m^3 change in PM_{10}. PM_{10}: 0 d. 3.92% (1.02, 6.90) 1.96% (−1.4, 5.4) with 4 gaseous pollutants

TABLE 8B-1 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR μg/m^3	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
United States (cont'd)			
Schwartz (1997) Tucson, AZ 1988-1990 mean, median, IQR: PM_{10} (μg/m^3): 42, 39, 23	Daily hospital admissions for total cardiovascular diseases (ICD9 codes 390-429) among persons over 65 years. Mean hospitalizations: 13.4/day. Covariates: O_3, NO_2, CO, SO_2, temperature, dewpoint temperature. Gases measured at multiple sites; daily PM_{10} at one site. Stats: robust Poisson regression; generalized additive model with LOESS smooth for controlling trends and seasons, and regression splines to control weather. Lags of 0-2 days examined.	Both PM_{10} (lag 0) and CO significantly and independently associated with admissions, whereas other gases were not. Sensitivity analyses reinforced these basic results. Results suggest independent effects of both PM_{10} and CO for total cardiovascular hospitalizations among the elderly. This study used the old GAM model. No reanalysis has been reported.	Percent Excess Risk (95% CI) per 50 μg/m^3 change in PM_{10}. PM_{10}: 0 d. 6.07% (1.12, 1.27) 5.22% (0.17, 10.54) w. CO
Gwynn et al (2000) Buffalo, NY mn/max PM_{10} = 24.1/90.8 μg/m^3 SO_4^- = 2.4/3.9 H^+ = 36.4/38.2 nmol/m^3 CoH = 0.2/0.9 10^{-3} ft	Air pollution health effects associations with total, respiratory, and CVD hospital admissions (HA's) examined using Poisson model controlling for weather, seasonality, long-wave effects, day of week, holidays.	Positive, but non-significant assoc. found between all PM indices and circulatory hospital admissions. Addition of gaseous pollutants to the model had minimal effects on the PM RR estimates. This study used the old GAM model. No reanalysis has been reported.	Percent excess CVD HA risks (95% CI) per PM_{10} = 50 μg/m^3; SO_4 = 15 μg/m^3; H^+ = 75 nmoles/m^3; COH = 0.5 units/1,000 ft: PM_{10} (lag 3) = 5.7% (−3.3, 15.5) SO_4 (lag 1) = 0.1% (−0.1, 0.4) H^+ (lag 0) = 1.9% (−0.3, 4.2) COH (lag 1) = 2.2% (−1.9, 6.3)
Lippmann et al. (2000) Detroit (Wayne County), MI 1992-1994 mean, median, IQR: $PM_{2.5}$ (μg/m^3): 18, 15, 11 PM_{10} (μg/m^3): 31, 28, 19 $PM_{10-2.5}$ (μg/m^3): 13, 12, 9	Various cardiovascular (CVD)-related hospital admissions (HA's) for persons 65+ yr. analyzed, using GAM Poisson models, adjusting for season, day of week, temperature, and relative humidity. The air pollution variables analyzed were: PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, sulfate, H^+, O_3, SO_2, NO_2, and CO. However, this study site/period had very low acidic aerosol levels. As noted by the authors 85% of H^+ data was below detection limit (8 nmol/m^3).	For heart failure, all PM metrics yielded significant associations. Associations for IHD, dysrhythmia, and stroke were positive but generally non-sig. with all PM indices. Adding gaseous pollutants had negligible effects on various PM metric RR estimates. The general similarity of the $PM_{2.5}$ and $PM_{10-2.5}$ effects per μg/m^3 in this study suggest similarity in human toxicity of these two inhalable mass components in study locales/periods where $PM_{2.5}$ acidity not usually present. However, small sample size limits power to distinguish between pollutant-specific effects.	Percent excess CVD HA risks (95% CI) per 50 μg/m^3 PM_{10}, 25 μg/m^3 $PM_{2.5}$ and $PM_{10-2.5}$: IHD: $PM_{2.5}$ (lag 2) 4.3 (−1.4, 10.4) PM_{10} (lag 2) 8.9 (0.5, 18.0) $PM_{10-2.5}$ (lag 2) 10.5 (2.7, 18.9) Dysrhythmia: $PM_{2.5}$ (lag 1) 3.2 (−6.5, 14.0) PM_{10} (lag 1) 2.9 (−6.8, 13.7) $PM_{10-2.5}$ (lag 0) 0.2 (−12.2, 14.4) Heart Failure: $PM_{2.5}$ (lag 1) 9.1 (2.4, 16.2) PM_{10} (lag 0) 9.7 (0.2, 20.1) $PM_{10-2.5}$ (lag 0) 5.2 (−3.3, 14.5) Stroke: $PM_{2.5}$ (lag 0) 1.8 (−5.3, 9.4) PM_{10} (lag 1) 4.8 (−5.5, 16.2) $PM_{10-2.5}$ (lag 1) 4.9 (−4.7, 15.5)

TABLE 8B-1 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
United States (cont'd)			
Ito 2003 Detroit (Wayne County), MI	Statistical reanalysis using GAM with improved convergence criterion (New GAM), and GLM with natural splines (GLM NS). Same model structure as before.		IHD: New GAM: 8.0% (-0.3-17.1) GLM NS: 6.2% (-2.0-15.0) New GAM: 3.65% (-2.05-9.7)* GLM NS: 3.0% (-2.7-9.0)* New GAM: 10.2% (2.4-18.6)** GLM NS: 8.1% (0.4-16.4)** Dysrhythmias: New GAM: 2.8% (-10.9-18.7) GLM NS: 2.0% (-11.7-17.7) New GAM: 3.2% (-6.6-14.0)* GLM NS: 2.6% (-7.1-13.3)* New GAM: 0.1% (-12.4-14.4)** GLM NS: 0.0% (-12.5-14.3)** Heart Failure: New GAM: 9.2% (-0.3-19.6) GLM NS: 8.4% (-1.0-18.7) New GAM: 8.0% (1.4-15.0)* GLM NS: 6.8% (0.3-13.8)* New GAM: 4.4% (-4.0-13.5)** GLM NS: 4.9% (-3.55-14.1)**

TABLE 8B-1 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
Moolgavkar (2000b) Three urban counties: Cook, IL; Los Angeles, CA; Maricopa, AZ. 1987-1995 Pollutant median, IQR: Cook: PM_{10}: 35, 22 LA: PM_{10}: 44, 26 $PM_{2.5}$: 22, 16 Maricopa: PM_{10}: 41, 19	Analysis of daily hospital admissions for total cardiovascular diseases, CVD, (ICD9 codes 390-429) and cerebrovascular diseases, CRD, (ICD9 430-448) among persons aged 65 and over. For Los Angeles, a second age group, 20-64, was also analyzed. Median daily CVD admissions were 110, 172, and 33 in Cook, LA, and Maricopa counties, respectively. PM_{10} available only every sixth day in LA and Maricopa counties. In LA, every-sixth-day $PM_{2.5}$ also was available. Covariates: CO, NO_2, O_3, SO_2, temperature, relative humidity. Stats: generalized additive Poisson regression, with controls for day of week and smooth temporal variability. Single-pollutant models estimated for individual lags from 0 to 5. Two-pollutant models also estimated, with both pollutants at same lag.	In single-pollutant models in Cook and LA counties, PM was significantly associated with CVD admissions at lags 0, 1, and 2, with diminishing effects over lags. $PM_{2.5}$ also was significant in LA for lags 0 and 1. For the 20-64 year old age group in LA, risk estimates were similar to those for 65+. In Maricopa county, no positive PM_{10} associations were observed at any lag. In two-pollutant models in Cook and LA counties, the $PM_{10}/PM_{2.5}$ risk estimates diminished and/or were rendered non-significant. Little evidence observed for associations between CRD admissions and PM. These results suggest that PM is not independently associated with CVD or CRD hospital admissions.	Percent Excess CVD Risk (95% CI) Effects computed for 50 $\mu g/m^3$ change in PM_{10} and 25 $\mu g/m^3$ change in $PM_{2.5}$. Cook 65+: PM_{10}, 0 d. 4.2 (3.0, 5.5) PM_{10}, 0 d. w/NO_2. 1.8 (0.4, 3.2) LA 65+: PM_{10}, 0 d. 3.2 (1.2, 5.3) PM_{10}, 0 d. w/CO −1.8 (−4.4, 0.9) $PM_{2.5}$, 0 d. 4.3 (2.5, 6.1) $PM_{2.5}$, 0 d. w/CO 0.8 (−1.3, 2.9) LA 20−64 years old: PM_{10}, 0 d. 4.4 (2.2, 6.7) PM_{10}, 0 d. w/CO 1.4 (−1.3, 4.2) $PM_{2.5}$, 0 d. 3.5 (1.8, 5.3) $PM_{2.5}$, 0 d., w/CO) 2.3 (−0.2, 4.8) Maricopa: PM_{10}, 0 d. −2.4 (−6.9, 2.3)

TABLE 8B-1 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
United States (cont'd)			
Moolgavkar (2003)	Statistical reanalysis using GAM with improved convergence criterion (New GAM), and GLM with natural splines (GLM NS). New analyses were run with variable and in some cases more extensive control of time than in original analysis.		Cook County, IL: New GAM100df: 4.05% (2.9-5.2) GLM NS100df: 4.25% (3.0-5.5) Los Angeles County, CA: New GAM30df: 3.35% (1.2-5.5) New GAM100df: 2.7% (0.6-4.8) GLM NS100df: 2.75% (0.1-5.4) New GAM30df: 3.95% (2.2-5.7)* New GAM100df: 2.9% (1.2-4.6)* GLM nspline100df: 3.15% (1.1-5.2)*
Zanobetti et al. (2000a) Cook County, IL 1985-1994 Median, IQR: PM_{10} ($\mu g/m^3$): 33, 23	Total cardivascular hospital admissions in persons 65 and older (ICD 9 codes390-429) in relation to PM_{10}. Data were analyzed to examine effect modification by concurrent or preexisting cardiac and/or respiratory conditions, age, race, and sex. No co-pollutants included.	Evidence seen for increased CVD effects among persons with concurrent respiratory infections or with previous admissions for conduction disorders.	Percent Excess CVD Risk (95% CI) Effects computed for 50 $\mu g/m^3$ PM_{10}, 0-1 D. AVG. CVD: 6.6 (4.9-8.3)

TABLE 8B-1 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
Tolbert et al. (2000a) Atlanta Period 1: 1/1/93-7/31/98 Mean, median, SD: PM_{10} ($\mu g/m^3$): 30.1, 28.0, 12.4 Period 2: 8/1/98-8/31/99 Mean, median, SD: PM_{10} ($\mu g/m^3$): 29.1, 27.6, 12.0 $PM_{2.5}$ ($\mu g/m^3$): 19.4, 17.5, 9.35 CP ($\mu g/m^3$): 9.39, 8.95, 4.52 10-100 nm PM counts ($count/cm^3$): 15,200, 10,900, 26,600 10-100 nm PM surface area (um^2/cm^3): 62.5, 43.4, 116 $PM_{2.5}$ soluble metals ($\mu g/m^3$): 0.0327, 0.0226, 0.0306 $PM_{2.5}$ Sulfates ($\mu g/m^3$): 5.59, 4.67, 3.6 $PM_{2.5}$ Acidity ($\mu g/m^3$): 0.0181, 0.0112, 0.0219 $PM_{2.5}$ organic PM ($\mu g/m^3$): 6.30, 5.90, 3.16 $PM_{2.5}$ elemental carbon ($\mu g/m^3$): 2.25, 1.88, 1.74	Preliminary analysis of daily emergency department (ED) visits for dysrhythmias, DYS, (ICD 9 code 427) and all cardiovascular diseases, CVD, (codes 402, 410-414, 427, 428, 433-437, 440, 444, 451-453) for persons aged 16 and older in the period before (Period 1) and during (Period 2) the Atlanta superstation study. ED data analyzed here from just 18 of 33 participating hospitals; numbers of participating hospitals increased during period 1. Mean daily ED visits for dysrhythmias and all CVD in period 1 were 6.5 and 28.4, respectively. Mean daily ED visits for dysrhythmias and all CVD in period 2 were 11.2 and 45.1, respectively. Covariates: NO_2, O_3, SO_2, CO temperature, dewpoint, and, in period 2 only, VOCs. PM measured by both TEOM and Federal Reference Method; unclear which used in analyses. For epidemiologic analyses, the two time periods were analyzed separately. Poisson regression analyses were conducted with cubic splines for time, temperature and dewpoint. Day of week and hospital entry/exit indicators also included. Pollutants were treated a-priori as three-day moving averages of lags 0, 1, and 2. Only single-pollutant results reported.	In period 1, significant negative association (p=0.02) observed between CVD and 3-day average PM_{10}. There was ca. 2% drop in CVD per 10 $\mu g/m^3$ increase in PM_{10}. CVD was positively associated with NO_2 (p=0.11) and negatively associated with SO_2 (p=0.10). No association observed between dysrhythmias and PM_{10} in period 1. However, dysrhythmias were positively associated with NO_2 (p=0.06). In period 2, i.e., the first year of operation of the superstation, no associations seen with PM_{10} or $PM_{2.5}$. However, significant positive associations observed between CVD and elemental carbon (p=0.005) and organic matter (p=0.02), as well as with CO (p=0.001). For dysrhythmias, significant positive associations observed with elemental carbon (p=0.004), CP (p=0.04), and CO (p=0.005). These preliminary results should be interpreted with caution given the incomplete and variable nature of the databases analyzed.	Percent Excess Risk (p-value): Effects computed for 50 $\mu g/m^3$ change in PM_{10}; 25 $\mu g/m^3$ for CP and $PM_{2.5}$; 25,000 $counts/cm^3$ for 10-100 nm counts. Period 1: PM_{10}, 0-2 d. avg. CVD: −8.2 (0.02) DYS: 4.6 (0.58) Period 2: 0-2 d. avg. in all cases CVD % effect; DYS % effect: PM_{10}: 5.1 (−7.9, 19.9); 13.1 (−14.1, 50.0) $PM_{2.5}$: 6.1 (−3.1, 16.2); 6.1 (−12.6, 28.9) CP: 17.6 (−4.6, 45.0); 53.2 (2.1, 129.6) 10-100 nm counts: −11.0 (0.17); 3.0 (0.87)

TABLE 8B-1 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
Canada			
Burnett et al. (1995) Ontario, Canada 1983-1988 Sulfate Mean: 4.37 µg/m^3 Median: 3.07 µg/m^3 95th percentile: 13 µg/m^3	168 Ontario hospitals. Hospitalizations for coronary artery disease, CAD (ICD9 codes 410,413), cardiac dysrhythmias, DYS (code 427), heart failure, HF (code 428), and all three categories combined (total CVD). Mean total CVD rate: 14.4/day. 1986 population of study area: 8.7 million. All ages, <65, >=65. Both sexes, males, females. Daily sulfates from nine monitoring stations. Ozone from 22 stations. Log hospitalizations filtered with 19-day moving average prior to GEE analysis. Day of week effects removed. 0-3 day lags examined. Covariates: ozone, ozone^2, temperature, temperature^2. Linear and quadratic sulfate terms included in model.	Sulfate lagged one day significantly assoc. with total CVD admissions with and without ozone in the model. Larger associations observed for coronary artery disease and heart failure than for cardiac dysrhythmias. Suggestion of larger associations for males and the sub-population 65 years old and greater. Little evidence for seasonal differences in sulfate effects after controlling for covariates.	Effects computed for 95th percentile change in SO_4 SO_4, 1d, no covariates: Total CVD: 2.8 (1.8, 3.8) CAD: 2.3 (0.7, 3.8) DYS: 1.3 (−2.0, 4.6) HF: 3.0 (0.6, 5.3) Males: 3.4 (1.8, 5.0) Females: 2.0 (0.2, 3.7) <65: 2.5 (0.5, 4.5) >=65: 3.5 (1.9, 5.0) SO_4, 1d, w. temp and O_3: Total CVD: 3.3 (1.7,4.8)
Burnett et al. (1997a) Canada's 10 largest cities 1981-1994 COH daily maximum Mean: 0.7 10^3 ln feet Median: 0.6 10^3 ln feet 95th percentile: 1.5 10^3 ln feet	Daily hospitalizations for congestive heart failure (ICD9 code 427) for patients over 65 years at 134 hospitals. Average hospitalizations: 39/day. 1986 population of study area: 12.6 million. Regressions on air quality using generalized estimating equations, controlling for long-term trends, seasonality, day of week, and inter-hospital differences. Models fit monthly and pooled over months. Log hospitalizations filtered with 19-day moving average prior to GEE analysis. 0-3 day lags examined. Covariates: CO, SO_2, NO_2, O_3, temperature, dewpoint temperature.	COH significant in single-pollutant models with and without weather covariates. Only *ln*CO and *ln* NO_2 significant in multi-pollutant models. COH highly colinear with CO and NO_2. Suggests no particle effect independent of gases. However, no gravimetric PM data were included.	Effects computed for 95% change in COH: 0 d lag: 5.5% (2.5, 8.6) 0 d lag w/weather: 4.7% (1.3, 8.2) 0 d lag w/CO, NO_2, SO_2, O_3: −2.26 (−6.5, 2.2)

TABLE 8B-1 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
Canada (cont'd)			
Burnett et al. (1997c) Metro-Toronto, Canada 1992-1994 Pollutant: mean, median, IQR: COH (10^3 ln ft): 0.8, 0.8, 0.6 H+ (nmol/m^3): 5, 1, 6 SO_4 (nmol/m^3): 57, 33, 57 PM_{10} (µg/m^3): 28, 25, 22 $PM_{2.5}$ (µg/m^3): 17, 14, 15 $PM_{10-2.5}$ (µg/m^3): 12, 10, 7	Daily unscheduled cardiovascular hospitalizations (ICD9 codes 410-414,427, 428) for all ages. Average hospital admissions: 42.6/day. Six cities of metro-Toronto included Toronto, North York, East York, Etobicoke, Scarborough, and York, with combined 1991 population of 2.36 million. Used same stat model as in Burnett et al., 1997c. 0- 4 day lags examined, as well as multi-day averages. Covariates: O_3, NO_2, SO_2, CO, temperature, dewpoint temperature.	Relative risks > 1 for all pollutants in univariate regressions including weather variables; all but H+ and FP statistically significant. In multivariate models, the gaseous pollutant effects were generally more robust than were particulate effects. However, in contrast to Burnett et al. (1997A), COH remained significant in multivariate models. Of the remaining particle metrics, CP was the most robust to the inclusion of gaseous covariates. Results do not support independent effects of FP, SO_4, or H+ when gases are controlled.	Percent excess risk (95% CI) per 50 µg/m^3 PM_{10}, 25 µg/m^3 $PM_{2.5}$ and $PM_{10-2.5}$, and IQR for other indicators. COH: 0–4 d. 6.2 (4.0, 8.4) 5.9 (2.8, 9.1) w. gases H+: 2–4 d. 2.4 (0.4, 4.5) 0.5 (–1.6, 2.7) w. gases SO_4: 2–4 d. 1.7 (–0.4, 3.9) –1.6 (–4.4, 1.3) w. gases PM_{10} : 1–4 d. 7.7 (0.9, 14.8) –0.9 (–8.3, 7.1) w. gases $PM_{2.5}$: 2–4 d. 5.9 (1.8, 10.2) –1.1 (–7.8, 6.0) w. gases $PM_{10-2.5}$: 0–4 d. 13.5 (5.5, 22.0) 8.1 (–1.3, 18.3) w. gases

TABLE 8B-1 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
Canada (cont'd)			
Burnett et al. (1999) Metro-Toronto, Canada 1980-1994 Pollutant: mean, median, IQR: FP_{est} (µg/m^3): 18, 16, 10 CP_{est} (µg/m^3): 12, 10, 8 $PM_{10\ est}$ (µg/m^3): 30, 27, 15	Daily hospitalizations for dysrhythmias, DYS (ICD9 code 427; mean 5/day); heart failure, HF (428; 9/d); ischemic heart disease, IHD (410-414; 24/d); cerebral vascular disease, CVD (430-438; 10/d); and diseases of the peripheral circulation, DPC (440-459; 5/d) analyzed separately in relation to environmental covariates. Same geographic area as in Burnett et al., 1997b. Three size-classified PM metrics were estimated, not measured, based on a regression on TSP, SO_4, and COH in a subset of every 6th-day data. Generalized additive models used and non-parametric LOESS prefilter applied to both pollution and hospitalization data. Day of week controls. Tested 1-3 day averages of air pollution ending on lags 0-2. Covariates: O_3, NO_2, SO_2, CO, temperature, dewpoint temperature, relative humidity.	In univariate regressions, all three PM metrics were associated with increases in cardiac outcome (DVS, HF, IHD). No associations with vascular outcomes, except for CPest with DPC. In multi-pollutant models, PM effects estimates reduced by variable amounts (often >50%) for specific endpoints and no statistically significant (at $p<0.05$) PM associations seen with any cardiac or circulatory outcome (results not shown). Use of estimated PM metrics limits interpretation of pollutant-specific results. However, results suggest that linear combination of TSP, SO_4, and COH does not have a strong independent association with cardiovascular admissions when full range of gaseous pollutants also modeled.	Single pollutant models: Percent excess risk (95% CI) per 50 µg/m^3 PM_{10}; 25 µg/m^3 $PM_{2.5}$; and 25 µg/m^3 $PM_{10-2.5}$. All cardiac HA (lags 2-5 d): $PM_{2.5}$ 1-poll = 8.1 (2.45, 14.1) $PM_{2.5}$ w/4 gases = −1.6 (−10.4, 8.2); w/CO = 4.60 (−3.39, 13.26) PM_{10} 1-poll = 12.07 (1.43, 23.81) w/4 gases = −1.40 (−12.53, 11.16) w/CO = 10.93 (0.11, 22.92) $PM_{10-2.5}$ 1-poll = 20.46 (8.24, 34.06) w/4 gases = 12.14 (−1.89, 28.2); w/CO = 19.85 (7.19, 34.0) DYS: FP_{est} (0 d): 6.1 (1.9, 10.4) CP_{est} (0 d): 5.2 (−0.21, 1.08) $PM_{10\ est}$: (0 d): 8.41 (2.89, 14.2) HF: FP_{est} (0−2 d): 6.59 (2.50, 10.8) CP_{est} (0−2 d): 7.9 (2.28, 13) $PM_{10\ est}$ (0−2 d): 9.7 (4.2, 15.5) IHD: FP_{est} (0−2 d): 8.1 (5.4, 10.8) CP_{est} (0 d): 3.7 (1.3, 6.3) $PM_{10\ est}$ (0−1 d): 8.4 (5.3, 11.5)

TABLE 8B-1 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
Canada (cont'd)			
Stieb et al. (2000) Saint John, Canada 7/1/92-3/31/96 mean and S.D.: PM_{10} ($\mu g/m^3$): 14.0, 9.0 $PM_{2.5}$ ($\mu g/m^3$): 8.5, 5.9 **HOSPITAL ADMISSIONS** H+ ($nmol/m^3$): 25.7, 36.8 Sulfate ($nmol/m^3$): 31.1, 29.7 COH mean (10^3 ln ft): 0.2, 0.2 COH max (10^3 ln ft): 0.6, 0.5	Study of daily emergency department (ED) visits for angina/myocardial infarction (mean 1.8/day), congestive heart failure (1.0/day), dysrhythmia/conduction disturbance (0.8/day), and all cardiac conditions (3.5/day) for persons of all ages. Covariates included CO, H_2S, NO_2, O_3, SO_2, total reduced sulfur (TRS), a large number of weather variables, and 12 molds and pollens. Stats: generalized additive models with LOESS prefiltering of both ED and pollutant variables, with variable window lengths. Also controlled for day of week and LOESS-smoothed functions of weather. Single-day, and five day average, pollution lags tested out to lag 10. The strongest lag, either positive or negative, was chosen for final models. Both single and multi-pollutant models reported. Full-year and May-Sep models reported.	In single-pollutant models, significant positive associations observed between all cardiac ED visits and PM_{10}, $PM_{2.5}$, H_2S, O_3, and SO_2. Significant negative associations observed with H+, sulfate, and COH max. PM results were similar when data were restricted to May-Sep. In multi-pollutant models, no PM metrics were significantly associated with all cardiac ED visits in full year analyses, whereas both O_3 and SO_2 were. In the May-Sep subset, significant negative association found for sulfate. No quantitative results presented for non-significant variables in these multi-pollutant regressions. In cause-specific, single-pollutant models, PM tended to be positively associated with dysrhythmia/conductive disturbances but negatively associated with congestive heart failure (no quantitative results presented). The objective decision rule used for selecting lags reduced the risk of data mining; however, the biological plausibility of lag effects beyond 3-5 days is open to question. Rich co-pollutant data base. Results imply no effects of PM independent of co-pollutants.	Percent Excess Risk (p-value) computed for 50 $\mu g/m^3$ PM_{10}, 25 $\mu g/m^3$ $PM_{2.5}$ and mean levels of sulfate and COH. Full year results for all cardiac conditions, single pollutant models: PM_{10}: 3d. 29.3 (P=0.003) $PM_{2.5}$: 3d. 14.4 (P=0.055) H+: 4–9 d. avg. –1.8 (0.010) Sulfate: 4d. –6.0 (0.001) COH max: 7d. –5.4 (0.027) Full year results for all cardiac conditions, multi-pollutant models: No significant PM associations.

TABLE 8B-1 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
Europe			
Le Tertre et al. (2002) Eight-City - APHEA 2 Study mean (SD) PM_{10} $\mu g/m^3$ Barcelona - 1/94-12/96 55.7 (18.4) Birmingham - 3/92-12/94 24.8 (13.1) London - 1/92-12/94 28.4 (12.3) Milan - No PM_{10} Netherlands - 1/92-9/95 39.5 (19.9) Paris - 1/92-9/96 PM_{13} - 22.7 (10.8) Rome - No PM_{10} Stockholm - 3/94-12/96 15.5 (7.2)	Examined the association between measures of PM to include PM_{10} and hospital admissions for cardiac causes in eight European cities with a combined population of 38 million. Examined age factors and ischemic heart disease and studies also stratified by age using autoregressive Poisson models controlled for long-term trends, season, influenza, epidemics, and meteorology, as well as confounding by other pollutants. In a second regression examined, pooled city-specific results for sources of heterogeneity.	Pooled results were reported for the cardiac admissions results in table format. City-specific and pooled results were depicted in figures only. Found a significant effect of PM_{10} and black smoke on admissions for cardiac causes (all ages) and cardiac causes and ischemic heart disease for people over 65 years with the impact of PM_{10} per unit of pollution being half that found in the United States. PM_{10} did not seem to be confounded by O_3 or SO_2. The effect was reduced when CO was incorporated in the regression model and eliminated when controlling for NO_2. There was little evidence of an impact of particles on hospital admissions for ischemic heart disease for people below 65 years or stroke for people over 65 years. The authors state results were consistent with a role for traffic exhaust/diesel in Europe.	For a 10 $\mu g/m^3$ increase in PM_{10} Cardiac admissions/all ages 0.5% (0.2, 0.8) Cardiac admissions/over 65 years 0.7% (0.4, 1.0) Ischemic heart disease/over 65 years 0.8% (0.3, 1.2) For cardiac admissions for people over 65 years: All the city-specific estimates were positive with London, Milan, and Stockholm significant at the 5% level.
Atkinson et al. (1999a) Greater London, England 1992-1994 Pollutant: mean, median, 90-10 percentile range: PM_{10} ($\mu g/m^3$): 28.5, 24.8, 30.7 Black Smoke ($\mu g/m^3$): 12.7, 10.8, 16.1	Daily emergency hospital admissions for total cardiovascular diseases, CVD (ICD9 codes 390-459), and ischemic heart disease, IHD (ICD9 410-414), for all ages, for persons less than 65, and for persons 65 and older. Mean daily admissions for CVD: 172.5 all ages, 54.5 <65, 117.8 ≥65; for IHD: 24.5 <65, 37.6 ≥65. Covariates: NO_2, O_3, SO_2, CO, temperature, relative humidity. Poisson regression using APHEA methodology; sine and cosine functions for seasonal control; day of week dummy variables. Lags of 0-3, as well as corresponding multi-day averages ending on lag 0, were considered.	In single-pollutant models, both PM metrics showed positive associations with both CVD and IHD admissions across age groups. In Two-pollutant models, the BS effect, but not the PM_{10} effect, was robust. No quantitative results provided for two-pollutant models. Study does not support a PM_{10} effect independent of co-pollutants.	Effects computed for 50 $\mu g/m^3$ PM_{10} and 25 $\mu g/m^3$ BS PM_{10} 0 d. All ages: CVD: 3.2 (0.9, 5.5) 0–64 yr: CVD: 5.6 (2.0, 9.4) IHD: 6.8 (1.3, 12.7) 65+ yr: CVD: 2.5 (–0.2, 5.3) IHD: 5.0 (0.8, 9.3) Black Smoke 0 d. All ages: CVD: 2.95 (1.00, 4.94) 0–64 yr: CVD: 3.12 (0.05, 6.29) IHD: 2.78 (–1.88, 7.63) 65+ yr: CVD: 4.24 (1.89, 6.64) IHD (lag 3): 4.57 (0.86, 8.42)

TABLE 8B-1 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
Europe (cont'd)			
Prescott et al. (1998) Edinburgh, Scotland 1981-1995 (BS and SO_2) 1992-1995 (PM_{10}, NO_2, O_3, CO) Means for long and short series: BS: 12.3, 8.7 PM_{10}: NA, 20.7	Daily emergency hospital admissions for cardiovascular disease (ICD9 codes 410-414, 426-429, 434-440) for persons less than 65 years and for persons 65 or older. Separate analyses presented for long (1981-1995) and short (1992-1995) series. Mean hospital admissions for long and short series: <65, 3.5, 3.4; 65+, 8.0, 8.7. Covariates: SO_2, NO_2, O_3, CO, wind speed, temperature, rainfall. PM_{10} measured by TEOM. Stats: Poisson log-linear regression; trend and seasons controlled by monthly dummy variables over entire series; day of week dummy variables; min daily temperature modeled using octile dummies. Pollutants expressed as cumulative lag 1-3 day moving avg.	In long series, neither BS nor NO_2 were associated with CVD admissions in either age group. In the short series, only 3-day moving average PM_{10} was positively and significantly associated with CVD admissions in single-pollutant models, and only for persons 65 or older. BS, SO_2, and CO also showed positive associations in this subset, but were not significant at the 0.05 level. The PM_{10} effect remained largely unchanged when all other pollutants were added to the model, however quantitative results were not given. Results appear to show an effect of PM_{10} independent of co-pollutants.	Percent Excess Risk (95% CI): Effects computed for 50 μg/m³ change in PM_{10} and 25 μg/m³ change in BS. Long series: BS, 1−3 d. avg. <65: −0.5 (−5.4, 4.6) 65+: −0.5 (−3.8, 2.9) Short series: BS, 1−3 d. avg. <65: −9.5 (−24.6, 8.0) 65+: 5.8 (−4.9, 17.8) PM_{10}, 1−3 d. avg. <65: 2.0 (−12.5, 19.0) 65+: 12.4 (4.6, 20.9)
Wordley et al. (1997) Birmingham, UK 4/1/92-3/31/94 mean, min, max: PM_{10} (μg/m³): 26, 3, 131	Daily hospital admissions for acute ischemic heart disease (ICD9 codes 410-429) for all ages. Mean hospitalizations: 25.6/day. Covariates: temperature and relative humidity. Stats: Linear regression with day of week and monthly dummy variables, linear trend term. Lags of 0-3 considered, as well as the mean of lags 0-2.	No statistically significant effects observed for PM_{10} on ischemic heart disease admissions for any lag. Note that PM_{10} was associated with respiratory admissions and with cardiovascular mortality in the same study (results not shown here).	% change (95% CI) per 50 μg/m³ change PM_{10} IHD admissions: PM_{10} 0-d lag: 1.4% (−4.4, 7.2) PM_{10} 1-d lag: −1.3% (−7.1, 4.4)
Díaz et al. (1999) Madrid, Spain 1994-1996 TSP by beta attenuation Summary statistics not given.	Daily emergency hospital admissions for all cardiovascular causes (ICD9 codes 390-459) for the Gregorio Maranon University Teaching Hospital. Mean admissions: 9.8/day. Covariates: SO_2, NO_2, O_3, temperature, pressure, relative humidity, excess sunlight. Stats: Box-Jenkins time-series methods used to remove autocorrelations, followed by cross-correlation analysis; sine and cosine terms for seasonality; details unclear.	No significant effects of TSP on CVD reported.	No quantitative results presented for PM.

TABLE 8B-1 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND CARDIOVASCULAR HOSPITAL ADMISSIONS

Reference citation. Location, Duration PM Index, Mean or Median, IQR	Study Description: Health outcomes or codes, Mean outcome rate, sample or population size, ages. Concentration measures or estimates. Modeling methods: lags, smoothing, co-pollutants, covariates, concentration-response	Results and Comments. Design Issues, Uncertainties, Quantitative Outcomes	PM Index, Lag, Excess Risk % (95% LCL, UCL), Co-Pollutants
Australia			
Morgan et al. (1998) Sydney, Australia 1990-1994 mean, median, IQR, 90-10 percentile range: Daily avg. bscat/10^4m: 0.32, 0.26, 0.23, 0.48 Daily max 1-hr bscat/10^4m: 0.76, 0.57, 60, 1.23	Daily hospital admissions for heart disease (ICD9 codes 410, 413, 427, 428) for all ages, and separately for persons less than 65 and persons 65 or greater. Mean daily admissions: all ages, 47.2; <65, 15.4; 65+, 31.8. PM measured by nephelometry (i.e., light scattering), which is closely associated with $PM_{2.5}$. Authors give conversion for Sydney as $PM_{2.5}$ =30 × bscat. Covariates: O_3, NO_2, temperature, dewpoint temperature. Stats: Poisson regression; trend and seasons controlled with linear time trend and monthly dummies; temperature and dewpoint controlled with dummies for eight levels of each variable; day of week and holiday dummies. Single and cumulative lags from 0-2 considered. Both single and multi-pollutant models were examined.	In single-pollutant models, NO_2 was strongly associated with heart disease admissions in all age groups. PM was more weakly, but still significantly associated with admissions for all ages and for persons 65+. The NO_2 association in the 65+ age group was unchanged in the multi-pollutant model, whereas the PM effect disappeared when NO_2 and O_3 were added to the model.. These results suggest that PM is not robustly associated with heart disease admissions when NO_2 is included, similar to the sensitivity of PM to CO in other studies.	Percent Excess Risk (95% CI): Effects computed for 25 μg/m^3 $PM_{2.5}$ (converted from bscat). 24-hr avg. $PM_{2.5}$ 0 d. <65: 1.8 (−2.9, 6.7) 65+: 4.9 (1.6, 8.4) All: 3.9 (1.1, 6.8) 24-hr $PM_{2.5}$, 0 d w. NO_2 and O_3. 65+: 0.12 (−1.3, 1.6) 1-hr $PM_{2.5}$, 0 d. <65: 0.19 (−1.6, 2.0) 65+: 1.8 (0.5, 3.2) All: 1.3 (0.3, 2.3)
Asia			
Wong et al. (1999a) Hong Kong 1994-1995 median, IQR for PM_{10} (μg/m^3): 45.0, 34.8	Daily emergency hospital admissions for cardiovascular diseases, CVD (ICD9 codes 410-417, 420-438, 440-444), heart failure, HF (ICD9 428), and ischemic heart disease, IHD (ICD9 410-414) among all ages and in the age categories 5-64, and 65+. Median daily CVD admissions for all ages: 101. Covariates: NO_2, O_3, SO_2, temperature, relative humidity. PM_{10} measured by TEOM. Stats: Poisson regression using the APHEA protocol; linear and quadratic control of trends; sine and cosine control for seasonality; holiday and day of week dummies; autoregressive terms. Single and cumulative lags from 0-5 days considered.	In single-pollutant models, PM_{10}, NO_2, SO_2, and O_3 all significantly associated with CVD admissions for all ages and for those 65+. No multi-pollutant risk coefficients were presented; however, the PM_{10} effect was larger when O_3 was elevated (i.e., above median). A much larger PM_{10} effect was observed for HF than for CVD or IHD. These results confirm the presence of PM_{10} associations with cardiovascular admissions in single-pollutant models, but do not address the independent role of PM_{10}.	Percent Excess Risk (95% CI): Effects computed for 50 μg/m^3 change in PM_{10}. PM_{10}, 0−2 d. avg. CVD: 5−64: 2.5 (−1.5, 6.7) 65+: 4.1 (1.3, 6.9) All: 3.0 (0.8, 5.4) HF (PM_{10}, 0-3 d ave.): All: 26.4 (17.1, 36.4) IHD (PM_{10}, 0-3 d ave.): All: 3.5 (−0.5, 7.7)

Appendix 8B.2

PM-Respiratory Hospitalization Studies

TABLE 8B-2. ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
United States			
Samet et al, (2000a,b)* Study Period: 84- 95 14 U.S. Cities: Birmingham, Boulder, Canton, Chicago, Col. Springs, Detroit, Minn./St. Paul, Nashville, New Haven, Pittsburgh, Provo/Orem, Seattle, Spokane, Youngstown. Mean pop. aged 65+ yr per city =143,000 PM_{10} mean = 32.9 µg/m^3 PM_{10} IQR = NR	Hospital admissions for adults 65+ yrs. for CVD (mean=22.1/day/city), COPD (mean=2.0/day/city), and Pneumonia (mean=5.6/day/city) related to PM_{10}, SO_2, O_3, NO_2, and CO. City-specific Poisson models used with adjustment for season, mean temperature (T) and relative humidity (RH) (but not their interaction), as well as barometric pressure (BP) using LOESS smoothers (span usually 0.5). Indicators for day-of-week and autoregressive terms also included.	PM_{10} positively associated with all three hospital admission categories, but city specific results ranged widely, with less variation for outcomes with higher daily counts. PM_{10} effect estimates not found to vary with co-pollutant correlation, indicating that results appear quite stable when controlling for confounding by gaseous pollutants. Analyses found little evidence that key socioeconomic factors such as poverty or race are modifiers, but it is noted that baseline risks may differ, yielding differing impacts for a given RR.	PM_{10} = 50 µg/m^3 <u>COPD HA's for Adults 65+ yrs.</u> Lag 0 ER = 7.4% (CI: 5.1, 9.8) Lag 1 ER = 7.5% (CI: 5.3, 9.8) 2 day mean (lag0,lag1) ER = 10.3% (CI: 7.7, 13) <u>Pneumonia HA's for Adults 65+ yrs.</u> Lag 0 ER =8.1% (CI: 6.5, 9.7) Lag 1 ER = 6.7% (CI: 5.3, 8.2) 2 day mean (lag0, lag1) = 10.3% (CI: 8.5, 12.1)
Reanalysis of Samet et al (2000a) by Zanobetti and Schwartz (2003a)	Re-analyses of Samet et al. (2000a) with more stringent GAM convergence criteria and alternative models.	Results differ somewhat from original analyses, especially for pneumonia. Results indicate that the stricter convergence criteria results in about a 14% lower GAM effect than in the originally published analyses method. Authors recommend the penalized spline model results.	COPD 2 day mean (lag 0, lag1): Default GAM ER=9.4 (5.9, 12.9) Strict GAM ER = 8.8 (4.8, 13.0) NS GLM ER=6.8 (2.8, 10.8) PS GLM ER = 8.0 (4.3, 11.9) Pneumonia 2 day mean (lag 0, lag1): Default GAM ER=9.9 (7.4, 12.4) Strict GAM ER =8.8(5.9, 11.8) NS GLM ER=2.9 (0.2,5.6) PS GLM ER = 6.3 (2.5,10.3)

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
United States (cont'd)			
Zanobetti et al. (2000b)+ 10 U.S. Cities	Derived from the Samet et al. (2000a,b) study, but for a subset of 10 cities. Daily hospital admissions for total cardiovascular and respiratory disease in persons aged 65 yr. Covariates: SO_2, O_3, CO, temperature, relative humidity, barometric pressure. In first stage, performed single-pollutant generalized additive robust Poisson regression with seasonal, weather, and day of week controls. Repeated analysis for days with PM_{10} less than 50 $\mu g/m^3$ to test for threshold. Lags of 0-5 d considered, as well as the quadratic function of lags 0-5. Individual cities analyzed first. The 10 risk estimates were then analyzed in several second stage analyses: combining risks across cities using inverse variance weights, and regressing risk estimates on potential effect-modifiers and pollutant confounders.	Same basic pattern of results as in Samet et al. (2000a,b). For distributed lag analysis, lag 0 had largest effect, lags 1 and 2 smaller effects, and none at larger lags. City-specific slopes were independent of percent poverty and percent non-white. Effect size increase when data were restricted to days with PM_{10} less than 50 $\mu g/m^3$. No multi-pollutant models reported; however, no evidence of effect modification by co-pollutants in second stage analysis. Suggests association between PM_{10} and total respiratory hospital admissions among the elderly.	Percent excess respiratory risk (95% CI) per 50 $\mu g/m^3$ PM_{10} increase: COPD (0-1 d lag) = 10.6 (7.9, 13.4) COPD (unconstrained dist. lag) = 13.4 (9.4, 17.4) Pneumonia (0-1 d lag) = 8.1 (6.5, 9.7) Pneumonia (unconstrained dist. lag) = 10.1 (7.7, 12.6)
Jamason et al. (1997) New York City, NY (82 - 92) Population = NR PM_{10} mean = 38.6 $\mu g/m^3$	Weather/asthma relationships examined using a synoptic climatological multivariate methodology. Procedure relates homogenous air masses to daily counts of overnight asthma hospital admission.	Air pollution reported to have little role in asthma variations during fall and winter. During spring and summer, however, the high risk categories are associated with high concentration of various pollutants (i.e., PM_{10}, SO_2,NO_2, O_3).	NR
Chen et al. (2000)+ Reno-Sparks, NV (90 - 94) Population = 307,000 B-Gauge PM_{10} mean=36.5 $\mu g/m^3$ PM_{10} IQR = 18.3-44.9 $\mu g/m^3$ PM_{10} maximum = 201.3 $\mu g/m^3$	Log of COPD (mean=1.72/day) and gastroenteritis (control) admissions from 3 hospitals analyzed using GAM regression, adjusting for effects of day-of-week, seasons, weather effects (T, WS), and long-wave effects. Only one LOESS used with GAM, so the default convergence criteria may be satisfactory in this case. No co-pollutants considered.	PM_{10} positively associated with COPD admissions, but no association with gastroenteritis (GE) diseases, indicating biologically plausible specificity of the PM_{10}-health effects association. Association remained even after excluding days with PM_{10} above 150 $\mu g/m^3$.	<u>COPD All age Admissions</u> 50 $\mu g/m^3$ IQR PM_{10} (single pollutant): ER = 9.4% (CI: 2.2, 17.1)

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
United States (cont'd)			
Gwynn et al. (2000)+ Buffalo, NY (5/88-10/90) PM_{10} mn./max. = 24.1/90.8 µg/m^3 PM_{10} IQR = 14.8-29.2 µg/m^3 $SO_4^=$ mn./max. = 2.4/3.9 µg/m^3 $SO_4^=$ IQR = 23.5 – 7.5 µg/m^3 H^+ mn/max = 36.4/382 nmol/m^3 H^+ IQR = 15.7-42.2 nmol/m^3 CoH mn/max = 0.2/0.9 10 3 ft. CoH IQR = 0.1-0.3	Air pollutant-health effect associations with total, respiratory, and circulatory hospital admissions and mortality examined using Poisson methods controlling for weather, seasonality, long-wave effects, day of week, and holidays using GAM with LOESS terms.	Strongest associations found between $SO_4^=$ and respiratory hospital admissions, while secondary aerosol H^+ and $SO_4^=$ demonstrated the most coherent associations across both respiratory hospital admissions and mortality. Addition of gaseous pollutants to the model had minimal effects on the PM RR estimates. CoH weakness in associations may reflect higher toxicity by acidic sulfur containing secondary particles versus carbonaceous primary particles.	<u>Respiratory Hospital Admissions(all ages) PM Index (using standardized conc. increment)</u> -Single Pollutant Models For PM_{10} = 50 µg/m^3; SO_4 = 15 µg/m^3; H^+ = 75nmoles/m^3;COH = 0.5 units/1000ft PM_{10}(lag 0) ER = 11% (CI: 4.0, 18) $SO_4^=$(lag 0) ER = 8.2% (CI: 4.1, 12.4) H^+(lag 0) ER = 6% (CI: 2.8, 9.3) CoH(lag0) ER = 3% (CI: -1.2, 7.4)
Gwynn and Thurston (2001)+ New York City, NY 1988, 89, 90 PM_{10} 37.4 µg/m^3 mean	Respiratory hospital admissions, race specific for PM_{10}, H^+, O_3, $SO_4^=$. LOESS GAM regression model used to model daily variation in respiratory hospital admissions, day-week, seasonal, and weather aspects addressed in modeling.	Greatest difference between the white and non-white subgroups was observed for O_3. However, within race analyses by insurable coverage suggested that most of the higher effects of air pollution found for minorities were related to socio-economic studies.	PM_{10} (max-min) increment 1 day lag white 1.027 (0.971-1.074) non-white (1.027 (0.988-1.069)
Jacobs et al. (1997) Butte County, CA (83 - 92) Population = 182,000 PM_{10} mean = 34.3 µg/m^3 PM_{10} min/max = 6.6 / 636 µg/m^3 CoH mean = 2.36 per 1000 lin. ft. CoH min/max = 0 / 16.5	Association between daily asthma HA's (mean = 0.65/day) and rice burning using Poisson GLM with a linear term for temperature, and indicator variables for season and yearly population. Co-pollutants were O_3 and CO. PM_{10} estimated for 5 of every 6 days from CoH.	Increases in rice straw burn acreage found to correlate with asthma HA's over time. All air quality parameters gave small positive elevations in RR. PM_{10} showed the largest increase in admission risk.	Asthma HA's (all ages) For an increase of 50 µg/m^3 PM_{10}: ER = 6.11% (not statistically significant)
Linn et al. (2000) Los Angeles, CA (92 - 95) Population = NR PM_{10} mean = 45.5 µg/m^3 PM_{10} Min/Max = 5/132 µg/m^3	Pulmonary hospital admissions (HA's) (mean=74/day) related to CO, NO_2, PM_{10}, and O_3 in Los Angeles using GLM Poisson model with long-wave spline, day of week, holidays, and weather controls.	PM_{10} positively associated with pulmonary admissions year-round, especially in winter. No association with cerebro-vascular or abdominal control diseases. However, use of linear temperature, and with no RH interaction, may have biased effect estimates downwards for pollutants here most linearly related to temperature (i.e., O_3 and PM_{10}).	<u>Pulmonary HA's (>29 yrs.)</u> PM_{10} = 50 µg/m^3 (Lag 0)ER = 3.3% (CI: 1.7, 5)

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
United States (cont'd)			
Moolgavkar et al. (1997)+ Minneapolis-St. Paul 86 - 91 Population.= NR Birmingham, AL '86-'91 Population. = NR PM_{10} mean = 34 µg/m^3 (M-SP) PM_{10} IQR =22-41 µg/m^3 (M-SP) PM_{10} mean =43.4 µg/m^3(Birm) PM_{10} IQR =26-56 µg/m^3(Birm)	Investigated associations between air pollution (PM_{10}, SO_2, NO_2 O_3, and CO) and hospital admissions for COPD (mean/day=2.9 in M-SP; 2.3 in Birm) and pneumonia (mean=7.6 in M-SP; 6.0 in Birm) among older adults (>64 yrs.). Poisson GAM's used, controlling for day-of-week, season, LOESS of temperature (but neither RH effects nor T-RH interaction considered).	In the M-SP area, PM_{10} significantly and positively associated with total daily COPD and pneumonia admissions among elderly, even after simultaneous inclusion of O_3. When four pollutants included in the model (PM_{10}, SO_2, O_3, NO_2), all pollutants remained positively associated. In Birm., neither PM_{10} nor O_3 showed consistent associations across lags. The lower power (fewer counts) and lack of T-RH interaction weather modeling in this Southern city vs. M-SP may have contributed to the differences seen between cities.	<u>COPD + Pneumonia Admissions (>64yrs.)</u> In M-SP, For PM_{10} = 50 µg/m^3 (max lg) ER(lg 1) = 8.7% (CI: 4.6, 13) With O_3 included simultaneously: ER(lg1)= 6.9% (95 CI: 2.7, 11.3) In Birm, For PM_{10}=50 µg/m^3 (max lg.) ER(lg 0) = 1.5% (CI: -1.5, 4.6) With O_3 included simultaneously: ER(lg0) = 3.2% (CI: -0.7, 7.2)
Nauenberg and Basu (1999) Los Angeles (91 - 94) Wet Season = 11/1-3/1 Dry Season = 5/1-8/15 Population .= 2.36 Million PM_{10} Mean = 44.81 µg/m^3 PM_{10} SE = 17.23 µg/m^3	The effect of insurance status on the association between asthma-related hospital admissions and exposure to PM_{10} and O_3 analyzed, using GLM Poisson regression techniques with same day and 8-day weighted moving average levels, after removing trends using Fourier series. Compared results during wet season for all asthma HA's (mean = 8.7/d), for the uninsured (mean=0.77/d), for MediCal (poor) patients (mean = 4.36/d), and for those with other private health or government insurance (mean = 3.62/d).	No associations found between asthma admissions and O_3. No O_3 or PM_{10} associations found in dry season. PM_{10} averaged over eight days associated with increase in asthma admissions, with even stronger increase among MediCal asthma admissions in wet season. The authors conclude that low income is useful predictor of increased asthma exacerbations associated with air pollution. Non-respiratory HA's showed no such association with PM_{10}.	<u>All Age Asthma HA's</u> PM_{10} = 50 µg/m^3, no co-pollutant, during wet season (Jan. 1 - Mar. 1): <u>All Asthma Hospital Admissions</u> 0-d lag PM_{10} ER = 16.2 (CI: 2.0, 30) 8-d avg. PM_{10} ER = 20.0 (CI: 5.3, 35) <u>MediCal Asthma Hospital Admissions</u> 8-d avg. PM_{10} ER = 13.7 (3.9, 23.4) <u>Other Insurance Asthma HA's</u> 8-d avg. PM_{10} ER = 6.2 (-3.6, 16.1)
Schwartz et al. (1996b) Cleveland (Cayahoga County), Ohio (88 - 90) PM_{10} mean = 43 µg/m^3 PM_{10} IQR = 26 – 56 µg/m^3	Review paper including an example drawn from respiratory hospital admissions of adults aged 65 yr and older (mean = 22/day) in Cleveland, OH. Categorical variables for weather and sinusoidal terms for filtering season employed.	Hospital admissions for respiratory illness of persons aged 65 yr and over in Cleveland strongly associated with PM_{10} and O_3, and marginally associated with SO_2 after control for season, weather, and day of the week effects.	<u>Respiratory HA's for persons 65+ years</u> 50 µg/m^3 PM_{10} ER = 5.8% (CI: 0.5, 11.4)

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
United States (cont'd)			
Zanobetti, et al. (2000a)+ Study Period: 86 - 94 Chicago (Cook Count), IL Population = 633,000 aged 65+ PM_{10} mean = 33.6 µg/m^3 PM_{10} range = 2.2, 157.3 µg/m^3	Analyzed HA's for older adults (65 + yr) for COPD (mean = 7.8/d), pneumonia (mean = 25.5/d), and CVD, using GLM Poisson regression controlling for temperature, dew point, barometric pressure, day of week, long wave cycles and autocorrelation, to evaluate whether previous admission or secondary diagnosis for associated conditions increased risk from air pollution. Effect modification by race, age, and sex also evaluated.	Air pollution- associated CVD HA's were nearly doubled for those with concurrent respiratory infections (RI) vs. those without concurrent RI. For COPD and pneumonia admissions, diagnosis of conduction disorders or dysrhythmias (Dyshr.) increased PM_{10} RR estimate. The PM_{10} RR effect size did not vary significantly by sex, age, or race, but baseline risks across these groups differ markedly, making such sub-population RR inter-comparisons difficult to interpret.	PM_{10} = 50 µg/m^3(average of lags 0,1) COPD (adults 65+ yrs.) W/o prior RI. ER = 8.8% (CI: 3.3, 14.6) With prior RI ER = 17.1% (CI: -6.7, 46.9) COPD (adults 65+ yrs.) W/o concurrent Dys. ER = 7.2% (CI: 1.3, 13.5) With concurrent Dys. ER = 16.5%(CI: 3.2, 31.5) Pneumonia (adults 65+ yrs.) W/o pr. Asthma ER = 11% (CI: 7.7, 14.3) With pr. Asthma ER = 22.8% (CI: 5.1, 43.6) Pneumonia (adults 65+ yrs.) W/o pr. Dyshr. ER = 10.4% (CI: 6.9, 14) With pr. Dyshr. ER = 18.8% (CI: 6.3, 32.7)

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
United States (cont'd)			
Lippmann et al. (2000)* Detroit, MI ('92-'94) Population = 2.1 million PM_{10} Mean = 31 µg/m^3 (IQR= 19, 38 µg/m^3; max=105 µg/m^3) $PM_{2.5}$ Mean = 18 µg/m^3 (IQR= 10, 21 µg/m^3; max=86 µg/m^3) $PM_{10-2.5}$ Mean = 12 µg/m^3 (IQR= 8, 17 µg/m^3; max=50 µg/m^3) $SO_4^=$Mean = 5 µg/m^3 (IQR=1.8, 6.3 µg/m^3; max=34.5 µg/m^3) H^+ Mean = 8.8 nmol/m^3 = 0.4 µg/m^3 (IQR=0, 7nmol/m^3;max=279)	Respiratory (COPD and Pneumonia) HA's for persons 65 + yr. analyzed, using GAM Poisson models, adjusting for season, day of week, temperature, and relative humidity using LOESS smooths. The air pollution variables analyzed were: PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, sulfate, H^+, O_3, SO_2, NO_2, and CO. However, this study site/period had very low acidic aerosol levels. As noted by the authors 85% of H^+ data was below detection limit (8 nmol/m^3).	For respiratory HA's, all PM metrics yielded RR's estimates >1, and all were significantly associated in single pollutant models for pneumonia. For COPD, all PM metrics gave RR's >1, with H^+ being associated most significantly, even after the addition of O_3 to the regression. Adding gaseous pollutants had negligible effects on the various PM metric RR estimates. The most consistent effect of adding co-pollutants was to widen the confidence bands on the PM metric RR estimates: a common statistical artifact of correlated predictors. Despite usually non-detectable levels, H^+ had strong association with respiratory admissions on the few days it was present. The general similarity of the $PM_{2.5}$ and $PM_{10-2.5}$ effects per µg/m^3 in this study suggest similarity in human toxicity of these two inhalable mass components in study locales/periods where $PM_{2.5}$ acidity is usually not present.	<u>Pneumonia HA's for 65+ yrs.</u> <u>No co-pollutant:</u> PM_{10} (50 µg/m^3) 1d lag ER = 22% (CI: 8.3, 36) $PM_{2.5}$ (25 µg/m^3) 1d lag: ER = 13% (CI: 3.7, 22) $PM_{2.5-10}$ (25 µg/m^3) 1d lag: ER = 12% (CI: 0.8, 24) H^+ (75 nmol/m^3) 3d lag: ER = 12% (CI: 0.8, 23) <u>O_3 co-pollutant (lag 3) also in model:</u> PM_{10} (50 µg/m^3) 1d lag, ER = 24% (CI: 8.2, 43) $PM_{2.5}$ (25 µg/m^3) 1d lag: ER = 12% (CI: 1.7, 23) $PM_{2.5-10}$ (25 µg/m^3) 1d lag: ER = 14% (CI: 0.0, 29) H^+ (75 nmol/m^3) 3d lag: ER = 11% (CI: -0.9, 24) <u>COPD Hospital Admissions for 65+ yrs.</u> <u>No co-pollutant:</u> PM_{10} (50 µg/m^3) 3d lag ER = 9.6% (CI: -5.1, 27) $PM_{2.5}$ (25 µg/m^3) 3d lag: ER = 5.5% (CI: -4.7, 17) $PM_{2.5-10}$ (25 µg/m^3) 3d lag: ER = 9.3% (CI: -4.4, 25) H^+ (75 nmol/m^3) 3d lag: ER = 13% (CI: 0.0, 28) <u>O_3 co-pollutant (lag 3) also in model:</u> PM_{10} (50 µg/m^3) 3d lag, ER = 1.0% (-15, 20) $PM_{2.5}$ (25 µg/m^3) 3d lag: ER = 2.8% (CI: -9.2, 16) $PM_{2.5-10}$ (25 µg/m^3) 3d lag: ER = 0.3% (CI: -14, 18) H^+ (75 nmol/m^3) 3d lag: ER = 13% (CI: -0.6, 28)

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
United States (cont'd)			
Reanalysis by Ito (2003)	Re-analyses of Lippmann et al. (2000) with more stringent GAM convergence criteria and alternative models.	More stringent GAM generally, but not always, resuled in reduced RR estimates, but effect sizes not significantly different from originals. Extent fo reuction independent of risk estimate size. The reductions were not differential across PM components, so study conclusions unchanged.	**Pneumonia** (PM_{10}= 50 ug/m^3, LAG= 1D, No Co Poll): Default GAM: ER= 21.5 (8.3, 36) Strict GAM: ER=18.1 (5.3, 32.5) NS GLM: ER=18.6 (5.6, 33.1) **COPD** (PM_{10}= 50 ug/m^3, LAG= 3D, No Co Poll): Default GAM: ER= 9.6 (-5.3, 26.8) Strict GAM: ER=6.5 (-7.8, 23.0) NS GLM: ER=4.6 (-9.4, 20.8) **COPD** ($PM_{2.5}$,=25 ug/m^3, Lag=1D, No Co Poll): Default GAM: ER =5.5 (-4.7, 16.8) Strict GAM: ER=3.0(-6.9, 13.9) NS GLM: ER=0.3(-9.3, 10.9) **Pneumonia** ($PM_{2.5}$,=25 ug/m^3, LAG= 1D,No Co Poll): Default GAM: ER = 12.5 (3.7, 22.1) Strict GAM:ER = 10.5 (1.8, 19.8) NS GLM: 10.1 (1.5, 19.5)
Lumley and Heagerty (1999) Seattle (King Cty.), WA (87-94) Population = NR PM_1 daily mean = NR PM_{1-10} daily mean = NR From Sheppard et al, 1999: PM_{10} mean = 31.5 µg/m^3 PM_{10} IQR = 19-39 µg/m^3 $PM_{2.5}$ mean = 16.7 µg/m^3 $PM_{2.5}$ IQR = 8-21 µg/m^3	Estimating equations based on marginal generalized linear models (GLM) applied to respiratory HA's for persons <65 yrs. of age (mean ˜ 8/day) using class of variance estimators based upon weighted empirical variance of the estimating functions. Poisson regression used to fit a marginal model for the log of admissions with linear temperature, day of week, time trend, and dummy season variables. No co-pollutants considered.	PM_1 at lag 1 day associated with respiratory HA's in children and younger adults (<65), but not PM_{10-1}, suggesting a dominant role by the submicron particles in $PM_{2.5}$–asthma HA associations reported by Sheppard et al. (1999). 0-day lag PM_1 and 0 and 1 day lag PM_{1-10} had RR near 1 and clearly non-significant. Authors note that model residuals correlated at r=0.2, suggesting the need for further long-wave controls in the model (e.g., inclusion of the LOESS of HA's).	<u>Respiratory HA's for persons <65 yrs. old</u> PM_1 = 25 µg/m^3, no co-pollutant: 1-d lag ER = 5.9 (1.1, 11.0)

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
United States (cont'd)			
Moolgavkar et al. (2000)+ King County, WA (87 - 95) Population = NR PM_{10} mean = 30.0 µg/m^3 PM_{10} IQR =18.9-37.3 µg/m^3 $PM_{2.5}$ mean =18.1 µg/m^3 $PM_{2.5}$ IQR =10-23 µg/m^3	Association between air pollution and hospital admissions (HA's) for COPD (all age mean=7.75/day; 0-19 yrs. mean=2.33/day) investigated using Poisson GAM's controlling for day-of-week, season, and LOESS of temperature. Co-pollutants addressed: O_3, SO_2, CO, and pollens. $PM_{2.5}$ only had one monitoring site versus multiple sites averaged for other pollutants.	Of the PM metrics, PM_{10} showed the most consistent associations across lags (0-4 d). $PM_{2.5}$ yielded the strongest positive PM metric association at lag3 days, but gave a negative association at lag4 days. That $PM_{2.5}$ only had one monitoring site may have contributed to its effect estimate variability. Residual autocorrelations (not reported) may also be a factor. Adding gaseous co-pollutants or pollens decreased the $PM_{2.5}$ effect estimate less than PM_{10}. Analyses indicated that asthma HA's among the young were driving the overall COPD-air pollution associations.	<u>COPD HA's all ages</u> (no co-pollutant) PM_{10} (50 µg/m^3, lag 2) ER = 5.1% (CI: 0, 10.4) $PM_{2.5}$ (25 µg/m^3, lag 3) ER = 6.4% (CI: 0.9, 12.1) COPD HA's all ages (CO as co-pollutant) PM_{10} (50 µg/m^3, lag 2) ER = 2.5% (CI: -2.5, 7.8) $PM_{2.5}$ (25 µg/m^3, lag 3) ER = 5.6% (CI: 0.2, 11.3)
Moolgavkar (2000a)* Study Period: 1987-1995 <u>Chicago (Cook County), IL</u> Population = NR PM_{10} median = 35 µg/m^3 PM_{10} IQR = 25-47 µg/m^3 <u>Los Angeles (LA County), CA</u> Population = NR PM_{10} median = 44 µg/m^3 PM_{10} IQR = 33-59 µg/m^3 $PM_{2.5}$ median = 22 µg/m^3 $PM_{2.5}$ IQR = 15-31 µg/m^3 <u>Phoenix (Maricopa County), AZ</u> Population = NR PM_{10} median = 41 µg/m^3 PM_{10} IQR = 32-51 µg/m^3	Investigated associations between air pollution (PM_{10}, O_3, SO_2, NO_2, and CO) and COPD Hospital Admissions (HA's). $PM_{2.5}$ also analyzed in Los Angeles. HA's for adults >65 yr.: median=12/day in Chicago, =4/d in Phoenix; =20/d in LA. Analyses employed 30df to fit long wave. In LA, analyses also conducted for children 0-19 yr. (med.=17/d) and adults 20-64 (med.=24/d). Poisson GAM's used controlling for day-of-week, season, and splines of temperature and RH (but not their interaction) adjusted for overdispersion. PM data available only every 6th day (except for daily PM_{10} in Chicago), vs. every day for gases. Power likely differs across pollutants, but number of sites and monitoring days not presented. Two pollutant models forced to have same lag for both pollutants. Autocorrelations or intercorrelations of pollutant coefficients not presented or discussed.	For >64 adults, CO, NO_2 and O_3 (in summer) most consistently associated with the HA's. PM effects more variable, especially in Phoenix. Both positive and negative significant associations for PM and other pollutants at different lags suggest possible unaddressed negative autocorrelation. In LA, PM associated with admissions in single pollutant models, but not in two pollutant models. The forcing of simultaneous pollutants to have the same lag (rather than maximum lag), which likely maximizes intercorrelations between pollutant coefficients, may have biased the two pollutant coefficients, but information not presented. Analysis in 3 age groups in LA yielded similar results. Author concluded that "the gases, other than ozone, were more strongly associated with COPD admissions than PM, and that there was considerable heterogeneity in the effects of individual pollutants in different geographic areas".	Most Significant Positive ER Single Pollutant Models: <u>COPD HA's (>64 yrs.)</u> (50 µg/m^3 PM_{10}): Chicago: Lag 0 ER =2.4% (CI: -0.2, 4.3) LA: Lag 2 ER = 6.1% (CI: 1.1, 11.3) Phoenix: Lag 0 ER = 6.9% (CI: -4.1, 19.3) <u>LA COPD HA's</u> (50 µg/m^3 PM_{10}, 25 µg/m^3 $PM_{2.5}$ or $PM_{2.5-10}$) (0-19 yrs.): PM_{10} lg2=10.7%(CI: 4.4, 17.3) (0-19 yrs.): $PM_{2.5}$ lg0=4.3%(CI: -0.1, 8.9) (0-19 yrs.): $PM_{(2.5-10)}$ lg2=17.1%(CI: 8.9, 25.8) (20-64 yrs.): PM_{10} lg2=6.5%(CI: 1.7, 11.5) (20-64 yrs.): $PM_{2.5}$ lg2=5.6%(CI: 1.9, 9.4) (20-64 yrs.): $PM_{2.5-10}$ lg2=9%(CI: 3, 15.3) (> 64 yrs): PM_{10} lg2 = 6.1% (1.1, 11.3) (> 64 yrs): $PM_{2.5}$ lg2 = 5.1% (0.9, 9.4) (>64 yrs.): $PM_{2.5-10}$ lg3=5.1% (CI: -0.4, 10.9) (>64 yr) 2 Poll. Models (CO = co-poll.) PM_{10}: Lag 2 ER = 0.6% (CI: -5.1, 6.7) $PM_{2.5}$: Lag 2 ER = 2.0% (-2.9, 7.1)

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
United States (cont'd)			
Reanalysis by Moolgavkar (2003)	Re-analyses of Moolgavkar (2000a) with more stringent GAM convergence criteria and alternative models.	GAM effect estimates virtually unchanged from originals using when GAM stringent criteria applied in LA (direct comparisons not possible in Chicago). In LA, changes in spline degrees of freedom had much more influence on effect size than the change in convergence criteria, especially for PM_{10}. In Chicago, small insignificant association of PM_{10} in the original work actually increased and became significant with the 100df model. Authors conclude the "basic qualitative conclusions unchanged".	LA COPD (all ages), LAG= 2D, PM_{10} =50ug/m3 Default GAM:30df** ER= 7.36% (CI:4.32-11.39) Strict GAM:30df ER= 7.78% (CI:4.32-10.51) Strict GAM: 100df ER = 7.78% (CI:4.32-10.51) NS GLM: 100df ER=5.00% (CI:1.22, 8.91) LA COPD (all ages), LAG=2D, $PM_{2.5}$ =25 ug/m3 Default GAM:30df** ER=4.82% (CI:2.44, 7.25) Strict GAM:30df ER=4.69% (CI:2.06, 7.38) Strict GAM: 100df ER=2.87% (CI:0.53, 5.27) NS GLM: 100df ER=2.59% (CI:-0.29, 5.56) Chicago COPD (>64yrs) LAG= 0D, PM_{10}=50ug/m^3 Default GAM (30df) ER =2.4% (CI: --0.2, 4.3) Default GAM (100df) not provided for comparison Strict GAM (100df) ER=3.24% (CI:0.031-6.24)
Sheppard et al. (1999)* Seattle, WA, Pop. = NR 1987-1994 PM_{10} mean = 31.5 µg/m^3 PM_{10} IQR = 19-39 µg/m^3 $PM_{2.5}$ mean = 16.7 µg/m^3 $PM_{2.5}$ IQR = 8-21 µg/m^3 $PM_{2.5-10}$ mean = 16.2 µg/m^3 $PM_{2.5-10}$ IQR = 9-21 µg/m^3	Daily asthma hospital admissions (HA's) for residents aged <65 (mean=2.7/day) regressed on PM_{10}, $PM_{2.5}$, $PM_{2.5-10}$, SO_2, O_3, and CO in a Poisson regression model with control for time trends, seasonal variations, and temperature-related weather effects. Appendicitis HA's analyzed as a control. Except O_3 in winter, missing pollutant measures estimated in a multiple imputation model. Pollutants varied in number of sites available for analysis, CO the most (4) vs. 2 for PM.	Asthma HA's significantly associated with PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ mass lagged 1 day, as well as CO. Authors found PM and CO to be jointly associated with asthma admissions. Highest increase in risk in spring and fall. Results conflict with hypothesis that wood smoke (highest in early study years and winter) would be most toxic. Associations of CO with respiratory HA's taken by authors to be an index of incomplete combustion, rather than direct CO biological effect.	<u>Asthma Admissions (ages 0-64)</u> PM_{10} (lag=1day); 50 µg/m^3 ER = 13.7% (CI: 5.5%, 22.6) $PM_{2.5}$ (lag=1day); 25 µg/m^3 ER = 8.7% (CI: 3.3%, 14.3) $PM_{2.5-10}$ (lag=1day); 25 µg/m^3 ER = 11.1% (CI: 2.8%, 20.1)

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
United States (cont'd)			
Reanalysis by Sheppard (2003)	Re-analyses of Sheppard et al. (1999) with more stringent GAM convergence criteria and alternative models.	The author notes that "While the biases from computational details of the fitting were small, they are not completely trivial given the small effects of interest." She concludes that: "Overall the results did not change meaningfully".	Asthma (ages 0-64) LAG=1day, PM_{10}=50 ug/m^3 No Co-Poll: Default GAM: ER = 13.7% (CI: 5.5%, 22.6) Strict GAM: ER= 8.1 (0.1, 16.7) NS GLM : ER=10.9 (2.8, 19.6) Asthma (all ages) LAG=1day, $PM_{2.5}$=25 ug/m^3 No Co-Poll: Default GAM : ER= 8.7% (3.3, 14.3) Strict GAM: ER=6.5% (1.1,12.0) NS GLM: ER= 8.7% (3.3,14.4) With Co-poll: Strict GAM: ER=6.5 (2.1, 10.9) NS GLM: ER=6.5 (2.1, 10.9)
Freidman et al. (2001) Atlanta, GA Summer 1996/control vs. Olympics PM_{10} decrease for 36.7 µg/m^3 to 30.8 µg/m^3	Asthma events in children aged 1 to 16 years were related to pollutant levels contrasting those during the Summer Olympics games during a 17 day period to control periods before and after the Olympics. GEE Poisson regression with autoregressive terms employed.	Asthma events were reduced during the Olympic period. A significant reduction in asthma events was associated with ozone concentration. The high correlation between ozone and PM limit the ability to determine which pollutants may have accounted for the reduction in asthma events.	3 day cumulative exposure PM_{10} per 10 µg/m^3 1.0 (0.80-2.48)
Zanobetti and Schwartz (2001)+ Cook County, Illinois 1988-1994 PM_{10}: 33 µg/m^3 median	Respiratory admissions for lung disease in persons with or without diabetes as a co-morbidity related to PM_{10} measures. The generalized additive model used nonparametric LOESS functions to estimate the relation between the outcome and each predictor. The covariates examined were temperature, prior day's temperature, relative humidity, barometric pressure, and day of week.	Weak evidence that diabetes modified the risks of PM_{10} induced respiratory hospital admissions while diabetes modified the risk of PM_{10} induced COPD admissions in older people. Found a significant interaction with hospital admissions for heart disease and PM with more than twice the risk in diabetics as in persons without diabetes.	<u>COPD</u> PM_{10} 10 µg/m^3 with diabetes 2.29 (-0.76-5.44) without diabetes 1.50 (0.42-2.60)
Janssen et al. (2002)+ 14 U.S. cities 1985-1994 see Samet et al. (2000a,b)	Regression coefficients of the relation between PM_{10} and hospital admissions for respiratory disease from Samet et al. (2000a,b) and prevalence of air conditioning (AC).	Regression coefficients of the relation between ambient PM_{10} and hospital admissions for COPD decreased with increasing percentage of homes with central AC.	—

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Canada (cont'd)			
Burnett et al. (1997b) Toronto, Canada (1992-1994), Pop. = 4 mill. $PM_{2.5}$ mean = 16.8 µg/m^3 $PM_{2.5}$ IQR = 8-23 µg/m^3 $PM_{2.5-10}$ mean = 11.6 µg/m^3 $PM_{2.5-10}$ IQR = 7-14 µg/m^3 PM_{10} mean = 28.4 µg/m^3 PM_{10} IQR = 16-38 µg/m^3 CoH mean = 0.8 (per 10^3 lin. ft.) CoH IQR = 0.5-1.1(per 10^3 lin ft) SO_4 mean = 57.1 nmole/m^3 SO_4 IQR = 14-71 nmole/m^3 H^+ mean = 5 nmole/m^3 H^+ IQR = 0-6 nmole/m^3	Hospital admissions (HA's) for respiratory diseases (tracheobronchitis, chronic obstructive long disease, asthma, pneumonia) analyzed using Poisson regression (adjusting for long-term temporal trends, seasonal variations, effects of short-term epidemics, day-of-week, ambient temperature and dew point). Both linear prefiltering Poisson regression and LOESS GAM models applied. Daily particle measures: $PM_{2.5}$, coarse particulate mass($PM_{10-2.5}$), PM_{10}, SO_4, H^+, and gaseous pollutants (O_3, NO_2, SO_2, and CO) evaluated.	Positive air pollution-HA associations found, with ozone being pollutant least sensitive to adjustment for co-pollutants. However, even after the simultaneous inclusion of O_3 in the model, the association with the respiratory hospital admissions were still significant for PM_{10}, $PM_{2.5}$, $PM_{2.5-10}$, $CoH_,$, SO_4, and H^+.	<u>Respiratory HA's all ages</u>(no co-pollutant) PM_{10} (50 µg/m^3, 4d avg. lag 0) ER = 10.6% (CI: 4.5 - 17.1) $PM_{2.5}$ (25 µg/m^3, 4d avg. lag 1) ER = 8.5% (CI: 3.4, 13.8) $PM_{2.5-10}$ (25 µg/m^3, 5d avg. lag 0) ER = 12.5% (CI: 5.2, 20.0) <u>Respiratory HA's all ages</u>(O_3 co-pollutant) PM_{10} (50 µg/m^3, 4d avg. lag 0) ER = 9.6% (CI: 3.5, 15.9) $PM_{2.5}$ (25 µg/m^3, 4d avg., lag 1) ER = 6.2% (1.0, 11.8) $PM_{2.5-10}$ (25 µg/m^3, 5d avg. lag 0) ER = 10.8% (CI: 3.7, 18.1)
Burnett et al. (1999)+ Metro-Toronto, Canada 1980-1994 Pollutant: mean, median, IQR: FP_{est} (µg/m^3): 18, 16, 10 CP_{est} (µg/m^3): 12, 10, 8 $PM_{10\ est}$ (µg/m^3): 30, 27, 15	Daily hospitalizations for asthma (493, mean 11/day), obstructive lung disease (490-492, 496, mean 5/day), respiratory infection (464, 466, 480-487, 494, mean 13/day) analyzed separately in relation to environmental covariates. Same geographic area as in Burnett et al., 1997b. Three size-classified PM metrics were <u>estimated</u>, not measured, based on a regression on TSP, SO_4, and COH in a subset of every 6th-day data. Generalized additive models. Applied with non-parametric LOESS prefilter applied to both pollution and hospitalization data. Day of week controls. Tested 1-3 day averages of air pollution ending on lags 0-2. Covariates: O_3, NO_2, SO_2, CO, temperature, dewpoint temperature, relative humidity.	In univariate regressions, all three PM metrics were associated with increases in respiratory outcome. In multi-pollutant models, there were no significant PM associations with any respiratory outcome (results not shown). Use of estimated PM metrics limits the interpretation of pollutant-specific results reported. However, results suggest that a linear combination of TSP, SO_4, and COH does not have a strong independent association with cardiovascular admissions when a full range of gaseous pollutants are also modeled.	Percent excess risk (95% CI) per 50 µg/m^3 PM_{10}; 25 µg/m^3 $PM_{2.5}$ and $PM_{(10-2.5)}$: <u>Asthma</u> $PM_{2.5}$ (0-1-2 d): 6.4 (2.5, 10.6) PM_{10} (0-1 d): 8.9 (3.7, 14.4) $PM_{10-2.5}$ (2-3-4 d): 11.1 (5.8, 16.6) <u>COPD</u> $PM_{2.5}$: 4.8 (-0.2, 10.0) PM_{10}: 6.9 (1.3, 12.8) $PM_{10-2.5}$ (2-3-4 d): 12.8 (4.9, 21.3) <u>Resp. Infection:</u> $PM_{2.5}$: 10.8 (7.2, 14.5) PM_{10}: 14.2 (9.3, 19.3) $PM_{10-2.5}$ (0-1-2 d): 9.3 (4.6, 14.2)
Burnett et al. (1997c) 16 Canadian Cities('81-91) Population=12.6 MM CoH mean=0.64(per 10^3 lin. ft) CoH IQR=0.3-0.8(per 10^3 lin ft)	Air pollution data were compared to respiratory hospital admissions (mean=1.46/million people/day) for 16 cities across Canada. Used a random effects regression model, controlling for long-wave trends, day of week, weather, and city-specific effects using a linear prefiltered random effects relative risk regression model.	The 1 day lag of 0_3 was positively associated with respiratory admissions in the April to December period, but not in the winter months. Daily maximum 1-hr. CoH from 11 cities and CO also positively associated with HA's, even after controlling for O_3.	<u>Respiratory HA's all ages (with O_3,CO)</u> CoH IQR = 0.5, lag 0: CoH ER = 3.1% (CI: 1.0-4.6%)

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Canada (cont'd)			
Burnett et al. (2001b)+ Toronto, Canada 1980-1994 $PM_{2.5}$: 18 µg/m^3 $PM_{10-2.5}$: 16.2 µg/m^3 (both estimated values)	Respiratory admissions in children aged <2 years relates to mean pollution levels. O_3, NO_2, SO_2, and CO (ICD-9: 493 asthma; 466 acute bronchitis; 464.4 croup or pneumonia, 480-486). Time-series analysis adjusted with LOESS.	Summertime urban air pollution, especially ozone, increases the risk that children less than 2 years of age will be hospitalized for respiratory disease.	$PM_{2.5}$ lag 0 15.8% (t=3.29) $PM_{2.5}$ lag 0 with O_3 1.4% (0.24) $PM_{10-2.5}$ lag 1 18.3% (t=3.29) with O_3 4.5% (0.72)
Europe			
Atkinson et al. (1999b) London (92 - 94) Population = 7.2 MM PM_{10} Mean = 28.5 10^{th}-90^{th} IQR = 15.8-46.5 µg/m^3 BS mean = 12.7 µg/m^3 10^{th}-90^{th} IQR = 5.5-21.6 µg/m^3	All-age respiratory (mean=150.6/day), all-age asthma (38.7/day), COPD plus asthma in adults >64 yr. (22.9/day), and lower respiratory (64.1/day) in adults >64 yr (16.7/day) hospital admissions in London hospitals considered. Counts for ages 0-14, 15-64, and >64 yr also examined. Poisson GLM regression used, controlling for season, day-of-week, meteorology, autocorrelation, overdispersion, and influenza epidemics.	Positive associations found between respiratory-related emergency hospital admissions and PM_{10} and SO_2, but not for O_3 or BS. When SO_2 and PM_{10} included simultaneously, size and significance of each was reduced. Authors concluded that SO_2 and PM_{10} are both indicators of the same pollutant mix in this city. SO_2 and PM_{10} analyses by temperature tertile suggest that warm season effects dominate. Overall, results consistent with earlier analyses for London, and comparable with those for North America and Europe.	PM_{10} (50 µg/m^3), no co-pollutant. All Respiratory Admissions: All age (lag 1d) ER = 4.9% (CI: 1.8, 8.1) 0-14 y (lag 1d) ER = 8.1% (CI: 3.5, 12.9) 15-64y (lag 2d) ER = 6.9% (CI: 2.1, 12.9) 65+ y (lag 3d) ER = 4.9% (CI: 0.8, 9.3) Asthma Admissions: All age (lag 3d) ER = 3.4% (CI: -1.8, 8.9) 0-14 y (lag 3d) ER = 5.4% (CI: -1.2, 12.5) 15-64 y(lag 3d) ER = 9.4% (CI: 1.1, 18.5) 65+ y.(lag 0d) ER = 12% (CI: -1.8, 27.7) COPD & Asthma Admissions (65+yrs.) (lag 3d) ER = 8.6% (CI: 2.6, 15) Lower Respiratory Admissions (65+ yrs.) (lag 3d) ER = 7.6% (CI: 0.9, 14.8)
Wordley et al. (1997) Study Period: 4/92 –3/94 Birmingham, UK Population = NR PM_{10} daily values: Mean = 25.6 µg/m^3 range = 2.8, 130.9 µg/m^3 PM_{10} 3 day running. mean: Mean = 25.5 µg/m^3 range = 7.3, 104.7 µg/m^3	Relation between PM_{10} and total HA's for respiratory (mean = 21.8/d), asthma (mn.=6.2/d), bronchitis (mn.=2.4/d), pneumonia (mn.=3.4/d), and COPD (mn.=3.2/d) analyzed, using log-linear regression after adjusting for day of week, month, linear trend, RH, and T (but not T-RH interaction). RR's compared for various thresholds vs. mean risk of HA.	PM_{10} positively associated with all HA's for respiratory, asthma, bronchitis, pneumonia, and COPD. Pneumonia, all respiratory, and asthma HA's also significantly positively associated with the mean of PM_{10} over the past three days, which gave 10 to 20% greater RR's per 10 µg/m^3, as expected given smaller day to day deviations. Other air pollutants examined but not presented, as "these did not have a significant association with health outcomes independent from that of PM_{10}".	50 µg/m^3 in PM_{10} All Respiratory HA's (all ages) (lag0d) ER = 12.6% (CI: 5.7, 20) Asthma HA's (all ages) (lag2d) ER = 17.6% (CI: 3, 34.4) Bronchitis HA's (all ages) (lag0d) ER= 32.6% (CI: 4.4, 68.3) Pneumonia HA's (all ages) (lag3d) ER = 31.9% (CI: 15, 51.4) COPD HA's (all ages) (lag1d) ER = 11.5% (CI: -3, 28.2)

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Europe (cont'd)			
Prescott et al. (1998) Edinburgh (10/92-6/95) Population = 0.45 MM PM_{10} mean. =20.7 µg/m^3 PM_{10} min/max=5/72 µg/m^3 PM_{10} 90th% - 10th% = 20 µg/m^3	Poisson log-linear regression models used to investigate relation of daily HA's with NO_2, O_3, CO, and PM_{10}. Adjustments made for seasonal and weekday variation, daily T (using 8 dummy variables), and wind speed. Separate analyses for age<65 yr. (mean resp HA = 3.4/day) and age >64 yr. (mean resp HA = 8.7/day), and for subjects with multiple HA's.	The two strongest findings were for cardiovascular HA's of people aged >64, which showed a positive association with PM_{10} as a mean of the 3 previous days. PM_{10} was consistently positively associated with Respiratory HA's in both age groups, with the greatest effect size in those >64, especially among those with >4 HA's during '81-'95. Weak significances likely contributed to by low population size.	Single Pollutant Models PM_{10} = 50 µg/m^3, mean of lags 1-3 <u>Respiratory HA's (age<65)</u> ER = 1.25 (-12.8, 17.5) <u>Respiratory HA's (age>64)</u> ER = 5.33 (-9.3, 22.3) <u>Respiratory HA's (age>64, >4 HA's)</u> ER = 7.93 (-19.0, 43.7)
McGregor et al. (1999) Birmingham, UK. Population = NR Mean PM_{10} = 30.0 µg/m^3	A synoptic climatological approach used to investigate linkages between air mass types (weather situations), PM_{10}, and all respiratory hospital admissions (mean= 19.2/day) for the Birmingham area.	Study results show distinct differential responses of respiratory admission rates to the six winter air mass types. Two of three types of air masses associated with above- average admission rates also favor high PM_{10} levels. This is suggestive of possible linkage between weather, air quality, and health.	NR
Hagen et al. (2000)+ Drammen, Sweden(11/94-12/97) Population = 110,000 PM_{10} mean = 16.8 µg/m^3 PM_{10} IQR = 9.8-20.9 µg/m^3	Examined PM_{10}, SO_2, NO_2, VOC's, and O_3 associations with respiratory hospital admissions from one hospital (mean = 2.2/day). Used Poisson GAM controlling for temperature and RH (but not their interaction), long-wave and seasonality, day-of-week, holidays, and influenza epidemics.	As a single pollutant, the PM_{10} effect was of same order of magnitude as reported in other studies. The PM_{10} association decreased when other pollutants were added to the model. However, the VOC's showed the strongest associations.	<u>Respiratory Hospital Admissions(all ages)</u> For IQR=50 µg/m^3 -Single Pollutant Model: PM_{10} (lag 0) ER = 18.3% (CI: -4.2, 46) -Two Pollutant Model (with O_3): PM_{10} (lag 0) ER = 18.3% (CI: -4.2, 45.4) -Two Pollutant Model (with Benzene): PM_{10} (lag 0) ER = 6.5% (CI:-14 , 31.8)
Dab et al. (1996) Paris, France (87 - 92) Population = 6.1 MM PM_{13} mean = 50.8 µg/m^3 PM_{13} 5th-95th range = 19.0-137.3 BS mean = 31.9 µg/m^3 BS 5th-95th Range =11.0-123.3	Daily mortality and general admissions to Paris public hospitals for respiratory causes were considered (means/day: all resp.=79/d, asthma=14/d, COPD=12/d). Time series analysis used linear regression model followed by a Poisson regression. Epidemics of influenza A and B, temperature, RH, holidays, day of week, trend, long-wave variability, and nurses' strike variables included. No two pollutant models considered.	For the all respiratory causes category, the authors found "the strongest association was observed with PM_{13}" for both hospital admissions and mortality, indicating a coherence of association across outcomes. Asthma was significantly correlated with NO_2 levels, but not PM_{13}.	For PM_{13} = 50 µg/m^3 ; BS = 25 µg/m^3; <u>Respiratory HA's (all ages):</u> PM_{13} Lag 0 ER = 2.2% (CI: 0.2, 4.3) BS Lag 0 ER = 1.0% (0.2, 1.8) <u>COPD HA's (all ages):</u> PM_{13} Lag 2 ER = 2.3% (CI: -6.7, 2.2) BS Lag 2 ER = 1.1% (-2.9, 0.6) <u>Asthma HA's (all ages):</u> PM_{13} Lg 2 ER = 1.3% (CI: -4.6, 2.2) BS Lg 0 ER = 1.2% (-0.5, 2.9)

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Europe (cont'd)			
Anderson et al. (1997) Amsterdam(77 - 89) Barcelona (86- 92) London (87 - 91) Milan (80- 89) Paris (87 - 92) Rotterdam (77 - 89) Populations .= 0.7(A), 1.7(B), 7.2(L),1.5(M),6.5(P),0.6(R)MM BS Means = 6, 41, 13, -, 26, 22 TSP Means = 41,155, -, 105, -,41	All-age daily hospital admissions (HA's) for COPD considered in 6 APHEA cities; Mean/day = 1.1(A), 11(B), 20(L), 5(M), 11(P), 1.1(R). Poisson GLM regression controlling for day of week, holidays, seasonal and other cycles, influenza epidemics, temperature, RH, and autocorrelation. Overall multi-city estimates made using inverse variance wts., allowing for inter-city variance.	Ozone gave the most consistent associations across models. Multi-city meta-estimates also indicated associations for BS and TSP. The warm/cold season RR differences were important only for ozone, having a much stronger effect in the warm season. COPD effect sizes found were much smaller than in U.S. studies, possibly due to inclusion of non-emergency admissions or use of less health-relevant PM indices.	BS (25 $\mu g/m^3$) 1d lag, no co-pollutant: All Age COPD Hospital Admissions ER = 1.7% (0.5, 2.97) TSP (100 $\mu g/m^3$) 1d lag, no co-pollutant: All Age COPD Hospital Admissions ER = 4.45% (CI: -0.53, 9.67)
Díaz et al. (1999) Madrid (94 - 96) Population = NR TSP mean 40 $\mu g/m^3$	ARIMA modeling used to analyze emergency respiratory and circulatory admissions (means/day=7.8,7.6) from one teaching hospital. Annual, weekly, and 3 day periodicities controlled, but no time trend included, and temperature crudely fit with v-shaped linear relationship.	Although TSP correlated at zero lag with admissions in winter and year-round, TSP was never significant in ARIMA models; so effect estimates not reported for TSP. Also, found biologically implausible u-shaped relationship for O_3, possibly indicating unaddressed temperature effects.	N/A
Spix et al. (1998) London (L) (87 - 91) Pop. =7.2 Million (MM) BS Mean = 13 $\mu g/m^3$ Amsterdam (A) (77 - 89) Pop. =0.7 MM BS Mean = 6 $\mu g/m^3$ TSP mean = 41 $\mu g/m^3$ Rotterdam (R) (77 - 89) Pop. =0.6MM BS Mean = 22 $\mu g/m^3$ TSP mean = 41 $\mu g/m^3$ Paris (P) (87 - 92), Pop.= 6.14 MM BS Mean = 26 $\mu g/m^3$ Milano (M) (80 - 89) Pop. = 1.5 MM TSP Mean =120 ($\mu g/m^3$)	Respiratory (ICD9 460-519) HA's in age groups 15-64 yr and 65 + yrs. related to SO_2, PM (BS or TSP), O_3, and NO_2 in the APHEA study cities using standardized Poisson GLM models with confounder controls for day of week, holidays, seasonal and other cycles, temperature, RH, and autocorrelation. PM lag considered ranged from 0-3 day, but varied from city to city. Quantitative pooling conducted by calculating the weighted means of local regression coefficients using a fixed-effects model when no heterogeneity could be detected; otherwise, a random-effects model employed.	Pollutant associations noted to be stronger in areas where more than one monitoring station was used for assessment of daily exposure. The most consistent finding was an increase of daily HA's for respiratory diseases (adults and elderly) with O_3. The SO_2 daily mean was available in all cities, but SO_2 was not associated consistently with adverse effects. Some significant PM associations were seen, although no conclusion related to an overall particle effect could be drawn. The effect of BS was significantly stronger with high NO_2 levels on the same day, but NO_2 itself was not associated with HA's. Authors concluded that "there was a tendency toward an association of respiratory admissions with BS, but the very limited number of cities prevented final conclusions."	Respiratory Admissions (BS = 25 $\mu g/m^3$) BS (L, A, R, P) 15-64 yrs: 1.4% (0.3, 2.5) 65+ yrs: 1.0% (-0.2, 2.2) TSP (A, R, M) (100 $\mu g/m^3$) 15-64 yrs: 2.0 (-2.1, 6.3) 65+ yrs: 3.2 (-1.2, 7.9) Respiratory HA's BS (L, A, R, P): Warm (25 $\mu g/m^3$) 15-64 yrs: -0.5% (-5.2, 4.4) 65+ yrs: 3.4% (-0.1, 7.1) BS (L, A, R, P): Cold (25 $\mu g/m^3$) 15-64 yrs: 2,0% (0.8, 3.2) 65+ yrs: 0% (-2.2, 2.3) TSP (A, R, M): Warm (100 $\mu g/m^3$) 15-64 yrs: 6.1% (0.1, 12.5) 65+ yrs: 2.0% (-3.9, 8.3) TSP (A, R, M): Cold (100 $\mu g/m^3$) 15-64 yrs: -5.9% (-14.2, 3.2) 65+ yrs: 4.0% (-0.9, 9.2)

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Europe (cont'd)			
Vigotti et al. (1996) Study Period.: 80 - 89 Milan, IT Population = 1.5 MM TSP mean = 139.0 µg/m^3 TSP IQR = 82.0, 175.7 µg/m^3	Association between adult respiratory HA's (15-64 yr mean =11.3/day, and 65 + yr mean =8.8/day) and air pollution evaluated, using the APHEA protocol. Poisson regression used with control for weather and long term trend, year, influenza epidemics, and season	Increased risk of respiratory HA was associated with both SO_2 and TSP. The relative risks were similar for both pollutants. There was no modification of the TSP effect by SO_2 level. There was a suggestion of a higher TSP effect on hospital admissions in the cool months.	Young Adult (15-64 yrs.) Resp. HA's 100 µg/m^3 increase in TSP Lag 2 ER = 5% (CI: 0, 10) Older Adult (65+ yrs.) Resp. HA's 100 µg/m^3 increase in TSP Lag 1 ER = 5% (CI: -1, 10)
Anderson et al. (1998) London (87 - 92) Population = 7.2 MM BS daily mean = 14.6 µg/m^3 BS 25-75th IQR = 24-38	Poisson GLM log-linear regression used to estimate the RR of London daily asthma hospital admissions associated with changes in O_3, SO_2, NO_2 and particles (BS) for all ages and for 0-14 yr. (mean=19.5/d), 15-64 yr. (mean=13.1/d) and 65 + yr. (mean =2.6/d). Analysis controlled for time trends, seasonal factors, calendar effects, influenza epidemics, RH, temperature, and auto-correlation. Interactions with co-pollutants and aeroallergens tested via 2 pollutant models and models with pollen counts (grass, oak and birch).	Daily hospital admissions for asthma found to have associations with O_3, SO_2, NO_2, and particles (BS), but there was lack of consistency across the age groups in the specific pollutant. BS association was strongest in the 65 + group, especially in winter. Pollens not consistently associated with asthma HA's, sometimes being positive, sometimes negative. Air pollution associations with HA's not explained by airborne pollens in simultaneous regressions, and there was no consistent pollen-pollutant interaction.	Asthma Admissions. BS=25 µg/m^3 BS Lag = 0-3 day average concentration All age ER = 5.98% (0.4, 11.9) <15yr. ER = 2.2% (-4.6, 9.5) 15-64yr ER = 1.2% (-5.3, 8.1) 65+ yr. ER = 22.8% (6.1, 42.5) BS=50 µg/m^3, 2d lag & co-pollutant: Older Adult (>64 yrs.) Asthma Visits: BS alone: ER = 14.6% (2.7, 27.8) &O_3: ER = 20.0% (3.0, 39.8) & NO_2: ER = 7.4% (-8.7, 26.5) SO_2: ER = 11.8% (-2.2, 27.8)
Kontos et al. (1999) Piraeus, Athens GR (87 - 92) Population = NR BS mean =46.5 µg/m^3 BS max =200 µg/m^3	Relation of respiratory HA's for children (0-14 yrs.) (mean = 4.3/day) to BS, SO_2, NO_2, and O_3 evaluated, using a nonparametric stochastic dynamical system approach and frequency domain analyses. Long wave and effects of weather considered, but non-linearity and interactions of T and RH relation with HA's not addressed.	Pollution found to explain significant portion of the HA variance. Of pollutants considered, BS was consistently among most strongly explanatory pollutants across various reported analyses.	NR

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Europe (cont'd)			
Ponce de Leon et al. (1996) London (4/87-2/92) Population = 7.3 million BS mean. =14.6 $\mu g/m^3$ BS 5^{th}-95^{th} %=6 - 27 $\mu g/m^3$	Poisson GLM log-linear regression analysis of daily counts of HA's (means/day: all ages=125.7; Ages 0-14=45.4; Ages 15-64=33.6; Ages 65+=46.7). Effects of trend, season and other cyclical factors, day of the week, holidays, influenza epidemic, temperature, humidity, and autocorrelation addressed. However, temperature modeled as linear, with no RH interaction. Pollution variables were BS, SO_2, O_3, and NO_2, lagged 0-3 days.	O_3 associated with increase in daily HA's, especially in the "warm" season. However, u-shape of the O_3 dose-response suggests that linear temperature control was not adequate. Few significant associations with other pollutants, but these tended to be positive (especially in cold season, Oct-March, and for older individuals for BS).	<u>Respiratory HA's (all ages)</u> Single Pollutant Models For Oct-Mar. BS = 25 $\mu g/m^3$ Lag 1 ER = 0.2% (–1.9, 2.3) For Apr-Sep. BS = 25 $\mu g/m^3$ Lag 1 ER = -2.7% (-6.0, 0.8) <u>Respiratory HA's (>65)</u> Single Pollutant Models For Oct-Mar. BS = 25 $\mu g/m^3$ Lag 2 ER = 1.2% (-2.1, 4.5) For Apr-Sep. BS = 25 $\mu g/m^3$ Lag 2 ER = 4.5% (-1.0, 10.4)
Schouten et al. (1996) Amsterdam/Rotterdam (77 - 89) Amsterdam Pop. = 0.69 Million Rotterdam Pop. = 0.58 Million Amsterdam, NE BS mean. =11 $\mu g/m^3$ BS 5^{th}-95^{th}% = 1 - 37 $\mu g/m^3$ Rotterdam, NE BS mean. =26 $\mu g/m^3$ BS 5^{th}-95^{th} %= 6 -61 $\mu g/m^3$	Daily emergency HA's for respiratory diseases (ICD 460-519), COPD (490-492, 494, 496), and asthma (493). The mean HA/d (range) for these were: 6.70 (0-23), 1.74 (0-9) and 1.13 (0-7) respectively in Amsterdam and 4.79 (0-19), 1.57 (0-9), and 0.53 (0-5) in Rotterdam. HA associations with BS, O_3, NO_2, and SO_2 analyzed, using autoregressive Poisson GLM regression allowing for overdispersion and controlling for season, day of week, meteorological factors, and influenza epidemics.	BS did not show any consistent effects in Amsterdam; but in Rotterdam BS was positively related to HA's. Most consistent BS associations in adults >64 yrs. in winter. Positive O_3 association in summer in people aged >64 in Amsterdam and Rotterdam. SO_2 and NO_2 did not show any clear effects. Results not changed in pollutant interaction analyses. The authors concluded short-term air pollution-emergency HA's association is not always consistent at these individual cities' relatively low counts of daily HA's and low levels of air pollution. Analyses for all ages of all the Netherlands gave a strong BS-HA association in winter.	Single Pollutant Models For BS=25 $\mu g/m^3$, 2 day lag For all of the Netherlands: <u>Respiratory HA's (all ages)</u> Winter: ER = 2.0% (-1.5, 5.7) Summer: ER = 2.4% (0.6, 4.3)

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Europe (cont'd)			
Sunyer et al. (1997) Barcelona (86 - 92) Population = NR BS Median: 40 µg/m^3 BS Range: 11-258 (B Helsinki (86 - 92) Population = NR BS Median: - BS Range: - Paris (86 - 92) Population = NR BS Median: 28 µg/m^3 BS Range: 4-186 µg/m^3 London (86 - 92) Population = NR BS Median: 13 µg/m^3 BS Range: 3-95 µg/m^3	Evaluated relations of BS, SO_2, NO_2, and O_3 to daily counts of asthma HA's and ED visits in adults [ages 15-64 years: mean/day = 3.9 (B); 0.7 (H); 13.1 (H); 7.3 (P)] and children [ages < 15 years: mean/day = 0.9 (H); 19.8 (L); 4.6 (P)]. Asthma (ICD9=493) studied in each city, but the outcome examined differed across cities: ED visits in Barcelona; emergency hospital asthma admissions in London and Helsinki, and total asthma admissions in Paris. Estimates from all cities obtained for entire period and also by warm or cold seasons, using Time-series GLM regression, controlling for temperature and RH, viral epidemics, day of week effects, and seasonal and secular trends applied using the APHEA study approach. Combined associations were estimated using meta-analysis.	Daily admissions for asthma in adults increased significantly with increasing ambient levels of NO_2, and positively (but non-significantly) with BS. The association between asthma admissions and pollution varied across cities, likely due to differing asthma outcomes considered. In children, daily admissions increased significantly with SO_2 and positively (but non-significantly) with BS and NO_2, though the latter only in cold seasons. No association observed in children for O_3. Authors concluded that "In addition to particles, NO_2 and SO_2 (by themselves or as a constituent of a pollution mixture) may be important in asthma exacerbations".	ER per 25 µg/m^3 BS (24 h Average) Asthma Admissions/Visits: <15 yrs.: London ER = 1.5% (lg 0d) Paris ER = 1.5% (lg 2d) Total ER = 1.5% (-1.1, 4.1) 15-64 yrs: Barcelona ER = 1.8% (lg 3d) London ER = 1.7% (lg 0d) Paris ER = 0.6% (lg 0d) Total ER = 1.0% (-0.8, 2.9) Two Pollutant (per 25 µg/m^3 BS) Asthma Admissions (24 h Avg) <15 yrs, (BS & NO_2): London ER = 0.6% (lg 0d) Paris ER = 2.9% (lg 2d) Total ER = 1.8% (-0.6, 4.3) <15 yrs, (BS & SO_2): London ER = -1.1% (lg 0d) Paris ER = -1.4% (lg 2d) Total ER = -1.3 (-5.0, 2.5) 15-64 yrs, (BS & NO_2): Barcelona ER = 1.5% (lg 0d) London ER = -4.7% (lg 0d) Paris ER = -0.7% (lg 1d) Total ER = -0.5% (-5.1, 4.4)
Tenías et al (1998) Study Period.: 94 - 95 Valencia, Spain Hosp. Cachment Pop. =200,000 BS mean = 57.7 µg/m^3 BS IQR = 25.6-47.7 µg/m^3	Associations between adult (14+ yrs.) emergency asthma ED visits to one city hospital (mean =1.0/day) and BS, NO_2, O_3, SO_2 analyzed, using GLM Poisson auto-regressive modeling, controlling for potential confounding weather and time (e.g., seasonal) and trends using the APHEA protocol.	Association with asthma was positive and more consistent for NO_2 and O_3 than for BS or SO_2. Suggests that secondary oxidative-environment pollutants may be more asthma relevant than primary reduction-environment pollutants (e.g., carbonaceous particles). NO_2 had greatest effect on BS in co-pollutant models, but BS became significant once 1993 was added, showing power to be a limitation of this study.	Adult Asthma HA's, BS = 25 µg/m^3 For 1993-1995: Lag 0 ER = 10.6% (0.9, 21.1) For 1994-1995: Lag 0 ER = 6.4% (-4.8, 18.8)

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Europe (cont'd)			
Anderson et al. (2001) West Midland, England (October 1994-December 1996) Population = 2.3 million PM_{10} mean = 23.3 µg/m^3 $PM_{2.5}$ mean = 14.5 µg/m^3 $PM_{10-2.5}$ = 9.0 µg/m^3 (by subtraction)	Respiratory hospital admissions (mean = 66/day) related to PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, BS, SO_4^-, NO_2, O_3, SO_2, CO. GLM regression with quasi-likelihood approach, controlling for seasonal patterns, temp, humidity, influenza episodes, day week. Adjusted for residual serial correlation and over-dispersion.	Respiratory admissions (all ages) not associated with any pollutant. Analyses by age revealed some associations to PM_{10} and $PM_{2.5}$ and respiratory admissions in the 0-14 age group. There was a striking seasonal interaction in the cool season versus the warm season. $PM_{10-2.5}$ effects cannot be excluded. Two pollutant models examined particulate measures. $PM_{2.5}$ effects reduced by inclusion of black smoke.	Respiratory HA - lag 0+1 days PM_{10} Increment10-90% (11.4-38.3 µg/m^3) All ages: 1.5 (-0.7 to 3.6) Ages 0-14: 3.9 (0.6 to 7.4) Ages 15-64: 0.1 (-4.0 to 4.4) Ages 65: -1.1 (-4.3 to 2.1) $PM_{2.5}$ (6.0-25.8) All ages: 1.2 (-0.9 to 3.4) Ages 0-14: 3.4 (-0.1 to 7.0) Ages 15-64: -2.1 (-6.4 to 2.4) Ages 65: -1.3 (-4.7 to 2.2) $PM_{10-2.5}$ (4.1 to 15.2) All ages: 0.2 (-2.5 to 3.0) Ages 0-14: 4.4 (-0.3 to 9.4) Ages 15-64: -4.9 (-9.9 to 0.4) Ages 65: -1.9 (-6.0 to 2.5) COPD (ICD-9 490-492, 494-496) PM_{10} Age 65: -1.8 (-6.9 to 3.5) $PM_{2.5}$ Age 65: -3.9 (-9.0 to 1.6) $PM_{10-2.5}$ Age 65: -1.7 (-8.9 to 5.3) Asthma (ICD- 9-493) (mean lag 0+1) PM_{10} Ages 0-14: 8.3 (1.7 to 15.3) Ages 15-64: -2.3 (-10.0 to 6.1) $PM_{2.5}$ Ages 0-14: 6.0 (-0.9 to 13.4) Ages 15-64: -8.4 (-16.4 to 0.3) $PM_{10-2.5}$ Ages 0-14: 7.1 (-2.1 to 17.2) Ages 15-64: -10.7 (-19.9 to -0.5)

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Europe (cont'd)			
Atkinson et al. (2001)+ Eight city study: Median/range Barcelona 1/94 - 12/96 PM_{10} 53.3 µg/m^3 (17.1, 131.7) Birmingham 3/92 -12/94 PM_{10} 21.5 µg/m^3 (6.5, 115) London 1/92 - 12/94 PM_{10} 24.9 µg/m^3 (7.2, 80.4) Milan -No PM_{10} Netherlands 1/92 - 9/95 PM_{10} 33.4 µg/m^3 (11.3, 130.8) Paris 1/92 - 9/96 PM_{10} 20.1 µg/m^3 (5.8, 80.9) Rome - No PM_{10} Stockholm 3/94 - 12/96 PM_{10} 13.6 µg/m^3 (4.3, 43.3)	As part of the APHEA 2 project, association between PM_{10} and daily counts of emergency hospital admissions for Asthma (0-14 and 15-64 yrs), COPD and all-respiratory disease (65+ yrs) regressed using GAM, controlling for environmental factors and temporal patterns.	This study reports that PM was associated with daily admissions for respiratory disease in a selection of European cities. Average daily ozone levels explained a large proportion of the between-city variability in the size of the particle effect estimates in the over 65 yr age group. In children, the particle effects were confounded with NO_2 on a day-to-day basis.	For 10 µg/m^3 increase **Asthma Admission Age 0-14 yrs**: PM_{10} for cities ranged from -0.9% (-2.1, 0.4) to 2.8% (0.8, 4.8) with an overall effect estimate of 1.2% (0.2, 2.3) **Asthma Admission Age 15-64 yrs:** Overall PM 1.1% (0.3, 1.8) **Admission of COPD and Asthma Age 65+ years:** Overall PM 1.0% (0.4, 1.5) **Admission All Respiratory Disease Age 65+ years:** Overall PM 0.9% (0.6, 1.3)
Thompson et al. (2001) Belfast, Northern Ireland 1/1/93 – 12/31/95. PM_{10} µg/m^3 mean (SD) May – October 24.9 (13.7) November – April 31.9 (24.3)	The rates of acute asthma admission to children's emergency was studied in relation to day-to-day fluctuation of PM_{10} and other pollutants using GLM Poisson regression.	A weak, but significant association between PM10 concentration and asthma emergency-department admissions was seen. After adjusting for multiple pollutants only the benzene level was independently associated with asthma emergency department admission. Benzene was highly correlated to PM_{10}, SO_2 and NO_2 levels.	—
Fusco et al. (2001)+ Rome, Italy 1995-1997 PM – suspended particles measured	Daily counts of hospital admissions for total respiratory conditions, acute respiratory infection including pneumonia, COPD, and asthma was analyzed in relation to PM measures and gaseous pollutants using generalized additive GAM models controlling for mean temperature, influenza, epidermics, and other factors using spline smooths.	No effect was found for PM. Total respiratory admission were significantly associated with same-day level of NO_2 and CO. There was no indication that the effects of air pollution were present at lags >2 days. Among children, total respiratory and asthma admissions were strongly associated with NO_2 and CO. Multipollutant model analysis yielded weaker and more unstable results.	—

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Latin America			
Braga et al. (1999) São Paulo, Brazil (92 - 93) Population = NR PM_{10} mean = 66.3 µg/m^3 PM_{10} Std. Deviation = 26.1 PM_{10} Min./Max. = 26.7/165.4	Pediatric (<13 yrs.) hospital admissions (mean=67.6/day) to public hospitals serving 40% of the population were regressed (using both GLM and GAM) on air pollutants, controlling for month of the year, day-of-week, weather, and the daily number of non-respiratory admissions (mean=120.7/day). Air pollutants considered included PM_{10}, O_3, SO_2, CO, and NO_2.	PM_{10} and O_3 were the two pollutants found to exhibit the most robust associations with respiratory HA's. SO_2 showed no correlation at any lag. Simultaneous regression of respiratory HA's on PM_{10}, O_3, and CO decreased effect estimates and their significance, suggesting that "there may not be a predominance of any one pollutant over the others". Associations ascribed primarily to auto emissions by the authors.	PM_{10} (50 µg/m^3), no-co-pollutant Respiratory Hospital Admissions (<13 yr.) GLM Model: (0-5day lg avg.) ER = 8.9% (CI: 4.6, 13.4) GAM Model (0-5day lg avg.) ER = 8.3% (CI: 4.1, 12.7)
Gouveia and Fletcher (2000) Study Period. 92-94 Sao Paulo, Brazil Population = 9.5 MM x 66% PM_{10} mean = 64.9 µg/m^3 PM_{10} IQR = 42.9-75.5 µg/m^3 PM_{10}10/90th% =98.1 µg/m^3 PM_{10} 95th% = 131.6 µg/m^3	Daily public hospital respiratory disease admissions for children (mean resp. < 5y = 56.1/d; mean pneumonia <5y =40.8/d; mean asthma <5 y = 8.5/d; mean pneum.<1y=24.0) and daily levels air pollutants (PM_{10}, SO_2, NO_2, O_3, and CO) and were analyzed with Poisson regression. GLM Models adjusted for time trends, seasonal patterns, weekdays, holidays, weather, and serial correlation. PM_{10} measured by Beta-gauge. Private hospitals serving wealthier citizens not in database.	Children's HA's for total respiratory and pneumonia positively associated with O_3, NO_2, and PM_{10}. Effects for pneumonia greater than for all respiratory diseases. Effects on infants (<1 yr. old) gave higher estimates. Similar results for asthma, but estimates higher than for other causes. Results noted to agree with other reports, but smaller RR's. This may be due to higher baseline admission rates in this poor sub-population vs. other studies, but this was not intercompared by the authors.	PM_{10} = 50 µg/m^3: All Respiratory HA's for children < 5yrs. ER = 2.0% (-0.8, 4.9) Pneumonia HA's for children <5 yrs. ER = 2.5% (-0.8, 6.0) Asthma HA's for children <5 yrs. ER = 2.6% (-4.0, 9.7) Pneumonia HA's for children <1 yrs. ER = 4.7% (0.7, 8.8)
Rosas et al. (1998) SW Mexico City (1991) Population = NR PM_{10} mean. =77 µg/m^3 PM_{10} min/max= 25/183 µg/m^3	Log-regression GLM analysis of relations between emergency hospital admissions for asthma for children <15 yrs (mean=2.5/day), adults (mean=3.0/day), and adults >59 yrs (mean=0.65/day) and lag 0-2 d pollen, fungal spores, air pollutants (O_3, NO_2, SO_2, and PM_{10}) and weather factors. Long wave controlled only by separating the year into two seasons: "dry" and "wet". Day-of-week not included in models.	Few statistical associations were found between asthma admissions and air pollutants. Grass pollen was associated with child and adult admissions, and fungal spores with child admissions. Authors conclude that aeroallergens may be more strongly associated with asthma than air pollutants, and may act as confounding factors in epidemiologic studies. Results are limited by low power and the lack of long-wave auto-correlation controls in the models.	NR

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Australia			
Morgan et al. (1998) Sydney, AU (90 - 94) Population = NR $PM_{2.5}$ 24 h mean = 9.6 µg/m^3 $PM_{2.5}$ 10th-90th% = 3.6-18 µg/m^3 $PM_{2.5}$ max-1 h mean = 22.8 µg/m^3 $PM_{2.5}$ 10th-90th% = 7.5-44.4 µg/m^3	A Poisson analysis, controlled for overdispersion and autocorrelation via generalized estimating equations (GEE), of asthma (means: 0-14 yrs.=15.5/day; 15-64=9/day), COPD (mean 65+yrs =9.7/day), and heart disease HA's. $PM_{2.5}$ estimated from nephelometry. Season and weather controlled using dummy variables.	Childhood asthma was primarily associated with NO_2, while COPD was associated with both NO_2 and PM. 1-hr. max $PM_{2.5}$ more consistently positively related to respiratory HA's than 24-h avg $PM_{2.5}$. Adding all other pollutants lowered PM effect sizes, although pollutant inter-correlations makes many pollutant model interpretations difficult. No association found between asthma and O_3 or PM. The authors cited the error introduced by estimating $PM_{2.5}$ and the low PM levels as possible reasons for the weak PM-respiratory HA associations.	<u>Asthma HA's</u> <u>Single Pollutant Model:</u> For 24 hr $PM_{2.5}$ = 25 µg/m^3 1-14 yrs.(lag1) ER = -1.5% (CI: -7.8, 5.3) 15-64 yrs.(lag0) ER = 2.3% (CI: -4, 9) For 1h $PM_{2.5}$ =25 µg/m^3 1-14 yrs.(lag1) ER = + 0.5% (CI: -1.9, 3.0) 15-64 yrs.(lag0) ER = 1.5% (CI: -0.9, 4) <u>Multiple Pollutant Model:</u> For 24h $PM_{2.5}$ = 25 µg/m^3 1-14 yrs.(lag1) ER = -0.6% (CI: -7.4, 6.7) <u>COPD (65+yrs.)</u> Single Pollutant Model: For 24h $PM_{2.5}$ = 25 µg/m^3 (lag 0) ER =4.2% (CI: -1.5, 10.3) For 1h $PM_{2.5}$ = 25 µg/m^3 (lag 0) ER = 2% (CI: -0.3, 4.4) <u>Multiple Pollutant Model:</u> For 1h $PM_{2.5}$ = 25 µg/m^3 (lag 0) ER = 1.5% (CI: -0.9, 4)
McGowan et al. (2002) Christchurch, New Zealand June 1988 through December 1998	The relationship between PM10 and admissions to hospital with cardiorespiratory illnesses for both adults and children using a time series analysis controlling for weather variables missing PM_{10} values were interpolated from CO data from the same period. GAM used with default criteria.	There was a significant association between PM_{10} levels and cardiorespiratory admissions. For all age groups combined there as a 3.37% increase in respiratory admissions for each interquartile value rise in PM_{10} (interquartile value 14.8. µg/m^3) and a 1.26% rise in cardiac admissions for each interquartile rise in PM_{10} (IQR = 14.8 µg/m^3).	—
Asia			
Tanaka et al. (1998) Stdy Pd.:1/92-12/93 Kushiro, Japan Pop. = 102 adult asthmatics PM_{10} mean = 24.0 µg/m^3 PM_{10} IQR = NR	Associations of HA's for asthma (in 44 non-atopic and 58 atopic patients) with weather or air pollutants (NO, NO_2, SO_2,PM_{10}, O_3, and acid fog) evaluated. Odds ratios (OR) and 95% CI's calculated between high and low days for each environmental variable. Poisson GLM regression was performed for the same dichototomized variables.	Only the presence of acid fog had a significant OR >1.0 for both atopics and non-atopics. PM_{10} associated with a reduction in risk (OR<1.0) for both atopics and non-atopics. Poisson regression gave a non-significant effect by PM_{10} on asthma HA's. However, no long-wave or serial auto-correlation controls applied, so the opposing seasonalities of PM vs. HA's indicated in time series data plots are likely confounding these results.	For same-day (lag=0) PM_{10} Adult Asthma HA's OR for <30 vs. >30 µg/m^3 PM_{10}: Non-atopic OR = 0.77 (CI: 0.61, 0.98) Atopic OR = 0.87 (CI: 0.75, 1.02) Poisson Coefficient for PM_{10} > 30 µg/m^3 Non-atopic = -0.01 (SE = 0.15) Atopic = -0.002 (SE = 0.09)

TABLE 8B-2 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY HOSPITAL ADMISSIONS STUDIES

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Asia (cont'd)			
Wong et al. (1999a) Study Period.: 94 - 95 Hong Kong Population = NR PM_{10} mean = 50.1 µg/m^3 PM_{10} median = 45.0 µg/m^3 PM_{10} IQR = 30.7, 65.5 µg/m^3	Poisson GLM regression analyses were applied to assess association of daily NO_2, SO_2, O_3, and PM_{10} with emergency HA's for all respiratory (median = 131/day) and COPD (median = 101/day) causes. Effects by age groups (0-4, 5-64, and 65+ yrs.) also evaluated. Using the APHEA protocol, models accounted for time trend, season and other cyclical factors, T, RH, autocorrelation and overdispersion. PM_{10} measured by TEOM, which likely underestimates mass.	Positive associations were found for HA's for all respiratory diseases and COPD with all four pollutants. PM_{10} results for lags 0-3 cumulative. Admissions for asthma, pneumonia, and influenza were associated with NO_2, O_3, and PM_{10}. Those aged > or = 65 years were at higher risk, except for PM_{10}. No significant respiratory HA interactions with PM_{10} effect were found for high NO_2, high O_3, or cold season.	PM_{10} = 50 µg/m^3 (Lags = 0-3 days) Respiratory HA's All age: ER = 8.3% (CI: 5.1, 11.5) 0-4yrs.: ER = 9.9% (CI: 5.4, 14.5) 5-64yrs.: ER = 8.8% (CI: 4.3, 13.4) 65+ yrs.: ER = 9.3% (CI: 5b.1, 13.7) Asthma HA's (all ages) ER = 7.7% (1.0, 14.9) COPD HA's (all ages) ER = 10.0% (5.6, 14.3) Pneumonia and Influenza HA's (all ages) ER = 13.1% (7.2, 19.4)

+ = Used GAM with multiple smooths, but have not yet reanalyzed. * = Used S-Plus Default GAM, and have reanalyzed results.
GAM=Generalized Additive Model, GLM=Generalized Linear Model; NS= Natural Spline, PS=Penalized Spline.

Appendix 8B.3

PM-Respiratory Visits Studies

TABLE 8B-3. ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
United States			
Choudhury et al. (1997) Anchorage, Alaska (90 - 92) Population = 240,000 PM_{10} mean = 41.5 µg/m^3 PM_{10} (SD) = 40.87 PM_{10} maximum=565 µg/m^3	Using insurance claims data for state employees and dependents living in Anchorage, Alaska, number of daily medical visits determined for asthma (mean = 2.42/day), bronchitis, and upper respiratory infections. Used GLM regression, including a time-trend variable, crude season indicator variables (i.e., spring, summer, fall, winter), and a variable for the month following a volcanic eruption in 1992.	Positive association observed between asthma visits and PM_{10}. Strongest association with concurrent-day PM_{10} levels. No co-pollutants considered. Temperature and RH did not predict visits, but did interact with the PM_{10} association. Morbidity relative risk higher with respect to PM_{10} pollution during warmer days.	Asthma Medical Visits (all ages): For mean = 50 µg/m^3 PM_{10} (single poll.) Lag = 0 days ER = 20.9% (CI: 11.8, 30.8)
Lipsett et al. (1997) Santa Clara County, CA Population = NR (Winters 88 - 92) PM_{10} mean = 61.2 µg/m^3 PM_{10} Min/Max = 9/165 µg/m^3	Asthma emergency department (ER) visits from 3 acute care hospitals (mean=7.6/day) related to CoH, NO_2, PM_{10}, and O_3 using Poisson GLM model with long-wave, day of week, holiday, and weather controls (analysis stratified by minimum T). Analyses using GAM also run for comparison. Every other day PM_{10} estimated from CoH. Residential wood combustion (RWC) reportedly a major source of winter PM. Gastro-enteritis (G-E) ER admissions also analyzed as a control disease.	Consistent relationships found between asthma ER visits and PM_{10}, with greatest effect at lower temperatures. Sensitivity analyses supported these findings. For example, .GAM model gave simi.lar, though sometimes less significant, results. NO_2 also associated, but in simultaneous regressions only PM_{10} stayed associated. ER visits for gastroenteritis not significantly associated with air pollution. Results demonstrate an association between wintertime ambient PM_{10} and asthma exacerbations in an area where RWC is a principal PM source.	Asthma ED Visits (all ages) PM_{10} = 50 µg/m^3 (2 day lag): GLM Results: At 20 F, ER = 34.7% (CI: 16, 56.5) At 30 F, ER = 22% (CI: 11, 34.2) At 41 F, ER = 9.1% (CI: 2.7, 15.9)
Norris et al. (1999)+ Seattle, WA (9/95-12/96) Pop. Of Children <18= 107,816 PM_{10} mean. =21.7 µg/m^3 PM_{10} IQR = 11.6 µg/m^3 $_{sp}$ mean = 0.4 m 1/10 4 (12.0 µg/m^3 $PM_{2.5}$) $_{sp}$ IQR = 0.3 m 1/10 4 (= 9.5 µg/m^3 $PM_{2.5}$)	The association between air pollution and childhood (<18 yrs.) ED visits for asthma from the inner city area with high asthma hospitalization rates (0.8/day, 23/day/10K persons) were compared with those from lower hospital utilization areas(1.1/day, 8/day/10K persons). Daily ED counts were regressed against PM_{10}, light scattering ($_{sp}$), CO, SO_2, and NO_2 using a semiparametric S-Plus Poisson regression model with spline smooths for season and weather variables, evaluated for over-dispersion and auto-correlation.	Associations found between ED visits for asthma in children and fine PM and CO. CO and PM_{10} highly correlated with each other (r=.74) and K, an indicator of woodsmoke pollution. There was no stronger association between ED visits for asthma and air pollution in the higher hospital utilization area than in the lower utilization area in terms of RR's. However, considering baseline risks/10K population indicates a higher PM attributable risk (AR) in the inner city.	Children's (<18 yrs.) Asthma ED Visits Single Pollutant Models: 24h PM_{10} =50 µg/m^3 Lag1 ER = 75.9% (25.1, 147.4) For 25 µg/m^3 $PM_{2.5}$ Lag1 ER = 44.5% (CI: 21.7, 71.4) Multiple Pollutant Models: 24h PM_{10} =50 µg/m^3 Lag1 ER = 75.9% (CI: 16.3, 166) For 25µg/m^3 $PM_{2.5}$ Lag1 ER = 51.2% (CI: 23.4, 85.2)

TABLE 8B-3 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
United States (cont'd)			
Norris et al. (2000)+ Spokane, WA (1/95 - 3/97) Population = 300,000 PM_{10} mean. = 27.9 µg/m^3 PM_{10} Min/Max =4.7/186.4 µg/m^3 PM_{10} IQR = 21.4 µg/m^3 Seattle, WA (9/95 - 12/96) Pop. Of Children <18 = 107,816 PM_{10} mean. = 21.5 µg/m^3 PM_{10} Min/Max = 8/69.3 µg/m^3 PM_{10} IQR = 11.7 µg/m^3	Associations investigated between an atmospheric stagnation index (# of hours below median wind speed), a "surrogate index of pollution", and asthma ED visits for persons <65 yr. (mean=3.2/d) in Spokane and for children <18 yr. (mean=1.8/d) in Seattle. Poisson GAM model applied, controlling for day of week, long-wave effects, and temperature and dew point (as non-linear smooths). Factor Analysis (FA) applied to identify PM components associated with asthma HA's.	Stagnation persistence index was strongly associated with ED visits for asthma in both cities. Factor analysis indicated that products of incomplete combustion (especially wood-smoke related K, OC, EC, and CO) are the air pollutants driving this association. Multi-pollutant models run with "stagnation" as the "co-pollutant" indicated importance of general air pollution over any single air pollutant index, but not of the importance of various pollutants relative to each other.	<u>Asthma ED Visits</u> Single Pollutant Models Persons<65 years (Spokane) For PM_{10} IQR = 50 µg/m^3 Lag 3 ER = 2.4% (CI: -10.9, 17.6) Persons<18 years (Seattle) For PM_{10} IQR = 50 µg/m^3 Lag 3 ER = 56.2% (95 CI: 10.4 , 121.1)
Tolbert et al. (2000b) Atlanta, GA (92 - 94 Summers) Population = 80% of children in total population of 3 million PM_{10} mn. (SE) = 38.9 (15.5) µg/m^3 PM_{10} Range = 9, 105 µg/m^3	Pediatric (<17 yrs. of age) ED visits (mean = 467/day) related to air pollution (PM_{10}, O_3, NO_x, pollen and mold) using GEE and logistic regression and Bayesian models. Autocorrelation, day of week, long-term trend terms, and linear temperature controls included.	Both PM_{10} and O_3 positively associated with asthma ED visits using all three modeling approaches. In models with both O_3 and PM_{10}, both pollutants become non-significant because of high collinearity of the variables (r=0.75).	<u>Pediatric (<17 yrs. of age) ED Visits</u> PM_{10} = 50 µg/m^3 Lag 1 day ER = 13.2% (CI: 1.2, 26.7) With O_3 8.2 (-7.1, 26.1)

TABLE 8B-3 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
United States (cont'd)			
Tolbert et al. (2000a) Atlanta Period 1: 1/1/93-7/31/98 Mean, median, SD: PM_{10} (µg/m^3): 30.1, 28.0, 12.4 Period 2: 8/1/98-8/31/99 Mean, median, SD: PM_{10} (µg/m^3): 29.1, 27.6, 12.0 $PM_{2.5}$ (µg/m^3): 19.4, 17.5, 9.35 CP (µg/m^3): 9.39, 8.95, 4.52 10-100 nm PM counts (count/cm^3): 15,200, 10,900, 26,600 10-100 nm PM surface area (um^2/cm^3): 62.5, 43.4, 116 $PM_{2.5}$ soluble metals (µg/m^3): 0.0327, 0.0226, 0.0306 $PM_{2.5}$ Sulfates (µg/m^3): 5.59, 4.67, 3.6 $PM_{2.5}$ Acidity (µg/m^3): 0.0181, 0.0112, 0.0219 $PM_{2.5}$ organic PM (µg/m^3): 6.30, 5.90, 3.16 $PM_{2.5}$ elemental carbon (µg/m^3): 2.25, 1.88, 1.74	Preliminary analysis of daily emergency department (ED) visits for asthma (493), wheezing (786.09) COPD (491, 492, 4966) LRI 466.1, 480, 481, 482, 483, 484, 485, 486), all resp disease (460-466, 477, 480-486, 491, 492, 493, 496, 786.09) for persons 16 yr in the period before (Period 1) and during (Period 2) the Atlanta superstation study. ED data analyzed here from just 18 of 33 participating hospitals; numbers of participating hospitals increased during period 1. Mean daily ED visits for dysrhythmias and all DVD in period 1 were 6.5 and 28.4, respectively. Covariates: NO_2, O_3, SO_2, CO temperature, dewpoint, and, in period 2 only, VOCs. PM measured by both TEOM and Federal Reference Method; unclear which used in analyses. For epidemiologic analyses, the two time periods were analyzed separately. Poisson GLM regression analyses were conducted with cubic splines for time, temperature and dewpoint. Day-of-week and hospital entry/exit indicators also included. Pollutants	In period 1, observed significant COPD association with 3-day average PM_{10}. COPD was also positively associated with NO_2, O_3, CO and SO_2. No statistically significant association observed between asthma and PM_{10} in period 1. However, asthma positively associated with ozone (p=0.03). In period 2, i.e., the first year of operation of the superstation, no statistically significant associations observed with PM_{10} or $PM_{2.5}$. These preliminary results should be interpreted with caution given the incomplete and variable nature of the databases analyzed.	Period 1: PM_{10} (0-2 d): asthma: 5.6% (-8.6, 22.1) COPD: 19.9% (0.1, 43.7) Period 2: (all 0-2 day lag) PM_{10}: asthma 18.8% (-8.7, 54.4) COPD -3.5% (-29.9, 33.0) $PM_{2.5}$: asthma 2.3% (-14.8, 22.7) COPD 12.4% (-7.9, 37.2) $PM_{10-2.5}$: asthma 21.1% (-18.2, 79.3) COPD -23.0% (-50.7, 20.1)
Yang et al (1997) Study Period: 92 - 94 Reno-Sparks, Nevada Population = 298,000 PM_{10} mean = 33.6 µg/m^3 PM_{10} range = 2.2, 157.3 µg/m^3	Association between asthma ER visits (mean = 1.75/d, SD=1.53/d) and PM_{10}, CO and O_3 assessed using linear WLS and ARIMA GLM regression, including adjustments for day-of-week, season, and temperature (but not RH or T-RH interaction). Season adjusted only crudely, using month dummy variable.	Only O_3 showed significant associations with asthma ER visits. However, the crude season adjustment and linear model (rather than Poisson) may have adversely affected results. Also, Beta-gauge PM_{10} mass index used, rather than direct gravimetric mass measurements.	NR

TABLE 8B-3 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Canada			
Delfino et al. (1997a) Montreal, Canada Population= 3 million 6-9/92, 6-9/93 1993 Means (SD): PM_{10}= 21.7 µg/m^3 (10.2) $PM_{2.5}$= 12.2 µg/m^3 (7.1) $SO_4^=$= 34.8 nmol/m^3 (33.1) H^+= 4 nmol/m^3 (5.2)	Association of daily respiratory emergency department (ED) visits (mean = 98/day from 25 of 31 acute care hospitals) with O_3, PM_{10}, $PM_{2.5}$, $SO_4^=$, and H^+ assessed using GLM regression with controls for temporal trends, auto-correlation, and weather. Five age sub-groups considered.	No associations with ED visits in '92, but 33% of the PM data missing then. In '93, only H^+ associated for children <2, despite very low H^+ levels. H^+ effect stable in multiple pollutant models and after excluding highest values. No associations for ED visits in persons aged 2-64 yrs. For patients >64 yr, O_3, PM_{10}, $PM_{2.5}$, and $SO_4^=$ positively associated with visits ($p < 0.02$), but PM effects smaller than for O_3.	<u>Respiratory ED Visits</u> Adults >64: (pollutant lags = 1 day) 50 µg/m^3 PM_{10} ER = 36.6% (10.0, 63.2) 25 µg/m^3 $PM_{2.5}$ ER = 23.9% (4.9, 42.8)
Delfino et al. (1998b) Montreal, Canada 6-8/89,6-8/90 Mean PM_{10}= 18.6 µg/m^3 (SD=9.3, 90th% = 30.0 µg/m^3)	Examined the relationship of daily ED visits for respiratory illnesses by age (mean/day: <2yr.=8.9; 2-34yr.=20.1; 35-64yr.=22.6; >64yr.=20.3) with O_3 and estimated $PM_{2.5}$. Seasonal and day-of-week trends, auto-correlation, relative humidity and temperature were addressed in linear time series GLM regressions.	There was an association between $PM_{2.5}$ and respiratory ED visits for older adults (>64), but this was confounded by both temperature and O_3. The fact that $PM_{2.5}$ was estimated, rather than measured, may have weakened its relationship with ED visits, relative to O_3.	<u>Older Adults(>64 yr) Respiratory ED Visits</u> Estimated $PM_{2.5}$ = 25 µg/m^3 Single Pollutant: (lag 1 $PM_{2.5}$) ER = 13.2 (-0.2, 26.6) With Ozone (lag 1 $PM_{2.5}$): Est. $PM_{2.5}$ (lag1) ER = 0.8% (CI: -14.4, 15.8)
Stieb et al. (1996) St. John, New Brunswick, Canada Population = 75,000 May-Sept. 84 - 92 SO_4^{2-} Mean = 5.5 µg/m^3 Range: 1-23, 95th% =14 µg/m^3 TSP Mean = 36.7 µg/m^3 Range:5-108, 95th% =70 µg/m^3	Asthma ED visits (mean=1.6/day) related to daily O_3 and other air pollutants (SO_2, NO_2, SO_4^{2-}, and TSP). PM measured only every 6th day. Weather variables included temperature, humidex, dewpoint, and RH. ED visit frequencies were filtered to remove day of week and long wave trends. Filtered values were GLM regressed on pollution and weather variables for the same day and the 3 previous days.	Positive, statistically significant ($p < 0.05$) association observed between O_3 and asthma ED visits 2 days later; strength of the association greater in nonlinear models. Ozone effect not significantly influenced by addition of other pollutants. However, given limited number of sampling days for sulfate and TSP, it was concluded that "a particulate effect could not be ruled out".	<u>Emergency Department Visits (all ages)</u> Single Pollutant Model 100 µg/m^3 TSP = 10.7% (-66.4, 87.8)

TABLE 8B-3 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Canada (cont'd)			
Stieb et al. (2000)+ Saint John, New Brunswick, Canada 7/1/92-3/31/96 mean and S.D.: PM_{10} (µg/m^3): 14.0, 9.0 $PM_{2.5}$ (µg/m^3): 8.5, 5.9 H+ (nmol/m^3): 25.7, 36.8 Sulfate (nmol/m^3): 31.1, 29.7 COH mean (10^3 ln ft): 0.2, 0.2 COH max (10^3 ln ft): 0.6, 0.5	Study of daily emergency department (ED) visits for asthma (mean 3.5/day), COPD (mean 1.3/day), resp infections (mean 6.2/day), and all respiratory conditions (mean 10.9/day) for persons of all ages. Covariates included CO, H_2S, NO_2, O_3, SO_2, total reduced sulfur (TRS), a large number of weather variables, and 12 molds and pollens. Stats: generalized additive models with LOESS prefiltering of both ED and pollutant variables, with variable window lengths. Also controlled for day of week and LOESS-smoothed functions of weather. Single-day, and five day average, pollution lags tested out to lag 10. The strongest lag, either positive or negative, was chosen for final models. Both single and multi-pollutant models reported. Full-year and May-Sep models reported.	In single-pollutant models, significant positive associations were observed between all respiratory ED visits and PM_{10}, $PM_{2.5}$, H_2S, O_3, and SO_2. Significant negative associations were observed with H+, and COH max. PM results were similar when data were restricted to May-Sep. In multi-pollutant models, no PM metrics significantly associated with all cardiac ED visits in full year analyses, whereas both O_3 and SO_2 were. In the May-Sep subset, significant negative association found for sulfate. No quantitative results presented for non-significant variables in these multi-pollutant regressions.	$PM_{2.5}$, (lag 3) 15.1 (-0.2, 32.8) PM_{10}, (lag 3) 32.5 (10.2, 59.3)
Europe			
Atkinson et al. (1999a) London (92 - 94) Population = NR PM10 Mean = 28.5 µg/m^3 10^{th}-90^{th} IQR = 15.8-46.5 µg/m^3 BS mean =12.7 µg/m^3 10^{th}-90^{th} IQR = 5.5-21.6 µg/m^3	All-age Respiratory (mean=90/day), Asthma (25.9/day), and Other Respiratory (64.1/day) ED visits from 12 London hospitals considered, but associated population size not reported. Counts for ages 0-14, 15-64, and >64 also examined. Poisson GLM regression used, controlling for season, day of week, meteorology, autocorrelation, overdispersion, and influenza epidemics.	PM_{10} positively associated, but not BS, for all-age/all-respiratory category. PM_{10} results driven by significant children and young adult associations, while older adult visits had negative (but non-significant) PM_{10}-ED visit relationship. PM_{10} positively associated for all ages, children, and young adults for asthma ED visits. However, PM_{10}-asthma relationship couldn't be separated from SO_2 in multi-pollutant regressions. Older adult ED visits most strongly associated with CO. No O_3-ED visits relationships found (but no warm season analyses attempted).	PM_{10} (50 µg/m^3) No co-pollutant: <u>All Respiratory ED visits</u> All age(lag 1d)ER = 4.9% (CI: 1.3, 8.6) <15yrs(lag 2d)ER = 6.4% (CI: 1, 12.2) 15-64yr(lag1d)ER = 8.6% (CI: 3.4, 14) <u>Asthma ED visits</u> All age (lag 1d) ER = 8.9% (CI: 3, 15.2) <15yrs (lag 2d) ER = 12.3% (CI: 3.4, 22) 15-64yr (lg 1d) ER = 13% (CI: 4.6, 22.1) PM_{10} (50 µg/m^3) 2d lag & co-pollutant: Children's (<15 yrs.) Asthma ED Visits: PM alone: ER = 12.3% (CI: 3.4, 22) &NO_2: ER = 7.8% (CI: -1.2, 17.6) & O_3: ER = 10.5% (CI: 1.6, 20.1) & SO_2: ER = 8.1% (CI: -1.1, 18.2) & CO: ER = 12.1% (CI: 3.2, 21.7)

TABLE 8B-3 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Europe (cont'd)			
Hajat et al. (1999) London, England (92 - 94) Population = 282,000 PM_{10} mean = 28.2 µg/m^3 PM_{10} 10^{t}-90^{th}%=16.3-46.4 µg/m^3 BS mean = 10.1 µg/m^3 BS 10^{t}-90^{th}%=4.5-15.9 µg/m^3	Examined associations of PM_{10}, BS, NO_2, O_3, SO_2, and CO, with primary care general practitioner asthma and "other LRD" consultations. Asthma consultation means per day = 35.3 (all ages); 14.(0-14 yrs,); 17.7 (15-64 yrs.); 3.6 (>64 yrs.). LRD means = 155 (all ages); 39.7(0-14 yrs,); 73.8 (15-64 yrs.); 41.1 (>64 yrs.). Time-series analyses of daily numbers of consultations performed, controlling for time trends, season factors, day of week, influenza, weather, pollen levels, and serial correlation.	Positive associations, weakly significant and consistent across lags, observed between asthma consultations and NO_2 and CO in children, and with PM_{10} in adults, and between other LRD consultations and SO_2 in children. Authors concluded that there are associations between air pollution and daily concentrations for asthma and other lower respiratory disease in London. In adults, the authors concluded that the only consistent association was with PM_{10}. Across all of the various age, cause, and season categories considered, PM_{10} was the pollutant most coherent in giving positive pollutant RR estimates for both asthma and other LRD (11 of 12 categories positive) in single pollutant models considered.	<u>Asthma Doctor's Visits:</u> 50 µg/m^3 PM_{10} -Year-round, Single Pollutant: All ages (lg 2): ER = 5.4% (CI: -0.6, 11.7) 0-14 yrs.(lg 1): ER = 6.4% (-1.5, 14.6) 15-64 yrs.(lg 0): ER = 9.2% (CI: 2.8, 15.9) >64yrs.(lg 2): ER = 11.7% (-1.8, 26.9) -Year-round, 2 Pollutant, Children (0, 14): (PM_{10} lag = 1 day) PM_{10} ER's: W/NO_2: ER = 0.8% (CI: -8.7, 11.4) W/O_3: ER = 5.5% (-2.1, 13.8) W/SO_2: ER = 3.2% (CI: -6.4, 13.7) <u>Other Lower Resp. Dis. Doctor's Visits:</u> 50 µg/m^3 PM_{10} -Year-round, Single Pollutant: All ages (lg 2): ER = 3.5% (CI: 0, 7.1) 0-14 yrs.(lg 1): ER = 4.2% (CI: -1.2, 9.9) 15-64 yrs.(lg 2): ER= 3.7% (CI: 0.0, 7.6) >64yrs.(lg 2): ER = 6.2% (CI: 0.5, 12.9)
Hajat et al. (2001)+ London (1992-1994) 44,406-49,596 registered patients <1 to 14 years PM_{10} mean 28.5 (13.9)	Daily physician consultations (mean daily 4.8 for children; 15.3 for adults) for allergic rhinitis (ICD-9, 477), SO_2, O_3, NO_2, CO, PM_{10}, and pollen using generalized additive models with nonparametric smoother.	SO_2 and O_3 show strong associations with the number of consultations for allergic rhinitis. Estimates largest for a lag of 3 or 4 days prior to consultations, with cumulative measures stronger than single day lags. Stronger effects were found for children than adults. The two-pollutant analysis of the children's model showed that PM_{10} and NO_2 associations disappeared once either SO_2 or O_3 was incorporated into the model.	PM_{10} - Increment (10-90%) (15.8-46.5) Age <1-14 years lag 3: 10.4 (2.0 to 19.4) Cum 0-3: 17.4 (6.8 to 29.0) Ages 15-64 years lag 2: 7.1 (2.6 to 11.7) Cum 0-6: 20.2 (14.1 to 26.6)

TABLE 8B-3 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Europe (cont'd)			
Medina et al. (1997)+ Greater Paris 91 - 95 Population.= 6.5 MM Mean PM_{13} = 25 µg/m^3 PM_{13} min/max = 6/95 µg/m^3 Mean BS = 21 µg/m^3 BS min/max = 3/130 µg/m^3	Evaluated short-term relationships between PM_{13} and BS concentrations and doctors' house calls (mean=8/day; 20% of city total) in Greater Paris. Poisson regression used, with non-parametric smoothing functions controlling for time trend, seasonal patterns, pollen counts, influenza epidemics, day-of-week, holidays, and weather.	A relationship between all age (0-64 yrs.) asthma house calls and PM_{13}, BS, SO_2, NO_2, and O_3 air pollution, especially for children aged 0-14 (mean = 2/day). In two-pollutant models including BS with, successively, SO_2, NO_2, and O_3, only BS and O_3 effects remained stable. These results also indicate that air pollutant associations noted for hospital ED visits are also applicable to a wider population that visits their doctor.	Doctor's Asthma House Visits: 50 µg/m^3 PM_{13} Year-round, Single Pollutant: All ages (lg 2): ER = 12.7% (CI: 4.1, 21.9) 0-14 yrs.(lg 0-3): ER = 41.5% (CI: 20, 66.8) 15-64 yrs.(lg 2): ER = 6.3% (CI: -4.6, 18.5)
Damiá et al. (1999) Valencia, Spain (3/94-3/95) Population = NR BS mean = 101 µg/m^3 BS range = 34-213 µg/m^3	Associations of BS and SO_2 with weekly total ED admissions for asthma patients aged > 12 yrs (mean = 10/week) at one hospital over one year assessed, using linear stepwise GLM regression. Season-specific analyses done for each of 4 seasons, but no other long-wave controls. Linear T, RH, BP, rain, and wind speed included as crude weather controls in ANOVA models.	Both BS and SO_2 correlated with ED admissions for asthma (SO_2: r=0.32; BS: r=0.35), but only BS significant in stepwise multiple regression. No linear relationship found with weather variables. Stratified ANOVA found strongest BS-ED association in the autumn and during above average temperatures. Uncontrolled autocorrelation (e.g., within-season) and weather effects likely remain in models.	Asthma ED Visits (all ages): BS = 40 µg/m^3 (single pollutant) BS as a lag 0 weekly average: ER = 41.5% (CI = 39.1, 43.9)
Pantazopoulou et al. (1995) Athens, GR (1988) Population = NR Winter (1/88-3/88,9/88-12/88) BS mean. =75 µg/m^3 BS 5th-95th %=26 - 161 µg/m^3 Summer (3/22/88-3/88,9/21/88) BS mean. =55 µg/m^3 BS 5th-95th %=19 - 90 µg/m^3	Examined effects of air pollution on daily emergency outpatient visits and admissions for cardiac and respiratory causes. Air pollutants included: BS, CO, and NO_2. Multiple linear GLM regression models used, controlling for linear effects of temperature and RH, day of week, holidays, and dummy variables for month to crudely control for season, separately for winter and summer.	Daily number of emergency visits related positively with each air pollutant, but only reached nominal level of statistical significance for NO_2 in winter. However, the very limited time for each within-season analysis (6 mo.) undoubtably limited the power of this analysis to detect significant effects. Also, possible lagged pollution effects were apparently not investigated, which may have reduced effect estimates.	Single Pollutant Models For Winter (BS = 25 µg/m^3) Outpatient Hospital Visits ER = 1.1% (-0.7, 2.3) Respiratory HA's ER = 4.3% (0.2, 8.3) For Summer, BS = 25 µg/m^3) Outpatient Hospital Visits ER = 0.6% (-4.7, 6.0) Respiratory HA's ER = 5.5% (-3.6, 14.7)

TABLE 8B-3 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Europe (cont'd)			
Garty et al. (1998) PM_{10} mean 45 µg/m^3 Tel Aviv, Israel (1993)	Seven day running mean of asthma ED visits by children (1-18 yrs.) to a pediatric hospital modeled in relation to PM_{10} in Tel Aviv, Israel.	No PM_{10} associations found with ED visits. The ER visits–pollutant correlation increased significantly when the September peak was excluded. Use of a week-long average and associated uncontrolled long-wave fluctuations (with resultant autocorrelation) likely prevented meaningful analyses of short –term PM associations with ED visits.	N/A
Latin America			
IIabaca et al. (1999) Santiago, Chile February 1995-August 1996 PM_{10}: warm: 80.3 µg/m^3 cold: 123.9 µg/m^3 $PM_{2.5}$: warm: 34.3 µg/m^3 cold: 71.3 µg/m^3	Number of daily respiratory emergency visits (REVs) related to PM by Poisson GLM model with longer- and short-term trend terms. SO_2, NO_2, O_3.	Stronger coefficients for models including $PM_{2.5}$ than for models including PM_{10} or $PM_{10\text{-}2.5}$. Copollutant effects were significantly associated with REVs. For respiratory patients, the median number of days between the onset of the first symptoms and REV was two to three days. For the majority of patients (70%) this corresponded to the lag observed in this study indicating that the timing of the pollutant effect is consistent with the temporal pattern of REV in this population.	REV, lag 2 Cold $PM_{2.5}$, lag 2 OR: 1.027 (1.01 to 1.04) for a 45 µg/m^3 increment PM_{10}, lag 2 OR: 1.02 (1.01 to 1.04) for a 76 µg/m^3 increment $PM_{2.5}$, lag 2 OR: 1.01 (1.00* to 1.03) for a 32 µg/m^3 increment Pneumonia, lag 2 PM_{10}: 1.05 (1.00* to 1.10) 64 µg/m^3 increment $PM_{2.5}$: 1.04 (1.00* to 1.09) 45 µg/m^3 increment $PM_{10\text{-}2.5}$: 10.5 (1.00* to 1.10) 32 µg/m^3 increment *decimals <1.00

TABLE 8B-3 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Latin America (cont'd)			
Lin et al. (1999) Sao Paulo, BR (91-93) Population=NR PM_{10} mean =65 µg/m^3 PM_{10} SD=27 µg/m^3 PM_{10} range=15-193 µg/m^3	Respiratory ED visits by children (0-12 yrs.) To a major pediatric hospital (mean=56/day) related to PM_{10}, SO_2, NO_2, CO, and O_3 using various GLM models: Gaussian linear regression modeling, Poisson modeling, and a polynomial distributed lag model. Lower respiratory (mean = 8/day) and upper respiratory (mean = 9/day) all evaluated. Analyses considered effects of season, day of week, and extreme weather (using T, RH dummy variables).	PM_{10} was found to be "the pollutant that exhibited the most robust and stable association with all categories of respiratory disease". O_3 was the only other pollutant that remained associated when other pollutants all simultaneously added to the model. However, some pollutant coefficients went negative in multiple pollutant regressions, suggesting coefficient intercorrelations in the multiple pollutant models. More than 20% increase in ED visits found on the most polluted days, "indicating that air pollution is a substantial pediatric health concern".	50 µg/m^3 PM_{10} (0-5-day lag mean) <u>Respiratory ED Visits (<13 yrs.)</u> Single pollutant model: PM_{10} ER=21.7% (CI: 18.2, 25.2) All pollutant models: PM_{10} ER=28.8% (CI: 21.4, 36.7) <u>Lower Respiratory ED Visits (<13 yrs.)</u> Single pollutant model: PM_{10} ER=22.8% (CI: 12.7, 33.9) All pollutant models: PM_{10} ER=46.9% (CI: 27.9, 68.8)
Ostro et al. (1999b)+ Santiago, CI (7/92—12/93) <2 yrs. Population 20,800 3-14 yrs. Population 128,000 PM_{10} mean. =108.6 µg/m^3 PM_{10} Min/Max=18.5/380 µg/m^3 PM_{10} IQR = 70.3 – 135.5 µg/m^3	Analysis of daily visits to primary health care clinics for upper (URS) or lower respiratory symptoms (LRS) for children 2-14 yr (mean LRS=111.1/day) and < age 2 (mean LRS=104.3/day). Daily PM_{10} and O_3 and meteorological variables considered. The multiple regression GAM included controls for seasonality (LOESS smooth), temperature, day of week, and month.	Analyses indicated an association between PM_{10} and medical visits for LRS in children ages 2-14 and in children under age 2 yr. PM_{10} was not related to non-respiratory visits (mean =208/day). Results unchanged by eliminating high PM_{10} (>235 µg/m^3) or coldest days (<8°C). Adding O_3 to the model had little effect on PM_{10}-LRS associations.	<u>Lower Resp. Symptoms Clinic Visits</u> PM_{10} = 50 µg/m^3 Single Pollutant Models: -Children<2 years Lag 3 ER = 2.5% (CI: 0.2, 4.8) -Children 2-14 years Lag 3 ER = 3.7% (CI: 0.8, 6.7%) Two Pollutant Models (with O_3): -Children<2 years Lag 3 ER = 2.2% (CI: 0, 4.4) -Children 2-14 years Lag 3 ER = 3.7% (CI: 0.9, 6.5)

TABLE 8B-3 (cont'd). ACUTE PARTICULATE MATTER EXPOSURE AND RESPIRATORY MEDICAL VISITS

Reference/Citation, Location, Duration, PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk %, (95% CI = LCI, UCL) Co-Pollutants
Australia			
Smith et al. (1996) Stdy Pd.: 12/92-1/93,12/93-1/94 West Sydney, AU Population = 907,000 -Period 1 (12/92-1/93) B_{scatt} median = 0.25 10 4/m B_{scatt} IQR = 0.18-0.39 10 4/m B_{scatt} 95^{th}% = 0.86 10 4/m -Period 2 (12/93-1/94) B_{scatt} median = 0.19 10 4/m B_{scatt} IQR = 0.1-0.38 10 4/m B_{scatt} 95^{th}5% = 3.26 10 4/m PM_{10} median = 18 µg/m^3 PM_{10} IQR = 11.5-28.8 µg/m^3 PM_{10} 95^{th}% = 92.5 µg/m^3	Study evaluated whether asthma visits to emergency departments (ED) in western Sydney (mean 10/day) increased as result of bushfire-generated PM (B_{scatt} from nephelometry) in Jan., 1994 (period 2). Air pollution data included nephelometry (B_{scatt}), PM_{10}, SO_2, and NO_2. Data analyzed using two methods: (1) calculation of the difference in proportion of all asthma ED visits between the time periods, and; (2) Poisson GLM regression analyses. Control variables included T, RH, BP, WS, and rainfall.	No difference found in the proportion of all asthma ED visits during a week of bushfire-generated air pollution, compared with the same week 12 months before, after adjusting for baseline changes over the 12-month period. The max. B_{scatt} reading was not a significant predictor of the daily asthma ED visits in Poisson regressions. However, no long-wave controls applied, other than indep. vars., and the power to detect differences was weak (90% for a 50% difference). Thus, the lack of a difference may be due to low statistical strength or to lower toxicity of particles from burning vegetation at ambient conditions vs. fossil fuel combustion.	<u>ED Asthma Visits (all ages)</u> Percent change between bushfire and non bushfire weeks: PM_{10} = 50 µg/m^3 ER = 2.1% (CI: -0.2, 4.5)
Asia			
Ye et al. (2001) Tokyo, Japan Summer months July-August, 1980-1995 PM_{10} 46.0 mean	Hospital emergency transports for respiratory disease for >65 years of age were related to pollutant levels NO_2, O_3, PM_{10}, SO_2, and CO.	For chronic bronchitis PM_{10} with a lag time of 2 days was the most statistically significant model covariate.	Asthma (ICD-9-493) Coefficienct estimate (SE) 0.003 (0.001)
Chew et al. (1999) Singapore (90 - 94) Population = NR TSP mean = 51.2 µg/m^3 TSP SD = 20.3 µg/m^3 TSP range = 13-184 µg/m^3	Child (3-13 yrs.) ED visits (mean = 12.8/day) and HA's (mean = 12.2/day) for asthma related to levels of SO_2, NO_2, TSP, and O_3 using GLM linear regression with weather, day-of-week controls. Auto-correlation effects controlled by including prior day response variable as a regression variable. Separate analyses done for adolescents (13-21 yrs.) (mean ED=12.2, mean HA=3.0/day).	Positive associations found between TSP, SO_2, and NO_2, and daily HA and ED visits for asthma in children, but only with ED visits among adolescents. Lack of power (low counts) for adolescents' HA's appears to have been a factor in the lack of associations. When ED visits stratified by year, SO_2 and TSP remained associated in every year, but not NO_2. Analyses for control diseases (appendicitis and urinary tract infections) found no associations.	TSP(100 µg/m^3) No co-pollutant: <u>Child (3-13 yrs.)Asthma ED visits</u> Lag 1d ER = 541% (CI: 198.4, 1276.8)

+ = Used GAM with multiple smooths, but have not yet reanalyzed. * = Used S-Plus Default GAM, and have reanalyzed results

Appendix 8B.4

Pulmonary Function Studies

TABLE 8B-4. SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON PULMONARY FUNCTION TESTS IN STUDIES OF ASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 $\mu g/m^3$ PM_{10} (25 $\mu g/m^3$ PM_{2-5}). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
United States			
Thurston et al. (1997) Summers 1991-1993. O_3, H+, sulfate	Three 5-day summer camps conducted in 1991, 1992, 1993. Study measured symptoms and change in lung function (morning to evening). Poisson regression for symptoms.	The O_3-ΔPEFR relationship was seen as the strongest.	—
Canada			
Vedal et al. (1998) Port Alberni, BC PM_{10} via a Sierra-Anderson dichotomous sampler. PM_{10} ranged from 1 to 159 $\mu g/m^3$.	Study of 206 children aged 6 to 13 years living in Port Alberni, British Columbia. 75 children had physician-diagnosed asthma, 57 had an exercised induced fall in FEV1, 18 children with airway obstruction, and 56 children without any symptoms. Respiratory symptom data obtained from diaries. An autoregressive model was fitted to the data, using GEE methods. Covariates included temp., humidity, and precipitation.	Ozone, SO_2 and sulfate levels low due to low vehicle emissions. PM_{10} associated with change in peak flow.	Lag 0, PM10 average PEF = 0.27 (−0.54, −0.01) per 10 $\mu g/m^3$ increment
Europe			
Gielen et al. (1997) Amsterdam, NL Mean PM_{10} level: 30.5 $\mu g/m^3$ (16, 60.3). Mean maximum 8 hr O_3: 67 $\mu g/m^3$.	Study evaluated 61 children aged 7 to 13 years living in Amsterdam, The Netherlands. 77 percent of the children were taking asthma medication and the others were being hospitalized for respiratory problems. Peak flow measurements were taken twice daily. Associations of air pollution were evaluated using time series analyses. The analyses adjusted for pollen counts, time trend, and day of week.	The strongest relationships were found with ozone, although some significant relationships found with PM_{10}.	Lag 0, PM_{10}: Evening PEF = −0.08 (−2.49, 2.42) Lag 1, PM_{10}: Morning PEF = 1.38 (−0.58, 3.35) Lag 2, PM_{10}: Morning PEF = 0.34 (−1.78, 2.46) Evening PEF = −1.46 (−3.23, 0.32)
Hiltermann et al. (1998) Leiden, NL July-Oct, 1995 O_3, NO_2, SO_2, BS, and PM_{10} ranged from 16.4 to 97.9 $\mu g/m^3$)	270 adult asthmatic patients from an out-patient clinic in Leiden, The Netherlands were studied from July 3 to October 6, 1995. Peak flow measured twice daily. An autoregressive model was fitted to the data. Covariates included temp. and day of week. Individual responses not modeled.	No relationship between ozone or PM_{10} and PFT was found	Lag 0, PM_{10}: Average PEF = −0.80 (−3.84, 2.04) 7 day ave., PM_{10}: Average PEF = −1.10 (−5.22, 3.02)

TABLE 8B-4 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON PULMONARY FUNCTION TESTS IN STUDIES OF ASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 $\mu g/m^3$ PM_{10} (25 $\mu g/m^3$ $PM_{2.5}$). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
Europe (cont'd)			
Peters et al. (1996) Erfurt and Weimar, Germany SO_2, TSP, PM_{10}, sulfate fraction, and PSA. Mean PM_{10} level was 112 $\mu g/m^3$. PM was measured by a Marple-Harvard impactor.	Panel of 155 asthmatic children in the cities of Erfurt and Weimar, E. Germany studied. Each panelist's mean PEF over the entire period subtracted from the PEF value to obtain a deviation. Mean deviation for all panelists on given day was analyzed using an autoregressive moving average. Regression analyses done separately for adults and children in each city and winter; then combined results calculated.	Five day average SO_2 was associated with decreased PEF. Changes in PEF were not associated with PM levels.	—
Peters et al. (1997b) Erfurt, Germany PM fractions measured over range of sizes from ultrafine to fine, including PM_{10}. Particles measured using size cuts of 0.01 to 0.1, 0.1 to 0.5, and 0.5 to 2.5 µm. Mean PM_{10} level: 55 $\mu g/m^3$ (max 71). Mean SO_2: 100 $\mu g/m^3$ (max 383). PM was measured using a Harvard impactor. Particle size distributions were estimated using a conduction particle counter.	Study of 27 non-smoking adult asthmatics living in Erfurt, Germany during winter season of 1991-1992. Morning and evening peak flow readings recorded. An auto-regressive model was used to analyze deviations in individual peak flow values, including terms for time trend, temp., humidity, and wind speed and direction.	Strongest effects on peak flow found with ultrafine particles. The two smallest fractions, 0.01 to 0.1 and 0.1 to 0.5 were associated with a decrease of PEF.	Lag 0, PM_{10}: Evening PEF = −0.38 (−1.83, 1.08) Lag 1, PM_{10}: Morning PEF = −1.30 (−2.36, 0.24) 5 Day Mean, PM_{10}: Morning PEF = −1.51 (−3.20, 0.19) Evening PEF = −2.31 (−4.54, −0.08) Lag 0, $PM_{2.5}$: Evening PEF = −0.75 (−1.66, 0.17) Lag 1, $PM_{2.5}$: Morning PEF = −0.71 (−1.30, 0.12) 5 Day Mean, $PM_{2.5}$: Morning PEF = −1.19 (−1.81, 0.57) Evening PEF = −1.79 (−2.64, −0.95)
Peters et al. (1997c) Sckolov, Czech Republic Winter 1991-1992 PM_{10}, SO_2, TSP, sulfate, and particle strong acid. Median PM_{10} level: 47 $\mu g/m^3$ (29, 73). Median SO_2: 46 $\mu g/m^3$ (22, 88). PM was measured using a Harvard impactor. Particle size distributions were estimated using a conduction particle counter.	89 children with asthma in Sokolov, Czech Republic studied. Subjects kept diaries and measured peak flow for seven months during winter of 1991-2. The analysis used linear regression for PFT. First order autocorrelations were observed and corrected for using polynomial distributed lag (PDL) structures.	Five day mean SO_2, sulfates, and particle strong acidity were also associated with decreases in PM PFT as well as PM_{10}.	Lag 0, PM_{10}: Morning PEF = −0.71 (−2.14, 0.70) Evening PEF = −0.92 (−1.96, 0.12) 5 Day mean PM_{10}: Evening PEF = −1.72 (−3.64, 0.19) Morning PEF = −0.94 (−2.76, 0.91

TABLE 8B-4 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON PULMONARY FUNCTION TESTS IN STUDIES OF ASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 $\mu g/m^3$ PM_{10} (25 $\mu g/m^3$ $PM_{2.5}$). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
Europe (cont'd)			
Timonen and Pekkanen (1997) Kupio, Finland PM_{10}, BS, NO_2, and SO_2. The intequartile range on PM_{10} was 8 to 23.	Studied 74 asthmatic children (7 to 12 yr) in Kuoio, Finland. Daily mean PEF deviation calculated for each child. Values were analyzed, then using linear first-order autoregressive model. PM was measured using single stage Harvard Impactors.	Lagged concentrations of NO_2 related to declines in morning PEF as well as PM_{10} and BS.	
Penttinen et al. (2001) studied adult asthmatics for 6 months in Helsinki, Findland. PM was measured using a single-stage Harvard impactor. Particle number concentrations were measured using an Electric Aerosol Spectrometer. NO_2PM_{10} ranged from 3.8 to 73.7 $\mu g/m^3$. $PM_{2.5}$ ranged from 2.4 to 38.3 $\mu g/m^3$.	57 asthmatics were followed with daily PEF measurements and symptom and medications diaries from November 1996 to April 1997. PEF deviations from averages were used as dependent variables. Independent variables included PM_1, $PM_{2.5}$, PM_{10}, particle counts, CO, NO, and	The strongest relationships were found between PEF deviations and PM particles below 0.1 µm. No associations were found between particulate pollution and respiratory symptoms.	AM PEF = -.115 (-.448, .218) $PM_{2.5}$ lag one day AM PEF = -.001 (-.334, .332) $PM_{2.5}$ lag two days
Pekkanen et al. (1997) Kuopio, Finland PM fractions measured over range of sizes from ultrafine to fine, including PM_{10}. Mean PM_{10} level: 18 $\mu g/m^3$ (10, 23). Mean NO_2 level: 28 $\mu g/m^3$.	Studied 39 asthmatic children aged 7-12 years living in Kuopio, Finland. Changes in peak flow measurements were analyzed using a linear first-order autoregressive model. PM was measured using single stage Harvard impactors.	Changes in peak flow found to be related to all measures of PM, after adjusting for minimum temperature. PN0.032−0.10 ($1/cm^3$) and PN1.0−3.2 ($1/cm^3$) were most strongly associated with morning PEF deviations.	Lag 0, PM_{10}: Evening PEF = −0.35 (−1.14, 0.96) Lag 1, PM_{10}: Morning PEF = −2.70 (−6.65, 1.23) Lag 2, PM_{10}: Morning PEF = −4.35 (−8.02, −0.67) Evening PEF = −1.10 (−4.70, 2.50) Small sized particles had relationships similar to those of PM_{10} for morning and evening PEF.
Segala et al. (1998) Paris, France Nov. 1992 - May 1993. BS, SO_2, NO_2, PM_{13} (instead of PM_{10}), measured. Mean PM_{13} level: 34.2 $\mu g/m^3$ (range 8.8, 95). Mean SO_2 level: 21.7 $\mu g/m^3$ (range 4.4, 83.8). Mean NO_2 level: 56.9 $\mu g/m^3$ (range 23.8, 121.9). PM was measured by β-radiometry.	Study of 43 mildly asthmatic children aged 7-15 years living in Paris, France from Nov. 15, 1992 to May 9, 1993. Peak flow measured three times a day. Covariates in the model included temperature and humidity. An autoregressive model was fitted to the data using GEE methods.	Effects found related to PM_{10} were less than those found related to the other pollutants. The strongest effects were found with SO_2.	Lag 4, PM_{13}: Morning PEF = −0.62 (−1.52, 0.28)

TABLE 8B-4 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON PULMONARY FUNCTION TESTS IN STUDIES OF ASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 $\mu g/m^3$ PM_{10} (25 $\mu g/m^3$ PM_{2-5}). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
Europe (cont'd)			
Gauvin et al. (1999) Grenoble, France Summer 1996, Winter 1997 Mean (SD) $\mu g/m^3$ PM_{10} Summer 23 (6.7) PM_{10} Winter 38 (17.3) Sunday 15.55 (5.12) Weekday 24.03 (7.2)	Two panels: mild adult asthmatics, ages 20-60 years, (summer-18 asthmatics, 20 control subjects; winter-19 asthmatics, 21 control subjects) were examined daily for FEV_1 and PEF. Bronchial reactivity was compared Sunday vs. weekday. Temperature and RH controlled.	Respiratory function decreased among asthmatic subjects a few days (lag 2/4 days) after daily PM_{10} levels had increased. Bronchial reactivity was not significantly different between the weekdays and weekends. No copollutant analysis conducted.	For a 10 $\mu g/m^3$ increase in PM_{10} Summer FEV_1 −1.25% (−0.58 to −1.92) PEF −0.87% (−0.1 to −1.63)
Agócs et al. (1997) Budapest, Hungary SO_2 and TSP were measured. TSP was measured by beta reactive absorption methods.	Panel of 60 asthmatic children studied for two months in Budapest, Hungary. Mixed model used relating TSP to morning and evening PEFR measurements, adjusting for SO_2, time trend, day of week, temp., humidity		No significant TSP-PEFR relationships found.
Australia			
Jaulaludin et al. (2000) Sydney, Austrlia 1 February 1994 to 31 December 1994 Six PM_{10} TEOM monitors PM_{10} Mean - 22.8 ±13.9 $\mu g/m^3$ (max 122.8 $\mu g/m^3$)	Population regression and GEE models used a cohort of 125 children (mean age of 9.6 years) in three groups; two with doctor's diagnoses of asthma. This study was designed to examine effects of ambient O_3 and peak flow while controlling for PM_{10}.	In Syndey, O_3 and PM_{10} poorly correlated (0.13). For PM_{10} with O_3, 0.0051 (0.0124) p-0.68 peak flow	PM_{10} only B(SE) = 0.0045 (0.0125) p-0.72 peak flow
Rutherford et al. (1999) Brisbane, Australia PM_{10}, TSP, and particle diameter. PM_{10} ranged form 11.4 to 158.6 $\mu g/m^3$. Particle sizing was done by a Coulter Multisizer.	Study examined effects of 11 dust events on peak flow and symptoms of people with asthma in Brisbane, Australia. PEF data for each individual averaged for a period of 7 days prior to the identified event. This mean was compared to the average for several days of PEF after the event, and the difference was tested using a paired t-test.	The paired t-tests were stat. significant for some days, but not others. No general conclusions could be drawn.	—

TABLE 8B-4 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON PULMONARY FUNCTION TESTS IN STUDIES OF ASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 $\mu g/m^3$ PM_{10} (25 $\mu g/m^3$ $PM_{2.5}$). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
Latin America			
Romieu et al. (1996) Mexico City, Mexico During study period, maximum daily 1-h O_3 ranged from 40 to 370 ppb (mean 190 ppb, SD = 80 ppb). 24 h ave, PM_{10} levels ranged from 29 to 363 $\mu g/m^3$ (mean 166.8 $\mu g/m^3$, SD 72.8 $\mu g/m^3$). For 53 percent of study days, PM_{10} levels exceeded 150 $\mu g/m^3$. PM_{10} was measured by a Harvard impactor.	Study of 71 children with mild asthma aged 5-7 years living in the northern area of Mexico City. Morning and evening peak flow measurements recorded by parents. Peak flow measurements were standardized for each person and a model was fitted using GEE methods. Model included terms for minimum temperature.	Ozone strongly related to changes in morning PEF as well as PM_{10}.	Lag 0, PM_{10}: Evening PEF = −4.80 (−8.00, −1.70) Lag 2, PM_{10}: Evening PEF = −3.65 (−7.20, 0.03) Lag 0, $PM_{2.5}$: Evening PEF = −4.27 (−7.12, −0.85) Lag 2, $PM_{2.5}$: Evening PEF = −2.55 (−7.84, 2.74) Lag 1, PM_{10} Morning PEF = −4.70 (−7.65, −1.7) Lag 2, PM_{10} Morning PEF = −4.90 (−8.4, −1.5)
Romieu et al. (1997) Mexico City, Mexico During study period, maximum daily 1-h ozone ranged from 40 to 390 ppb (mean 196 ppb SD = 78 ppb) PM_{10} daily average ranged from 12 to 126 $\mu g/m^3$. PM_{10} was measured by a Harvard impactor.	Study of 65 children with mild asthma aged 5-13 yr in southwest Mexico City. Morning and evening peak flow measurements made by parents. Peak flow measurements standardized for each person and model was fitted using GEE methods. Model included terms for minimum temperature.	Strongest relationships were found between ozone (lag 0 or 1) and both morning and evening PFT.	Lag 0, PM_{10}: Evening PEF = −1.32 (−6.82, 4.17) Lag 2, PM_{10}: Evening PEF = −0.04 (−4.29, 4.21) Morning PEF = 2.47 (−1.75, 6.75) Lag 0, PM_{10}: Morning PEF = 0.65 (−3.97, 5.32)

Appendix 8B.5

Short-Term PM Exposure Effects on Symptoms in Asthmatic Individuals

TABLE 8B-5. SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON SYMPTOMS IN STUDIES OF ASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 $\mu g/m^3$ PM_{10} (25 $\mu g/m^3$ PM_{2-5}). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
United States			
Delfino et al. (1996) San Diego, CA Sept-Oct 1993 Ozone and $PM_{2.5}$ measured. PM was measured by a Harvard impactor. $PM_{2.5}$ ranged from 6 to 66 $\mu g/m^3$ with a mean of 25.	Study of 12 asthmatic children with history of bronchodilator use. A random effects model was fitted for ordinal symptoms scores and bronchodilator use in relation to 24-hr $PM_{2.5}$.	Pollen not associated with asthma symptom scores. 12-hr personal O_3 but not ambient O_3 related to symptoms.	No significant relationships with PM_{10}.
Delfino et al. (1997b) San Diego County, CA PM_{10} and ozone PM was measured using a tapered-element oscillating microbalance. PM_{10} ranged from 6 to 51 $\mu g/m^3$ with a mean of 26.	A panel of 9 adults and 13 children were followed during late spring 1994 in semi-rural area of San Diego County at the inversion zone elevation of around 1,200 feet. A random effects model was fitted to ordinal symptom scores, bronchodilator use, and PEF in relation to 24-hour PM_{10}. Temp., relative humidity, fugal spores, day of week and O_3 evaluated	Although PM_{10} never exceeded 51 $\mu g/m^3$, bronchodilator use was significantly associated with PM_{10}(0.76 [0.027, 0.27]) puffs per 50 $\mu g/m^3$. Fungal spores were associated with all respiratory outcomes.	—
Delfino et al. (1998a) So. California community Aug. - Oct. 1995 Highest 24-hour PM_{10} mean: 54 $\mu g/m^3$. PM_{10} and ozone PM was measured using a tapered-element oscillating microbalance. PM_{10} ranged from 6 to 51 $\mu g/m^3$ with a mean of 26.	Relationship of asthma symptoms to O_3 and PM_{10} examined in a So. California community with high O_3 and low PM. Panel of 25 asthmatics ages 9 - 17 followed daily, Aug. - Oct., 1995. Longitudinal regression analyses utilized GEE model controlling for autocorrelation, day of week, outdoor fungi and weather.	Asthma symptoms scores significantly associated with both outdoor O_3 and PM_{10} in single pollutant and co-regressions. 1-hr and 8-hr maxi PM_{10} had larger effects than 24-hr mean.	24-h - 1.47 (0.90-2.39) 8-h - 2.17 (1.33-3.58) 1-h - 1.78 (1.25-2.53)
Yu et al. (2000) study of a panel of 133 children aged 5-12 years in Seattle, WA. PM was measured by gravimetric and nephelometry methods. $PM_{1.0}$ ranged from 2 to 62 $\mu g/m^3$ with a mean of 10.4. PM_{10} 9 to 86 $\mu g/m^3$ mean 24.7.	Daily diary records were collected from November 1993 through August 1995 during screening for the CAMP study. A repeated measures logistic regression analysis was used applied using GEE methods	One day lag CO and PM_{10} levels and the same day PM_{10} and SO_2 levels had the strongest effects on asthma symptoms after controlling for subject specific variables and time-dependent confounders.	OR symptom = 1.18 (1.05, 1.33) (PM_{10} same day) OR symptom = 1.17 (1.04, 1.33) (PM_{10} one day lag)
Ostro et al. (2001) studied exacerbation of asthma in African-American children in Los Angeles. PM was measured by a beta-attenuated Andersen monitor. PM_{10} ranged from 21 to 119 $\mu g/m^3$ with a mean of 51.8.	138 children aged 8 to 13 years who had physician diagnosed asthma were included. A daily diary was used to record symptoms and medication use. GEE methods were used to estimate the effects of air pollution on symptoms controlling for meteorological and temporal variables.	Symptoms were generally related to PM_{10} and NO_2, but not to ozone. Reported associations were for pollutant variables lagged 3 days. Results for other lag times were not reported.	24-h OR wheeze = 1.02 (0.99, 106))PM_{10} lag 3 days) OR cough = 1.06 (1.02, 1.09) (PM_{10} lag 3 days) OR shortness of breath = 1.08 (1.02, 1.13) (PM_{10} lag 3 days) 1-h OR cough = 1.05 (1.02, 1.18) lag 3 days

TABLE 8B-5 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON SYMPTOMS IN STUDIES OFASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 $\mu g/m^3$ PM_{10} (25 $\mu g/m^3$ $PM_{2.5}$). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
United States (cont'd)			
Delfino et al. (2002) PM_{10}, ozone, NO_2, fungi, pollen, temperature, relative humidity	22 asthmatic children aged 9-19 were followed March through April of 1996. Study used an asthma symptom score.	No relationship between PM_{10} and symptom score was found	Lag 0 Score OR = 1.17 (0.53, 2.59) 3 Day moving average Score OR = 1.49 (0.71, 2.59) all for 50 $\mu g/m^3$ increase in PM_{10}
Mortimer et al. (2002) Eight U.S. urban areas Daily PM10 were collected in Chicago, Cleveland, and Detroit with an average intra-diary range of 53 $\mu g/m^3$ from the Aerometric Information Retrieval System of EPA.	Study of 846 asthmatic children in the eight urban area National Cooperative Inner City Asthma study. Peak flow and diary symptom data are the outcome measures. Morning symptoms consist of cough, chest tightness, and wheeze. Mixed linear and GEE models were used.	In the three cities with PM_{10} data, a stronger association was seen for PM_{10} than ozone for respiratory symptoms.	Morning symptoms PM_{10} - 2day ave. OR = 1.26 (1.0-1.59)
Thurston et al. (1997) Summers 1991-1993. O_3, H+, sulfate, pollen, daily max temp. measured.	Three 5-day summer camps conducted in 1991, 1992, 1993. Study measured symptoms and change in lung function (morning to evening). Poisson regression for symptoms.	Ozone related to respiratory symptoms No relationship between symptoms and other pollutants.	—
Canada			
Vedal et al. (1998) PM_{10} measured by Sierra-Anderson dichotomous sampler PM_{10} range: −1 to 159 $\mu g/m^3$ Port Alberrni British, Columbia	206 children aged 6 to 13 years, 75 with physician's diagnosis of asthma. Respiratory symptom data from diaries, GEE model. Temp., humidity.	PM_{10} associated with respiratory symptoms.	Lag 0 Cough OR = 1.08 (1.00, 1.16) per 10 $\mu g/m^3$ PM_{10} increments
Europe			
Gielen et al. (1997) Amsterdam, NL PM_{10} and ozone. PM_{10} was measured using a Sierra-Anderson dichotomous sampler. PM_{10} ranged from 15 to 60 $\mu g/m^3$.	Study of 61 children aged 7 to 13 years living in Amsterdam, NL. 77 percent were taking asthma medication and the others were being hospitalized for respiratory problems. Respiratory symptoms recorded by parents in diary. Associations of air pollution evaluated using time series analyses, adjusted for pollen counts, time trend, and day of week.	Strongest relationships found with O_3, although some significant relationships found with PM_{10}.	Lag 0, Symptoms: Cough OR = 2.19 (0.77, 6.20) Bronch. Dial. OR = 0.94 (0.59, 1.50) Lag 2, Symptoms: Cough OR = 2.19 (0.47, 10.24) Bronch. Dial. OR = 2.90 (1.80, 4.66)

TABLE 8B-5 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON SYMPTOMS IN STUDIES OF ASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 μg/m^3 PM_{10} (25 μg/m^3 $PM_{2.5}$). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
Europe (cont'd)			
Hiltermann et al. (1998) Leiden, NL July-Oct 1995. Ozone, PM_{10}, NO_2, SO_2, BS PM_{10} ranged from 16 to 98 μg/m^3 with a mean of 40.	Study of 270 adult asthmatic patients from an out-patient clinic in Leiden, NL from July 3, to October 6, 1995. Respiratory symptom data obtained from diaries. An autoregressive model was fitted to the data. Covariates included temperature and day of week.	PM_{10}, O_3, and NO_2 were associated with changes in respiratory symptoms.	Lag 0, Symptoms: Cough OR = 0.93 (0.83, 1.04) Short. breath OR = 1.17 (1.03, 1.34) 7 day average, Symptoms: Cough OR = 0.94 (0.82, 1.08) Short. breath OR = 1.01 (0.86, 1.20)
Hiltermann et al. (1997) The Netherlands Ozone and PM_{10} PM_{10} averaged 40 μg/m^3,	Sixty outpatient asthmatics examined for nasal inflammatory parameters in The Netherlands from July 3 to October 6, 1995. Associations of log transformed inflammatory parameters to 24-h PM_{10} analyzed, using a linear regression model. Mugwort-pollen and O_3 were evaluated.	Inflammatory parameters in nasal lavage of patients with intermittent to severe persistent asthma were associated with ambient O_3 and allergen exposure, but not with PM_{10} exposure.	—
Peters et al. (1997b) Erfurt, Germany PM fractions measured over range of sizes from ultrafine to fine, including PM_{10}. Mean PM_{10} level: 55 μg/m^3 (max 71). Mean SO_2: 100 μg/m^3 (max 383). PM was measured using a Harvard impactor.	Study of 27 non-smoking adult asthmatics living in Erfurt, Germany during winter season 1991-1992. Diary used to record presence of cough. Symptom information analyzed using multiple logistic regression analysis.	Weak associations found with 5 day mean sulfates and respiratory symptoms.	Lag 0, PM_{10}: Cough OR = 1.32 (1.16, 1.50) Feeling ill OR = 1.20 (1.01, 1.44) 5 Day Mean, PM_{10}: Cough OR = 1.30 (1.09, 1.55) Feeling ill OR = 1.47 (1.16, 1.86) Lag 0, $PM_{2.5}$: Cough OR = 1.19 (1.07, 1.33) Feeling ill OR = 1.24 (1.09, 1.41) 5 Day Mean, $PM_{2.5}$: Cough OR = 1.02 (0.91, 1.15) Feeling ill OR = 1.21 (1.06, 1.38)
Peters et al. (1997c) Sokolov, Czech Republic Winter 1991-1992 PM_{10}, SO_2, TSP, sulfate, and particle strong acid. Median PM_{10}: 47 μg/m^3 (29, 73). Median SO_2: 46 μg/m^3 (22, 88). PM was measured using a Harvard impactor. Particle size distributions were estimated using a conduction particle counter.	Study of 89 children with asthma in Sokolov, Czech Republic. Subjects kept diaries and measured peak flow for seven months during winter of 1991-2. Logistic regression for binary outcomes used. First order autocorrelations were observed and corrected for using polynomial distributed lag structures.	Significant relationships found between TSP and sulfate with both phlegm and runny nose.	Lag 0, Symptoms: Cough OR = 1.01 (0.97, 1.07) Phlegm OR = 1.13 (1.04, 1.23) 5 Day Mean, Symptoms: Cough OR = 1.10 (1.04, 1.17) Phlegm OR = 1.17 (1.09, 1.27)

TABLE 8B-5 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON SYMPTOMS IN STUDIES OF ASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 μg/m^3 PM_{10} (25 μg/m^3 $PM_{2.5}$). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
Europe (cont'd)			
Peters et al. (1997c) Sokolov, Czech Republic PM_{10} one central site. SO_4 reported. Mean PM_{10}: 55 μg/m^3, max 177 μg/m^3. SO_4 - fine: mean 8.8 μg/m^3, max 23.8 μg/m^3. PM was measured using a Harvard impactor. Particle size distributions were estimated using a conduction particle counter.	Role of medication use evaluated in panel study of 82 children, mean ages 9.8 yr., with mild asthma in Sokolov, Czech Republic Nov. 1991 - Feb 1992. Linear and logistic regression evaluated PM_{10}, SO_2, temp, RH relationships to respiratory symptoms.	Medicated children, as opposed to those not using asthma medication, increased their beta-agonist use in direct association with increases in 5-day mean of SO_4 particles <2.5 μm, but medication did not prevent decrease in PEF and increase in prevalence of cough attributable to PM air pollution.	Cough 1.16 (1.00, 1.34) 6.5 μg/m^3 increase 5-day mean SO_4 5-d Mean SO_4/increase of 6.5 μg/m^3 Beta-Agonist Use 1.46 (1.08, 1.98) Theophylline Use 0.99 (0.77, 1.26) No PM_{10} analysis
Neukirch et al. (1998) Paris, France SO_2, NO_2, PM_{13} and BS. PM was measured by radiometry. PM_{13} ranged from 9 to 95 μg/m^3 with a mean of 34.	Panel of 40 nonsmoking adult asthmatics in Paris studied. GEE models used to associate health outcomes with air pollutants. Models allowed for time-dependent covariates, adjusting for time trends, day of week, temp. and humidity.	Significant relationships found for incidence of respiratory symptoms and three or more day lags of SO_2, and NO_2. Only selected results were given.	Significant relationships found between incidence of respiratory symptoms and three or more day lags of PM_{13}.
Segala et al. (1998) Paris, France SO_2, NO_2, PM_{13} (instead of PM_{10}), and BS. PM was measured by β-radiometry.	Study of 43 mildly asthmatic children aged 7-15 yr in Paris. Patients followed Nov. 15, 1992 to May 9, 1993. Respiratory symptoms recorded daily in diary. An autoregressive model fitted to data using GEE methods. Covariates included temp. and humidity.	Effects found related to PM_{13} were less than those found related to the other pollutants.	Lag 2, Symptoms: Short. Breath OR = 1.22 (0.83, 1.81) Resp. Infect. OR = 1.66 (0.84, 3.30)
Güntzel et al. (1996) Switzerland SO_2, NO_2, TSP	An asthma reporting system was used in connection with pollutant monitoring in Switzerland from fall of 1988 to fall 1990. A Box-Jenkins ARIMA time series model was used to relate asthma to TSP, O_3, SO_2, and NO_2 after adjusting for temperature.	No significant relationships found.	—
Taggart et al. (1996) Northern England SO_2, NO_2 and BS.	Panel of 38 adult asthmatics studied July 17 to Sept. 22, 1993 in northern England. Used generalized linear model to relate pollutants to bronchial hyper-responsiveness, adjusting for temperature.	Small effects seen in relation to NO_2 and BS.	—
Just et al. (2002) PM_{13}, SO_2, NO_2, O_3	82 medically diagnosed asthmatic children living in Paris, followed for 3 months. Study measured asthma attacks and nocturnal cough, symptoms, and PEF	PM_{13} was only associated with eye irritation.	Lag 0 Asthma episodes OR = 1.34 (0.08, 20.52) for 50 μg/m^3 PM_{13}.

TABLE 8B-5 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON SYMPTOMS IN STUDIES OF ASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 μg/m^3 PM_{10} (25 μg/m^3 $PM_{2.5}$). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
Von Klot et al. (2002) $PM_{2.5-10}$, PM_{10}, NO_2, SO_2, CO, temperature	53 adult asthmatics in Erfurt, Germany in the winter 1996/1997. Study measured inhaled medication use, wheezing, shortness of breath, phlegm and cough	Medication use and wheezing were associated with $PM_{2.5-10}$	5 Day mean Corticosteroid use OR = 1.12 (1.04-1.20) for 12 μg/m^3 $PM_{2.5-10}$. Wheezing OR = 1.06 (0.98, 1.15) for 12 μg/m^3 $PM_{2.5-10}$.
Desqueyroux et al. (2002) PM_{10}, O_3, SO_2, and NO_2	60 severe asthmatic adults in Paris were followed for 13 months. Study measured incident asthma attacks	Attacks were associated with PM_{10} for lags 4 and 5 but not for lags 1, 2, and 3	Lag 1 Attack OR = 0.50 (0.18, 1.34) Lag 2 Attack OR = 0.67 (0.33, 1.47) Lag 3 Attack OR = 1.69 (0.90, 3.18) Lag 4 Attack OR = 2.19 (1.16, 4.16) Lag 5 Attack OR = 2.10 (1.05, 4.32) all for 50 μg/m^3 increase in PM_{10}
Latin America			
Romieu et al. (1997) Mexico City, Mexico During study period, max daily 1-h O_3 range: 40 to 390 ppb (mean 196 ppb SD = 78 ppb) PM_{10} daily average range: 12 to 126 μg/m^3. PM was measured by a Harvard impactor.	Study of 65 children with mild asthma aged 5-13 yr living in southwest Mexico City. Respiratory symptoms recorded by the parents in daily diary. An autoregressive logistic regression model used to analyze presence of respiratory symptoms.	Strongest relationships found between O_3 and respiratory symptoms.	Lag 0, Symptoms: Cough OR = 1.05 (0.92, 1.18) Phlegm OR = 1.05 (0.83, 1.36) Diff. Breath OR = 1.13 (0.95, 1.33) Lag 2, Symptoms: Cough OR = 1.00 (0.92, 1.10) Phlegm OR = 1.00 (0.86, 1.16) Diff. Breath OR = 1.2 (1.1, 1.36)
Romieu et al. (1996) During study period, max daily range: 40 to 370 ppb (mean 190 ppb, SD = 80 ppb). 24 h ave. PM_{10} levels range: 29 to 363 μg/m^3 (mean 166.8 μg/m^3, SD 72.8 μg/m^3). PM_{10} levels exceeded 150 μg/m^3 for 53% of study days. 24-h ave. $PM_{2.5}$ levels range 23-177 μg/m^3 (mean 85.7 μg/m^3) PM was measured by a Harvard impactor.	Study of 71 children with mild asthma aged 5-7 yr living in northern Mexico City. Respiratory symptoms recorded by parents in daily diary. An autoregressive logistic regression model was used to analyze the presence of respiratory symptoms.	Cough and LRI were associated with increased O_3 and PM_{10} levels.	PM_{10} (lag 0) increase of 50 μg/m^3 related to: LRI = 1.21 (1.10, 1.42) Cough = 1.27 (1.16, 1.42) Phlegm = 1.21 (1.00, 1.48) $PM_{2.5}$ (lag 0) increase of 25 μg/m^3 related to: LRI = 1.18 (1.05, 1.36) Cough = 1.21 (1.05, 1.39) Phlegm = 1.21 (1.03, 1.42)

Appendix 8B.6

Short-Term PM Exposure Effects on Pulmonary Function in Nonasthmatics

TABLE 8B-6. SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON PULMONARY FUNCTION TESTS IN STUDIES OF NONASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 μg/m^3 PM_{10} (25 μg/m^3 PM_{2-5}). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
United States			
Hoek et al. (1998) (summary paper)	Results summarized from several other studies reported in the literature. These included: asymptomatic children in the Utah Valley (Pope et al., 1991), children in Bennekom, NL (Roemer et al., 1993), children in Uniontown, PA (Neas et al., 1995), and children in State College, PA (Neas et al., 1996). Analyses done using a first-order autoregressive model with adjustments for time trend and ambient temp.	Other pollutants not considered.	Significant decreases in peak flow found to be related to PM_{10} increases.
Lee and Shy (1999) North Carolina Mean 24 h PM_{10} conc. over two years: 25.1 μg/m^3.	Study of the respiratory health status of residents whose households lived in six communities near an incinerator in southwestern North Carolina. Daily PEFR measured in the afternoon was regressed against 24 hour PM_{10} level lagged by one day. Results were adjusted for gender, age, height, and hypersensitivity.	PM_{10} was not related to variations in respiratory health as measured by PEFR.	—
Korrick et al. (1998) Mt. Washington, NH O_3 levels measured at 2 sites near top of the mountain. $PM_{2.5}$ measured near base of the mountain. PM was measured by a Harvard impactor.	Study of the effects of air pollution on adult hikers on Mt. Washington, NH. Linear and non-linear regressions used to evaluate effects of pollution on lung function.	$PM_{2.5}$ had no effect on the O_3 regression coefficient.	—
Naeher et al. (1999) Virginia PM_{10}, $PM_{2.5}$, sulfate fraction, H+, and ozone	Daily change in PEF studied in 473 non-smoking women in Virginia during summers 1995-1996. Separate regression models run, using normalized morning and evening PEF for each individual.	Ozone was only pollutant related to evening PEF.	Morning PEF decrements were associated with PM_{10}, $PM_{2.5}$, and H+. Estimated effect from $PM_{2.5}$ and PM_{10} was similar. No PM effects found for evening PEF.
Neas et al. (1996) State College, PA $PM_{2.1}$: mean 23.5; max 85.8 μg/m^3.	Study of 108 children in State College, PA, during summer of 1991 for daily variations in symptoms and PEFRs in relation to $PM_{2.1}$ An autoregressive linear regression model was used. The regression was weighted by reciprocal number of children of each reporting period. Fungus spore conc., temp., O_3 and SO_2 were examined.	Spore concentration associated with deficient in morning PERF.	$PM_{2.1}$ (25 μg/m^3) related to RR of: PM PFER (lag 0) = −0.05 (−1.73, 0.63) PM PEFR (lag 1) = −0.64 (−1.73, 0.44)

TABLE 8B-6 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON PULMONARY FUNCTION TESTS IN STUDIES OF NONASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 μg/m^3 PM_{10} (25 μg/m^3 PM_{2-5}). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
United States (cont'd)			
Neas et al. (1999) Philadelphia, PA Median PM_{10} level: 31.6 in SW camps, 27.8 in NE camps (IQR ranges of about 18). Median $PM_{2.5}$ level: 22.2 in the SW camps, 20.7 in NE camps (IQR ranges about 16.2 and 12.9, respectively). Particle-strong acidity, fine sulfate particle, and O_3 also measured.	Panel study of 156 normal children attending YMCA and YWCA summer camps in greater Philadelphia area in 1993. Children followed for at most 54 days. Morning and evening deviations of each child's PEF were analyzed using a mixed-effects model adjusting for autocorrelation. Covariates included time trend and temp. Lags not used in the analysis.	Analyses that included sulfate fraction and O_3 separately also found relationship to decreased flow. No analyses reported for multiple pollutant models.	Lag 0, PM_{10}: Morning PEF = -8.16 (−14.81, −1.55) Evening PEF = −1.44 (−7.33, 4.44) 5 day ave, PM_{10} Morning PEF = 2.64 (−6.56, 11.83) Evening PEF = 1.47 (−7.31, 10.22) Lag 0, $PM_{2.5}$ Morning PEF = −3.28 (−6.64, 0.07) Evening PEF = −0.91 (−4.04, 2.21) 5 day ave., $PM_{2.5}$ Morning PEF = 3.18 (−2.64, 9.02) Evening PEF = 0.95 (−4.69, 6.57)
Schwartz and Neas (2000) Eastern U.S. $PM_{2.5}$ and CM ($PM_{10-2.5}$) measured. Summary levels not given.	Analyses for 1844 school children in grades 2-5 from six urban areas in eastern U.S. and from separate studies from Uniontown and State College, PA. Lower resp. symptoms, cough and PEF used as endpoints. The authors replicated models used in the original analyses. CM and were used individually and jointly in the analyses. Sulfate fractions also used in the analyses. Details of models not given.	Sulfate fraction was highly correlated with $PM_{2.5}$ (0.94), and, not surprisingly, gave similar answers.	Uniontown Lag 0,$PM_{2.5}$: Evening PEF = −1.52 (−2.80, −0.24) State College Lag 0, $PM_{2.5}$: Evening PEF = −0.93 (−1.88, 0.01) Results presented for CM showed no effect. Results for PM_{10} were not given.
Linn et al. (1996) So. California NO_2 ozone, and PM_5 measured. PM_5 was measured using a Marple low volume sampler PM_5 ranged from 1-145 μg/m^3 with a mean of 24.	Study of 269 school children in Southern California twice daily for one week in fall, winter and spring for two years. A repeated measures analysis of covariance was used to fit an autoregressive model, adjusting for year, season, day of week, and temperature.	Morning FVC was significantly decreased as a function of PM_5 and NO_2	—

TABLE 8B-6 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON PULMONARY FUNCTION TESTS IN STUDIES OF NONASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 μg/m^3 PM_{10} (25 μg/m^3 PM_{2-5}). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
Canada			
Vedal et al. (1998) Port Alberni, BC PM_{10} via a Sierra-Anderson dichotomous sampler. PM_{10} ranged from 1 to 159 μg/m^3.	Study of 206 children aged 6 to 13 years living in Port Alberni, British Columbia. 75 children had physician-diagnosed asthma, 57 had an exercised induced fall in FEV1, 18 children with airway obstruction, and 56 children without any symptoms. Respiratory symptom data obtained from diaries. An autoregressive model was fitted to the data, using GEE methods. Covariates included temp., humidity, and precipitation.	No consistent evidence for adverse health effects was seen in the nonasthmatic control group.	—
Europe			
Boezen et al. (1999) Netherlands PM_{10}, BS, SO_2, and NO_2 measured, but methods were not given. PM_{10} ranged from 4.8 to 145 μg/m^3 with site means ranging from 26 to 54 μg/m^3.	Data collected from children during three winters (1992-1995) in rural and urban areas of The Netherlands. Study attempted to investigate whether children with bronchial hyperresponsiveness and high serum Ige levels were more susceptible to air pollution. Prevalence of a 10 percent PEF decrease was related to pollutants for children with bronchial hyperresponsiveness and high serum Ige levels.	No consistent pattern of effects observed with any of the pollutants for 0, 1, and 2 day lags.	—
Frischer et al. (1999) Austria PM_{10} measured gravimettrically for 14-d periods. Annual mean PM_{10} levels range: 13.6 - 22.9 μg/m^3. O_3 range: 39.1 ppb - 18.5 pbs between sites.	At nine sites in Austria during 1994, 1995, and 1996, a longitudinal study designed to evaluate O_3 was conducted. During 1994 - 1996, children were measured for FVC, FEV_1 and MEF_{50} six times, twice a year in spring and fall. 1060 children provided valid function tests. Mean age 7.8 ± 0.7 yr. GEE models used. PM_{10}, SO_2, NO_2, and temp. evaluated.	Small but consistent lung function decrements in cohort of school children associated with ambient O_3 exposure.	PM_{10} showed little variation in exposure between study site. For PM_{10}, positive effect seen for winter exposure but was completely confounded by temperature. PM_{10} Summertime β = 0.003 SE 0.012 p=0.77
Grievink et al. (1999) Netherlands PM_{10} and BS. PM_{10} ranged from 12 to 123 μg/m^3 with a mean of 44.	A panel of adults with chronic respiratory symptoms studied over two winters in The Netherlands starting in 1993/1994. Logistic regression analysis was used to model the prevalence of large PEF decrements. Individual linear regression analysis of PEF on PM was calculated and adjusted for time trends, influenza incidence, and meteorological variables.	Subjects with low levels of serum β-carotene more often had large PEF decrements when PM_{10} levels were higher, compared with subjects with high serum β-carotene. Results suggested serum β-carotene may attenuate the PM effects on decreased PEF.	—

TABLE 8B-6 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON PULMONARY FUNCTION TESTS IN STUDIES OF NONASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 μg/m^3 PM_{10} (25 μg/m^3 PM_{2-5}). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
Europe (cont'd)			
Künzli et al. (2000)	Ackermann-Liebrich et al. (1997) data reanalyzed. Authors showed that a small change in FVC (-3.14 percent) can result in a 60% increase in number of subjects with FVC less than 80 percent of predicted.	The results were for two hypothetical communities, A and B.	—
Roemer et al. (2000) PM_{10} means for 17 panels ranged 11.2 to 98.8 μg/m^3. SO_2, NO_2, and elemental content of PM also measured. Measurement methods were not described.	Combined results from 1208 children divided among 17 panels studied. Separate results reported by endpoints included symptoms as reported in a dairy and PEF. Individual panels were analyzed using multiple linear regression analysis on deviations from mean PEF adjusting for auto-correlation. Parameter estimates were combined using a fixed-effects model where heterogeneity was not present and a random-effects model where it was present.	Daily concentrations of most elements were not associated with the health effects.	PM_{10} analyses not focus of this paper.
Scarlett et al. (1996) PM_{10}, O_3, and NO_2 measured.	In study of 154 school children, pulmonary function was measured daily for 31 days. Separate autoregressive models for each child were pooled, adjusting for pollen, machine, operator, time of day, and time trend.	PM_{10} was related to changes in FEV and FVC	—
van der Zee et al. (1999) Netherlands PM_{10} averages ranged 20 to 48 μg/m^3. BS, sulfate fraction, SO_2, and NO_2 also measured.	Panel study of 795 children aged 7 to 11 years, with and without chronic respiratory symptoms living in urban and nonurban areas in the Netherlands. Peak flow measured for three winters starting in 1992/1993. Peak flow dichotomized at 10 and 20% decrements below the individual median. Number of subjects was used as a weight. Minimum temperature day of week, and time trend variables were used as covariates. Lags of 0, 1 and 2 days were used, as well as 5 day moving average.	In children with symptoms, significant associations found between PM_{10}, BS and sulfate fraction and the health endpoints. No multiple pollutant models analyses reported.	Lag 0, PM_{10}, Urban areas Evening PEF OR = 1.15 (1.02, 1.29) Lag 2, PM_{10}, Urban areas Evening PEF OR = 1.07 (0.96, 1.19) 5 day ave, PM_{10}, Urban areas Evening PEF = 1.13 (0.96, 1.32)

TABLE 8B-6 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON PULMONARY FUNCTION TESTS IN STUDIES OF NONASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 μg/m^3 PM_{10} (25 μg/m^3 PM_{2-5}). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
Europe (cont'd)			
van der Zee et al. (2000) Netherlands PM_{10} averages ranged 24 to 53 μg/m^3. BS, sulfate fraction, SO_2, and NO_2 also measured. PM_{10} was measured using a Sierra Anderson 241 dichotomous sampler.	Panel study of 489 adults aged 50-70 yr, with and without chronic respiratory symptoms, living in urban and nonurban areas in the Netherlands. Resp. symptoms and peak flow measured for three winters starting in 1992/1993. Symptom variables analyzed as a panel instead of using individual responses. The analysis was treated as a time series, adjusting for first order autocorrelation. Peak flow dichotomized at 10 and 20% decrements below the individual median. The number of subjects used as a weight. Minimum temp., day of week, and time trend variables used as covariates. Lags of 0, 1 and 2 days used, as well as 5 day moving average.	BS tended to have the most consistent relationship across endpoints. Sulfate fraction also related to increased respiratory effects. No analyses reported for multiple pollutant models. Relationship found between PM_{10} and the presence of 20% decrements in symptomatic subjects from urban areas.	Lag 0, PM_{10}, Urban areas Morning large decrements OR = 1.44 (1.02, 2.03) Lag 2, PM_{10}, Urban areas Morning large decrements OR = 1.14 (0.83, 1.58) 5 day ave, PM_{10}, Urban areas Morning large decrements OR = 1.16 (0.64, 2.10) Results should be viewed with caution because of problems in analysis.
Tiittanen et al. (1999) Kupio, Finland Median PM_{10} level: 28 (25^{th}, 75^{th} percentiles = 12, 43). Median $PM_{2.5}$ level: 15 (25^{th}, 75^{th} percentiles = 9, 23). Black carbon, CO, SO_2, NO_2, and O_3 also measured. PM was measured using single stage Harvard samplers.	Six-week panel study of 49 children with chronic respiratory disease followed in the spring of 1995 in Kuopio, Finland. Morning and evening deviations of each child's PEF analyzed, using a general linear model estimated by PROC MIXED. Covariates included a time trend, day of week, temp., and humidity. Lags of 0 through 3 days were used, as well as a 4-day moving average. Various fine particles were examined.	Ozone strengthened the observed associations. Introducing either NO_2 or SO_2 in the model did not change the results markedly. Effects varied by lag. Separating effects by size was difficult.	Lag 0, PM_{10}: Morning PEF = 1.21 (−0.43, 2.85) Evening PEF = 0.72 (−0.63, 1.26) 4 day ave, PM_{10} Morning PEF = −1.26 (−5.86, 3.33) Evening PEF = 2.33 (−2.62, 7.28) Lag 0, $PM_{2.5}$ Morning PEF = 1.11 (−0.64, 2.86) Evening PEF = 0.70 (−0.81, 2.20) 4 day ave., $PM_{2.5}$ Morning PEF = −1.93 (−7.00, 3.15) Evening PEF = 1.52 (−3.91, 6.94)

TABLE 8B-6 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON PULMONARY FUNCTION TESTS IN STUDIES OF NONASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 μg/m^3 PM_{10} (25 μg/m^3 PM_{2-5}). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
Europe (cont'd)			
Ward et al. (2000) West Midlands, UK Daily measurements of PM_{10}, $PM_{2.5}$, SO_2, CO, O_3, and oxides of nitrogen. Details on PM monitoring were inomplete.	Panel study of 9 yr old children in West Midlands, UK for two 8-week periods representing winter and summer conditions. Individual PEF values converted to z-values. Mean of the z-values analyzed in a linear regression model, including terms for time trend, day of week, meteorological variables, and pollen count. Lags up to four days also used.	Results on effects of pollution on lung function to be published elsewhere.	—
Osunsanya et al. (2001) studied 44 patients aged > 50 with COPD in Aberdeen, UK. PM was measured using tapered element oscillating microbalance. Particle sizes were measured a TSI model 3934 scanning particle sizer. PM_{10} ranged from 6 to 34 μg/m^3 with a median of 13.	Symptom scores, bronchodilator use, and PEF were recorded daily for three months. GEE methods were used to analyze the dichotomous outcome measures. PEF was converted to a dichotomous measure by defining a 10 percent decrement as the outcome of interest.	No associations were found between actual PEF and $_{PM10}$ or ultrafine particles. A change of $_{PM10}$ from 10 to 20 μg/m^3 was associated with a 14 percent decrease in the rate of high scores of shortness of breath. A similar change in PM_{10} was associated with a rate of high scores of cough.	The endpoint was measured in terms of scores rather than L/min.
Cuijpers et al. (1994) Maastricht, NL SO_2, NO_2, BS, ozone, and H+ measured. PM measurements were made with a modified Sierra Anderson sampler. PM_{10} ranged from 23 to 54 μg/m^3.	Summer episodes in Maastricht, The Netherlands studied. Paired t tests used for pulmonary function tests.	Small decreases in lung function found related to pollutants.	Quantitative results not given.
Latin America			
Gold et al. (1999) Mexico City, Mexico Mean 24 h O_3 levels: 52 ppb. Mean $PM_{2.5}$: 30 μg/m^3. Mean PM_{10}: 49 μg/m^3.	Peak flow studied in a panel of 40 school-aged children living in southwest Mexico City. Daily deviations from morning and afternoon PEFs calculated for each subject. Changes in PEF regressed on individual pollutants allowing for autocorrelation and including terms for daily temp., season, and time trend.	O_3 significantly contributed to observed decreases in lung function, but there was an independent PM effect.	Both $PM_{2.5}$ and PM_{10} significantly related to decreases in morning and afternoon peak flow. Effects of the two pollutants similar in magnitude when compared on percent change basis.

TABLE 8B-6 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON PULMONARY FUNCTION TESTS IN STUDIES OF NONASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 μg/m^3 PM_{10} (25 μg/m^3 PM_{2-5}). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
New Zealand			
Harré et al. (1997) Christchurch, NZ SO_2, NO_2, PM_{10}, and CO measured. Details on monitoring methods and pollutant ranges were not given.	Study of 40 subjects aged over 55 years with COPD living in Christchurch, New Zealand conducted during winter of 1994. Subjects recorded their peak flow measurements. A log-linear regression model with adjustment for first order auto-correlation was used to analyze peak flow data and a Poisson regression model was used to analyze symptom data.	Few significant associations found between the health endpoints and the pollutants.	Lag 0, PM_{10}: PEF = −0.86 (−2.33, 0.61)
Jalaludin et al. (2000) studied PEF in 148 children 6 primary schools in Sydney, Australia. PM was measured by tapered element oscillating microbalance. Mean PM_{10} was 22.8 +- 13.9 μg/m^3.	148 children in grades 3-5 were followed for 11 months, recording PEF twice daily. The normalized change in PEF was analyzed using GEE methods. PEF was related to SO_3, PM_{10}, NO_2, as well as meteorological variables.	Daily mean deviations in PEF were related to ozone, but no relationships were found with PM_{10} or NO_2. Multiple pollutant models gave similar results to those given by the single pollutant models.	Change from AM to PM PEF = 0.045 (−.205, 2.95) lag one day
Asia			
Chen et al. (1999) Taiwan Beta-gauge PM_{10} ranged 44.5 to 189.0 μg/m^3 for peak concentrations.	In 3 Taiwan communities in 1995, PM_{10} by B-gauge measured at selected primary schools in each community. Spirometry tests (FVC, $FEV_{1.0}$, $FEF_{25-75\%}$, PEF) obtained in period May 1995 to Jan. 1996 using ATS protocol in study pop. aged 8 to 13 yr. 895 children were analyzed. Study was designed to investigate short-term effect of ambient air pollution in cross-sectional survey. Multivariate linear model analysis used in both one pollutant and multipollutant models, with 1-, 2-, and 7-day lags. SO_2, CO, O_3, NO_2 and PM_{10} examined, as were meteorol. variables.	In the one-pollutant model, daytime peak O_3 conc. with a 1-day lag significantly affected both FVC and FEV_1. NO_2, SO_2, CO affected FVC. PM_{10} showed nonsignificant decrement. No significant result demonstrated in the model for the exposure with 7 days lag. In the multi-pollutant model, only peak O_3 conc. with 1-day lag showed sig. effect on FVC and $FEV_{1.0}$.	One pollutant model daytime average PM_{10} – 2 day lag FVC −0.37 se 0.39
Tan et al. (2000) Southeast Asian smoke-haze event 9/29 – 10/27 1997 PM_{10} mean daily was 125.4 ± 44.9 μg/m^3 ultra range of 47 to 216 μg/m^3 in Singapore	Examined the association between acute air pollution caused by biomass burning and peripheral UBC counts in human serial measurement made during the event were compared with a period after the haze cleared (Nov. 21 – Dec. 5, 1997)	Indices of atmospheric pollution were significantly associated in the elevated band neutrophil counts expressed as a percentage of total polymonphonuclear leukocytes (PMN). No statistically significant difference in FEU_1 and FUC were observed during and after haze exposure.	

Appendix 8B.7

Short-Term PM Exposure Effects on Symptoms in Nonasthmatics

TABLE 8B-7. SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON SYMPTOMS IN STUDIES OF NONASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 μg/m^3 PM_{10} (25 μg/m^3 $PM_{2.5}$). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
United States			
Schwartz and Neas (2000) Eastern U.S. $PM_{2.5}$ and CM ($PM_{10-2.5}$ by substation).. Summary levels not given	Reported on analysis of 1844 school children in grades 2–5 from six urban areas in the eastern U.S., and from separate studies from Uniontown and State College, PA. Lower respiratory symptoms, and cough used as endpoints. The authors replicated the models used in the original analyses. CM and $PM_{2.5}$ were used individually and jointly in the analyses. Sulfates fractions were also used in the analyses. Details of the models were not given.	Sulfate fraction was highly correlated with $PM_{2.5}$ (0.94), and not surprisingly gave similar answers.	$PM_{2.5}$ was found to be significantly related to lower respiratory symptoms even after adjusting for CM, whereas the reverse was not true. However, for cough, CM was found to be significantly related to lower respiratory symptoms even after adjusting for $PM_{2.5}$, whereas the reverse was not true.
Zhang et al. (2000) Vinton, Virginia 24- h PM_{10}, $PM_{2.5}$, sulfate and strong acid measured in 1995.	In southwestern Virginia, 673 mothers were followed June 10 to Aug. 31, 1995 for the daily reports of present or absence of runny or stuffy nose. PM indicator, O_3, NO_2 temp., and random sociodemographic characteristics considered.	Of all pollutants considered, only the level of coarse particles as calculated (PM_{10} - $PM_{2.5}$) independently related to incidence of new episode of runny noses.	—
Canada			
Vedal et al. (1998) Port Alberni, BC PM_{10} via a Sierra-Anderson dichotomous sampler. PM_{10} ranged from 1 to 159 μg/m^3.	Study of 206 children aged 6 to 13 years living in Port Alberni, British Columbia. 75 children had physician-diagnosed asthma, 57 had an exercised induced fall in FEV1, 18 children with airway obstruction, and 56 children without any symptoms. Respiratory symptom data obtained from diaries. An autoregressive model was fitted to the data, using GEE methods. Covariates included temp., humidity, and precipitation.	No consistent evidence for adverse health effects was seen in the nonasthmatic control group.	—
Long et al. (1998) Winnepeg, CN PM_{10}, TSP, and VOC measured. Methods for PM monitoring not given. Ranges of values also not given.	Study of 428 participants with mild airway obstruction conducted during a Winnepeg pollution episode. Gender specific odds ratios of symptoms were calculated for differing PM_{10} levels using the Breslow-Day test.	Cough, wheezing, chest tightness, and shortness of breath were all increased during the episode	—
Europe			
Boezen et al. (1998) Amsterdam, NL PM_{10}, SO_2, and NO_2 measured. PM_{10} ranged from 7.9 to 242.2 μg/m^3 with a median of 43.	Study of 75 symptomatic and asymp. adults near Amsterdam for three months during winter 1993-1994. An autoregressive logistic model was used to relate PM_{10} to respiratory symptoms, cough, and phlegm, adjusting for daily min. temp., time trend, day of week.	No relationship found with pulmonary function. Some significant relationships with respiratory disease found in subpopulations	—

TABLE 8B-7 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON SYMPTOMS IN STUDIES OF NONASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 μg/m^3 PM_{10} (25 μg/m^3 PM_{2-5}). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
Europe (cont'd)			
Howel et al. (2001) study of children's respiratory health in 10 non-urban communities of northern England. PM levels were measured using a single continuous real-time monitor. PM_{10} levels ranged from 5 to 54 μg/m^3.	The study included 5 pairs of non-urban communities near and not so near 5 coal mining sites. 1405 children aged 1-11 years were included. 275 of the children reported having asthma. Diaries of respiratory symptoms were collected over a 6 week period. PM_{10}, measured by a single continuous real-time monitor, ranged from 5 to 54 μg/m^3.	The associations found between daily PM_{10} levels and respiratory symptoms were frequently small and positive and sometimes varied by community.	OR wheeze = 1.16 (1.05, 1.28 (PM_{10}) OR cough = 1.09 (1.02, 1.16) (PM_{10}) OR reliever use = 1.00 (0.94, 1.06) (PM_{10})
Roemer et al. (1998) Mean PM_{10} levels measured at local sites ranged 11.2 to 98.8 μg/m^3 over the 28 sites.	Pollution Effects on Asthmatic Children in Europe (PEACE) study was a multi-center study of PM_{10}, BS, SO_2, and NO_2 on respiratory health of children with chronic respiratory symptoms. Results from individual centers were reported by Kotesovec et al. (1998), Kalandidi et al. (1998), Haluszka et al. (1998), Forsberg et al. (1998), Clench-Aas et al. (1998), and Beyer et al. (1998). Children with chronic respiratory symptoms were selected into the panels. The symptom with one of the larger selection percentages was dry cough (range over sample of study communities 29 to 92% [22/75; 84/91] with most values over 50%). The group as a whole characterized as those with chronic respiratory disease, especially cough.	These studies modeled group rates and are an example of the panel data problem.	—
Roemer et al. (2000) PM_{10} means for the 17 panels ranged 11.2 to 98.8 μg/m^3. SO_2, NO_2, and PM elemental content also measured. Measurement methods were not described.	Combined results from 1208 children divided among 17 panels studied. Endpoints included symptoms as reported in a dairy and PEF. Symptom variables analyzed as a panel instead of using individual responses. The analysis was treated as a time series, adjusting for first order autocorrelation. Parameter estimates were combined using a fixed-effects model where heterogeneity was not present and a random-effects model where it was present.	Daily concentrations of most elements were not associated with the health effects.	The analysis of PM_{10} was not a focus of this paper.

TABLE 8B-7 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON SYMPTOMS IN STUDIES OF NONASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 μg/m^3 PM_{10} (25 μg/m^3 $PM_{2.5}$). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
Europe (cont'd)			
van der Zee et al. (1999) Netherlands PM_{10} averages ranged 20 to 48 μg/m^3. BS, sulfate fraction, SO_2, and NO_2 also measured.	A panel study of 795 children aged 7 to 11 yr, with and without chronic respiratory symptoms, living in urban and nonurban areas in the Netherlands. Respiratory symptoms measured for 3 winters starting 1992/1993. Symptom variables analyzed as a panel instead of using individual responses. The analysis was treated as a time series, adjusting for first order autocorrelation. The number of subjects was used as a weight. Minimum temp., day of week, and time trend variables used as covariates. Lags of 0, 1 and 2 days used, as well as 5 day moving average.	In children with symptoms, significant associations found between PM_{10}, BS and sulfate fraction and the health endpoints. No analyses reported with multiple pollutant models.	Lag 0, PM_{10}, Urban areas Cough OR = 1.04 (0.95, 1.14) Lag 2, PM_{10}, Urban areas Cough OR = 0.94 (0.89, 1.06) 5 day ave, PM_{10}, Urban areas Cough OR = 0.95 (0.80, 1.13)
van der Zee et al. (2000) Netherlands Daily measurements of PM_{10}, BS, fine sulfate, nitrate, ammonium and strong acidity. PM_{10} was measured using a Sierra Anderson 241 dichotomous sampler.	Panel study of adults aged 50 to 70 yr during 3 consecutive winters starting in 1992/1993. Symptom variables analyzed as a panel instead of using individual responses. Analysis treated as a time series, adjusting for first order autocorrelation. Number of subjects used as a weight. Min. temp., day of week, time trend variables used as covariates. Lags 0, 1 and 2 days used, as well as 5 day moving average.	BS was associated with upper respiratory symptoms.	Lag 0, Symptoms, Urban areas LRS OR = 0.98 (0.89, 1.08) URS OR = 1.04 (0.96, 1.14) Lag 2, Symptoms, Urban areas LRS OR = 1.01 (0.93, 1.10) URS OR = 1.04 (0.96, 1.13) 5 day ave, Symptoms, Urban areas LRS OR = 0.95 (0.82, 1.11) URS OR = 1.17 (1.00, 1.37)
Tiittanen et al. (1999) Kupio, Finland Median PM_{10} level: 28 (25^{th}, 75^{th} percentiles = 12, 43). Median $PM_{2.5}$: 15 (25^{th} and 75^{th} percentiles of 9 and 23). Black carbon, CO, SO_2, NO_2, and O_3 also measured. PM was measured using single stage Harvard samplers.	Six-week panel study of 49 children with chronic respiratory disease followed in spring 1995 in Kuopio, Finland. Cough, phlegm, URS, LRS and medication use analyzed, using a random effects logistic regression model (SAS macro GLIMMIX). Covariates included a time trend, day of week, temp., and humidity. Lags of 0 to 3 days used, as well as 4-day moving average.	Ozone strengthened the observed associations. Introducing either NO_2 or SO_2 in the model did not change the results markedly.	Lag 0, PM_{10}: Cough OR = 1.00 (0.87, 1.16) 4 day ave, PM_{10} Cough OR = 1.58 (0.87, 2.83) Lag 0, $PM_{2.5}$ Cough OR = 1.04 (0.88, 1.23) 4 day ave., $PM_{2.5}$ Cough OR = 2.01 (1.04, 3.89)
Keles et al. (1999) Istanbul, Turkey Nov. 1996 to Jan. 1997. TSP levels ranged from annual mean of 22 μg/m^3 in unpolluted area to 148.8 μg/m^3 in polluted area.	Symptoms of rhinitis and atopic status were evaluated in 386 students grades 9 and 10 using statistical package for the social sciences, Fisher tests, and multiple regression model as Spearman's coefficient of correlation.	No difference found for atopic status in children living in area with different air pollution levels.	—

TABLE 8B-7 (cont'd). SHORT-TERM PARTICULATE MATTER EXPOSURE EFFECTS ON SYMPTOMS IN STUDIES OF NONASTHMATICS

Reference citation, location, duration, pollutants measured, summary of values	Type of study, sample size, health outcomes measured, analysis design, covariates included, analysis problems, etc.	Results and Comments Effects of co-pollutants	Effect measures standardized to 50 μg/m^3 PM_{10} (25 μg/m^3 PM_{2-5}). Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest PM effects
New Zealand			
Harré et al. (1997) Christchurch, NZ SO_2, NO_2, PM_{10}, and CO measured. Details on monitoring methods and pollutant ranges were not given.	Study of 40 subjects aged 55 years with COPD living in Christchurch, New Zealand during winter 1994. Subjects recorded completed diaries twice daily. Poisson regression model used to analyze symptom data.	NO_2 was associated with increased bronchodilator use.	PM_{10} was associated with increased nighttime chest symptoms.
Asia			
Awasthi et al. (1996) India Suspended particulate matter, SO_2, nitrates, coal, wood, PM and kerosene measured. SPM was measured using a high-volume sampler.	A cohort of 664 preschool children studied for two weeks each in northern India. Ordinary least squares was used to relate a respiratory symptom complex pollutants.	A significant regression coefficient between PM and symptoms was found	—

Appendix 8B.8

Long-Term PM Exposure Effects on Respiratory Health Indicators, Symptoms, and Lung Function

TABLE 8B-8. LONG-TERM PARTICULATE MATTER EXPOSURE RESPIRATORY HEALTH INDICATORS: RESPIRATORY SYMPTOM, LUNG FUNCTION

Reference citation, location, duration, type of study, sample size, pollutants measured, summary of values	Health outcomes measured, analysis design, covariates included, analysis problems	Results and Comments Effects of co-pollutants	Effect estimates as reported by study authors. Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest effects of PM
United States			
Abbey et al. (1998) California Communities 20 year exposure to respirable particulates, suspended sulfates, ozone, and PM_{10}. PM_{10} ranged from 1 to 145 µg/m^3 with a mean value of 32.8.	Sex specific multiple linear regressions were used to relate lung function measures to various pollutants in long-running cohort study of Seven Day Adventists (ASHMOG Study).	Sulfates were associated with decreases in FEV.	Frequency of days where PM_{10} > 100 µg/m^3 associated with FEV decrement in males whose parents had asthma, bronchitis, emphysema, or hay fever. No effects seen in other subgroups.
Berglund et al.. (1999) California communities	Cohort study of Seventh Day Adventists. Multivariate logistic regression analysis of risk factors (e.g., PM) for chronic airway disease in elderly non-smokers, using pulmonary function test and respiratory symptom data.	Significant risk factors identified: childhood respiratory illness, reported ETS exposure, age, sex and parental history.	For PM_{10} > 100µg/m^3, 42 d/yr: RR = −1.09 CT (0.92, 1.30) for obstructive disease determined by pulmonary function tests.
Peters et al. (1999b,c) 12 southern California communities 5 year exposure to PM_{10}, ozone, NO_2, acid levels. PM_{10} annual averages ranged from 13 to 70 µg/m^3.	Asthma, bronchitis, cough and wheeze rates were adjusted for individual covariates. Community rates were then regressed on pollutant averages for 1986-1990.	Wheeze was associated with NO_2 and acid levels. No symptoms were associated with PM_{10} levels.	OR for PM_{10} (per 25 µg/m^3): Asthma 1.09 (0.86, 1.37) Bronchitis 0.94 (0.74, 1.19) Cough 1.06 (0.93, 1.21) Wheeze 1.05 (0.89, 1.25)
Avol et al. (2001) Subjects living in Southern California in 1993 that moved to other western locations in 1998. Pollutants O_3, NO_2, PM_{10} differences 15 to 66 µg/m^3.	Studied 110 children who were 10 yrs of age at enrollment and 15 at follow-up who had moved from communities filled out health questions and underwent spirometry. Linear regression used to determine whether annual average change in lung function correlated with average changes in PM.	As a group, subjects who moved to areas of lower PM_{10} showed increased growth in lung function and subjects who moved to communities with a higher PM_{10} showed decreased growth in lung function.	PM_{10} 24 hr average PERF ml/s per 10 µg/m^3 mean = −34.9 95% CI −59.8, −10.1
Gauderman et al. (2000) 12 So. California communities 1993 to 1997 Pollutants: O_3, NO_2, PM_{10}, and $PM_{2.5}$. PM_{10} levels ranged from 16.1 to 67.6 µg/m^3 across the communities.	Studies of lung function growth of 3035 children in 12 communities within 200-mile radius of Los Angeles during 1993 to 1997. Cohorts of fourth, seventh, and tenth-graders studied. By grade cohort, a sequence of linear regression models were used to determine over the 4yr of follow-up, if average lung function growth rate of children was associated with average pollutant levels. Adjustment were made for height, weight, body mass index, height by age interaction, report of asthma activity or smoking. Two-pollutant models also used.	Lung growth rate for children in most polluted community, as compared to least polluted, was estimated to result in cumulative reduction of 3.4% in FEV_1 and 5.0% in MMEF over 4-yr study period. Estimated deficits mostly larger for children spending more time outdoors. Due to the high correlation in concentrations across communities, not able to separate effects of each pollutant. No sig. associations seen with O_3.	From the lowest to highest observed concentration of each pollutant, the predicted differences in annual growth rates were: −0.85% for PM_{10} (p = 0.026); −0.64% for $PM_{2.5}$ (p = 0.052); −0.90% for $PM_{10-2.5}$ (p = 0.030); −0.77% for NO_2 (p = 0.019); and −0.73% for inorganic acid vapor (p = 0.042).

TABLE 8B-8 (cont'd). LONG-TERM PARTICULATE MATTER EXPOSURE RESPIRATORY HEALTH INDICATORS: RESPIRATORY SYMPTOM, LUNG FUNCTION

Reference citation, location, duration, type of study, sample size, pollutants measured, summary of values	Health outcomes measured, analysis design, covariates included, analysis problems	Results and Comments Effects of co-pollutants	Effect estimates as reported by study authors. Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest effects of PM
United States (cont'd)			
Gauderman et al. (2002) Follow-up on 12 southern California communities 5 year exposure to PM_{10}, ozone, NO_2, acid levels. PM_{10} annual averages ranged from 5 to 27 µg/m^3.	Linear regression analysis was used to estimate the individual lung function growth adjusted for height, weight, body mass index, and smoking. Growth rates were then adjusted for individual covariates to obtain community adjusted growth rates. These rates were then related to pollutant averages for 1996-1999.	Lung function growth was related to total acid.	From the lowest to highest observed concentration of each pollutant, the predicted differences in annual growth rates of FEV1 were: PM_{10} −0.21 (−1.04, 0.64), ozone −0.55 (−1.27, 0.16), NO_2 −0.48 (−1.12, 0.17), $PM_{2.5}$ −0.39 (−1.06, 0.28), total acid −0.63 (−1.21, 0.17)
McConnell et al. (1999) 12 Southern California communities 1994 air monitoring data. PM_{10} (mean 34.8; range 13.0 - 70.7 µg/m^3). $PM_{2.5}$ (yearly mean 2 week averaged mean 15.3 µg/m^3; range 6.7 - 31.5 µg/m^3).	Cross-sectional study of 3,676 school children whose parents completed questionnaires in 1993 that characterized the children's history of respiratory illness. Three groups examined: (1) history of asthma; (2) wheezing but no asthma; and (3) no history of asthma or wheezing. Logistic regression model used to analyze PM, O_3, NO_2, acid vapor effects. This study also described in Peters et al. (1999b,c).	Positive association between air pollution and bronchitis and phlegm observed only among children with asthma. As PM_{10} increased across communities, a corresponding increase in risk of bronchitis per interquartile range occurred. Strongest association with phlegm was for NO_2. Because of high correlation of PM air pollution, NO_2, and acid, not possible to distinguish clearly which most likely responsible for effects.	PM_{10} Asthma Bronchitis 1.4 CI (1.1 – 1.8) Phlegm 2.1 (1.4 – 3.3) Cough 1.1 (0.8 – 1.7) No Asthma/No Wheeze Bronchitis 0.7 (0.4 – 1.0) Phlegm 0.8 (0.6 – 1.3) Cough 0.9 (0.7 – 1.2)
McConnell et al. (2002) 12 Southern California communities 1994-1997 4-year mean conc. PM_{10} µg/m^3 High community: 43.3 (12.0) Low community: 21.6 (3.8)	In 3,535 children assessed, the association of playing team sports with subsequent development of asthma during 4 yrs of follow-up. Comparing high pollutant communities to low pollutant communities. Relative risks of asthma adjusted for ethnic origin were evaluated for every pollutant with a multivariate proportional hazards model. See also Peters et al. (1999b,c).	Across all communities there was a 1.8-fold increased risk (95% CI 1.2-2.8) for asthma in children who had played three or more team sports in the previous year. In high ozone (10:00 h to 18:00 h mean concentration) communities, there was a 3.3-fold increase risk of asthma in children playing three or more sports, an increase not seen in low ozone communities.	The effect of team sports was similar in communities with high and low PM with a small increase in asthma among children playing team sports.
Dockery et al. (1996) 24 communities in the U. S. and Canada. PM_{10}, $PM_{2.5}$, sulfate fraction, H^+, ozone, SO_2, and other measures of acid were monitored. PM was measured using a Harvard impactor. PM_{10} ranged form 15.4 to 32.7 with a mean of 23.8. $PM_{2.5}$ ranged form 5.8 to 20.7 µg/m^3 with a mean of 14.5.	Respiratory health effects among 13,369 white children aged 8 to 12 yrs analyzed in relation to PM indices. Two-stage logistic regression model used to adjust for gender, history of allergies, parental asthma, parental education, smoking in home.	Although bronchitis endpoint was significantly related to fine PM sulfates, no endpoints were related to PM_{10} levels.	—

TABLE 8B-8 (cont'd). LONG-TERM PARTICULATE MATTER EXPOSURE RESPIRATORY HEALTH INDICATORS: RESPIRATORY SYMPTOM, LUNG FUNCTION

Reference citation, location, duration, type of study, sample size, pollutants measured, summary of values	Health outcomes measured, analysis design, covariates included, analysis problems	Results and Comments Effects of co-pollutants	Effect estimates as reported by study authors. Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest effects of PM
United States (cont'd)			
Raizenne et al. (1996) 24 communities in the U.S. and Canada Pollutants measured for at least one year prior to lung function tests: PM_{10}, $PM_{2.1}$, particle strong acidity, O_3, NO_2, and SO_2. PM was measured with a Harvard impactor. For pollutant ranges, see Dockery et al. (1996).	Cross-sectional study of lung function. City specific adjusted means for FEV and FVC calculated by regressing the natural logarithm of the measure on sex, ln height, and ln age. These adjusted means were then regressed on the annual pollutant means for each city.	PM measures (e.g., particle strong acidity) associated with FEV and FVC decrement.	—
Europe			
Ackermann-Liebrich et al. (1997) Eight Swiss regions Pollutants: SO_2, NO_2, TSP, O_3, and PM_{10}. PM was measured with a Harvard impactor. PM_{10} ranged from 10 to 53 µg/m^3 with a mean of 37.	Long-term effects of air pollution studied in cross-sectional population-based sample of adults aged 18 to 60 yrs. Random sample of 2,500 adults in each region drawn from registries of local inhabitants. Natural logarithms of FVC and FEV_1 regressed against natural logarithms of height, weight, age, gender, atopic status, and pollutant variables.	Significant and consistent effects on FVC and FEV were found for PM_{10}, NO_2 and SO_2.	Estimated regression coefficient for PM_{10} versus FVC = −0.035 (95% CI −0.041, −0.028). Corresponding value for FEV_1 −0.016 (95% CI −0.023 to −0.01). Thus, 10 µg/m^3 PM_{10} increase estimated to lead to estimated 3.4 percent decrease in FVC and 1.6 percent decrease in FEV_1.
Braun-Fahrländer et al. (1997) 10 Swiss communities Pollutants: PM_{10}, NO_2, SO_2, and O_3. PM was measured with a Harvard impactor. PM_{10} ranged from 10 to 33 µg/m^3.	Impacts of long-term air pollution exposure on respiratory symptoms and illnesses were evaluated in cross-sectional study of Swiss school children, (aged 6 to 15 years). Symptoms analyzed using a logistic regression model including covariates of family history of respiratory and allergic diseases, number of siblings, parental education, indoor fuels, passive smoking, and others.	Respiratory endpoints of chronic cough, bronchitis, wheeze and conjunctivitis symptoms were all related to the various pollutants. The colinearity of the pollutants including NO_2, SO_2, and O_3, prevented any causal separation.	PM_{10} Chronic cough OR 11.4 (2.8, 45.5) Bronchitis OR 23.2 (2.8, 45.5) Wheeze OR 1.41 (0.55, 3.58)
Zemp et al. (1999) 8 study sites in Switzerland. Pollutants: TSP, PM_{10}, SO_2, NO_2, and O_3. PM was measured with a Harvard impactor. PM_{10} ranged from 10 to 33 µg/m^3 with a mean of 21.	Logistic regression analysis of associations between prevalences of respiratory symptoms in random sample of adults and air pollution. Regressions adjusted for age, BMI, gender, parental asthma, education, and foreign citizenship.	Chronic cough and chronic phlegm and breathlessness were related to TSP, PM_{10} and NO_2.	Chronic cough, chronic phlegm and breathlessness were related to PM_{10}, and TSP.

TABLE 8B-8 (cont'd). LONG-TERM PARTICULATE MATTER EXPOSURE RESPIRATORY HEALTH INDICATORS: RESPIRATORY SYMPTOM, LUNG FUNCTION

Reference citation, location, duration, type of study, sample size, pollutants measured, summary of values	Health outcomes measured, analysis design, covariates included, analysis problems	Results and Comments Effects of co-pollutants	Effect estimates as reported by study authors. Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest effects of PM
Europe (cont'd)			
Heinrich et al. (1999) Bitterfeld, Zerbstand Hettstedt areas of former East Germany, During Sept. 1992 to July 1993 TSP ranged from 44 to 65 µg/m^3; PM_{10} measured October 1993 - March 1994 ranged from 33 to 40; and BS ranged from 26 to 42 µg/m^3. PM was measured with a Harvard impactor.	Parents of 2470 school children (5-14 yr) completed respiratory health questionnaire. Children excluded from analysis if had lived < 2 years in their current home, yielding an analysis group of 2,335 children. Outcomes studied: physician diagnosis for asthma, bronchitis, symptom, bronchial reactivity, skin prick test, specific IgE. Multiple logistic regression analyses examined regional effects.	Controlling for medical, socio-demographic, and indoor factors, children in more polluted area had circa 50% increase for bronchitic symptoms and physician-diagnosed allergies compared to control area and circa twice the respiratory symptoms (wheeze, shortness of breath and cough). Pulmonary function tests suggested slightly increased airway reactivity to cold for children in polluted area.	No single pollutant could be separated out as being responsible for poor respiratory health.
Heinrich et al. (2000) Three areas of former E. Germany Pollution measures: SO_2, TSP, and some limited PM_{10} data. TSP decreased from 65, 48, and 44 µg/m^3 to 43, 39, and 36 µg/m^3 in the three areas. PM was measured with a Harvard impactor.	Cross-sectional study of children (5-14 yr). Survey conducted twice, in 1992-1993 and 1995-1996; 2,335 children surveyed in first round, and 2,536 in second round. Only 971 children appeared in both surveys. The frequency of bronchitis, otitus media, frequent colds, febrile infections studied. Because changes measured over time in same areas, covariate adjustments not necessary.	PM and SO_2 levels both decreased in the same areas; so results are confounded.	The prevalence of all respiratory symptoms decreased significantly in all three areas over time.
Heinrich et al. (2002) Surveyed children aged 5-14 in 1992-3, 1995-6, 1998-9. Annual TSP levels ranged from 25-79 µg/m^3. Smallparticles ($NC_{0.01-2.5}$ per $10^3 cm^{-3}$) remained relatively constant.	A two-stage logistic regression model was used to analyze the data which adjusted for age, gender, educational level of parents, and indoor factors. The model included fixed area effects, random deviations, and errors from the adjustments. Parameters were estimated using GEE methods.	The study found bronchitis and frequency of colds were significantly related to TSP.	An increment of 50 µg/m^3 TSP was associated with an odds ratio for bronchitis of 3.02 (1.72-5.29) and an odds ratio of 1.90 (1.17-3.09) for frequency of colds.
Krämer et al. (1999) Six East and West Germany communities (Leipzig, Halle, Maddeburg, Altmark, Duisburg, Borken) Between 1991 and 1995 TSP levels in six communities ranged from 46 to 102 µg/m^3. Each East Germany community had decrease in TSP between 1991 and 1995. TSP was measured using a low volume sampler.	The study assessed relationship between TSP and airway disease and allergies by parental questionnaires in yearly surveys of children (5-8 yr) between February and May. The questions included pneumonia, bronchitis ever diagnosed by physician, number of colds, frequent cough, allergic symptoms. In all, 19,090 children participated. Average response was 87%. Analyses were conducted on 14,144 children for whom information on all covariates were available. Variables included gender; parent education, heating fuel, ETS. Logistic regression used to allow for time trends and SO_2 and TSP effects. Regression coefficients were converted to odds ratios.	TSP and SO_2 simultaneously included in the model. Bronchitis ever diagnosed showed a significant association. A decrease in raw percentage was seen between the start of the study and the end for bronchitis. Bronchitis seemed to be associated only with TSP in spite of huge differences in mean SO_2 levels.	Bronchitis ever diagnosed TSP per 50 µg/m^3 OR 1.63 CI (1.37 – 1.93) Halle (East) TSP µg/m^3 — % Bronchitis 1991 102 — 60.5 1992 73 — 54.7 1993 62 — 49.6 1994 52 — 50.4 1995 46 — 51.9

TABLE 8B-8 (cont'd). LONG-TERM PARTICULATE MATTER EXPOSURE RESPIRATORY HEALTH INDICATORS: RESPIRATORY SYMPTOM, LUNG FUNCTION

Reference citation, location, duration, type of study, sample size, pollutants measured, summary of values	Health outcomes measured, analysis design, covariates included, analysis problems	Results and Comments Effects of co-pollutants	Effect estimates as reported by study authors. Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest effects of PM
Europe (cont'd)			
Baldi et al. (1999) 24 areas of seven French towns 1974-1976 Pollutants: TSP, BS, and SO_2, NO_4 3-year average TSP-mean annual values ranging 45-243 µg/m^3. TSP was measured by the gravimetric method.	Reanalysis of Pollution Atmospheric of Affection Respiratory Chroniques (PAARC) survey data to search for relationships between mean annual air pollutant levels and prevalence of asthma in 1291 adult (25-59 yrs) and 195 children (5-9 yrs) asthmatics. Random effects logistic regression model used and included age, smoking, and education level in the final model.	Only an association between SO_2 and asthma in adults observed. No other pollutant was associated. Nor was relationship with children seen. Meteorological variables and O_3 not evaluated.	For a 50 µg/m^3 increase in TSP Adult asthma prevalence OR 1.01 CI 0.92–1.11 SO_2 Adult asthma prevalence OR 1.26 CI 1.04–1.53
Zeghnoun et al. (1999) La Havre, France during 1993 and 1996. Daily mean BS levels measured in three stations ranged 12 - 14 µg/m^3.	Respiratory drug sales for mucolytic and anticough medications (most prescribed by a physician) were evaluated versus BS, SO_2, and NO_2 levels. An autoregressive Poisson regression model permitting overdispersion control was used in the analysis.	Respiratory drug sales associated with BS, NO_2, and SO_2 levels. Both an early response (0 to 3 day lag) and a longer one (lags of 6 and 9 days) were associated.	—
Leonardi et al. (2000) 17 cities of Central Europe Yearly average concentration (Nov. 1995 - Oct. 1996) across the 17 study areas varied from 41 to 96 µg/m^3 for PM_{10}, from 29 to 67 µg/m^3 for $PM_{2.5}$, and from 12 to 38 µg/m^3 for $PM_{10\text{-}2.5}$.	Cross-sectional study collected blood and serum samples from 10-61 school children aged 9 to 11 in each community 11 April to 10 May 1996. Blood and serum samples examined for parameters in relation to PM. Final analysis group of 366 examined for peripheral lymphocyte type and total immunoglobulin classes. Association between PM and each log transformed biomarker studied by linear regression in two-stage model with adjustment for confounding factors (age, gender, number of smokers in house, laboratory, and recent respiratory illness). This survey was conducted within the frame work of the Central European study of Air Quality and Respiratory Health (CEASAR) study.	Number of lymphocytes (B, $CD4^+$, $CD8^d$, and NK) increased with increasing concentration of PM adjusted for confounders. The adjusted regression slopes are largest and statistically significant for $PM_{2.5}$ as compared to PM_{10}, but small and non statistically signif. for $PM_{10\text{-}2.5}$. Positive relationship found between concentration of IgG in serum and $PM_{2.5}$ but not for PM_{10} or $PM_{10\text{-}2.5}$. Two other models produced similar outcomes: a multi-level linear regression model and an ordinal logistic regression model.	Adjusted Regression slope $PM_{2.5}$ $CD4^+$ 80% 95% CI (34; 143) $p < 0.001$ Total IgG 24% 95% CI (2; 52) p 0.034

TABLE 8B-8 (cont'd). LONG-TERM PARTICULATE MATTER EXPOSURE RESPIRATORY HEALTH INDICATORS: RESPIRATORY SYMPTOM, LUNG FUNCTION

Reference citation, location, duration, type of study, sample size, pollutants measured, summary of values	Health outcomes measured, analysis design, covariates included, analysis problems	Results and Comments Effects of co-pollutants	Effect estimates as reported by study authors. Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest effects of PM
Europe (cont'd)			
Turnovska and Kostiranev (1999) Dimitrovgrad, Bulgaria, May 1996 Total suspended particulate matter (TSPM) mean levels were 520 ± I 61 µg/m^3 in 1986 and 187 ± 9 µg/m^3 in 1996. SO_2, H_2S, and NO_2 also measured.	Respiratory function of 97 schoolchildren (mean age 10.4 ± 0.6 yr) measured in May 1996 as a sample of 12% of all four-graders in Dimitrovgrad. The obtained results were compared with reference values for Bulgarian children aged 7 to 14 yr, calculated in the same laboratory in 1986 and published (Gherghinova et al., 1989; Kostianev et al., 1994). Variation analysis technique were used to treat the data.	Vital capacity and FEV_1 were significantly lower (mean value. = 88.54% and 82.5% respectfully) comparing values between 1986 and 1996. TSPM pollution had decreased by 2.74 times to levels still higher than Bulgarian and WHO standards.	—
Jedrychowski et al. (1999) In Krakow, Poland in 1995 and 1997 Spacial distributions for BS and SO_2 derived from network of 17 air monitoring stations. BS 52.6 µg/m ± 53.98 in high area and 33.23 ± 35.99 in low area.	Effects on lung function growth studied in preadolescent children. Lung function growth rate measured by gain in FVC and FEV_1 and occurrence of slow lung function growth (SLFG) over the 2 yr period defined as lowest quintile of the distribution of a given test in gender group. 1129 children age 9 participated in first year and 1001 in follow-up 2 years later. ATS standard questionnaire and PFT methods used. Initially univariate descriptive statistics of pulmonary function indices and SLFG were established, followed by multivariate linear regression analyses including gender, ETS, parental education, home heating system and mold. SO_2 also analyzed.	Statistically significant negative association between air pollution level and lung function growth (FVC and FEV_1) over the follow up in both gender groups. SLFG was significantly higher in the more polluted areas only among boys. In girls there was consistency in the direction of the effect, but not stat. significant. Could not separate BS and SO_2 effects on lung function growth. Excluding asthma subjects subsample (size 917) provided similar results.	<u>Boys</u> SLFG (FVC) OR = 2.15 (CI 1.25 – 3.69) SLFG (FEV_1) OR = 1.90 (CI 1.12 – 3.25) <u>Girls</u> FVC OR = 1.50 (CI 0.84 – 2.68) FEV1 OR = 1.39 (CI 0.78 – 2.44)
Jedrychowski and Flak (1998) In Kracow Poland, in 1991-1995 Daily 24 h concentration of SPM (black smoke) measured at 17 air monitoring stations. High areas had 52.6 µg/m^3 mean compared to low areas at 33.2 µg/m^3.	Respiratory health survey of 1,129 school children (aged 9 yr). Respiratory outcomes included chronic cough, chronic phlegm, wheezing, difficulty breathing and asthma. Multi-variable logistic regression used to calculate prevalence OR for symptoms adjusted for potential confounding.	The comparison of adjusted effect estimates revealed chronic phlegm as unique symptom related neither to allergy nor to indoor variable but was associated significantly with outdoor air pollution category (APL). No potential confounding variable had major effect.	It was not possible to assess separately the contribution of the different sources of air pollutants to the occurrence of respiratory symptoms. ETS and household heating (coal vs. gas vs. central heating) appeared to be of minimal importance.
Horak et al. (2002) Frischer et al. (1999) Eight communities in lower Austria between 1994-1997. PM_{10} mean summer value of 17.36 µg/m^3 and winter value of 21.03 µg/m^3.	Lung function assessed in 975 school children in grade 2-3. A several step analysis included GEE and sensitivity analyses.	Concluded that long term exposure to PM_{10} had a significant negative effect on lung function with additional evidence for a further effect for O_3 and NO_2.	After adjusting for confounders an increase in PM_{10} by 10 µg/m^3 was associated with a decrease in FEV_1 growth at 84 mL/yr and 329 mL/5 yr for MEF_{25-75}.

TABLE 8B-8 (cont'd). LONG-TERM PARTICULATE MATTER EXPOSURE RESPIRATORY HEALTH INDICATORS: RESPIRATORY SYMPTOM, LUNG FUNCTION

Reference citation, location, duration, type of study, sample size, pollutants measured, summary of values	Health outcomes measured, analysis design, covariates included, analysis problems	Results and Comments Effects of co-pollutants	Effect estimates as reported by study authors. Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest effects of PM
Europe (cont'd)			
Gehring et al. (2002) In Munich, Germany December 1997 - January 1999 Annual $PM_{2.5}$ levels determined by 40 sites and a GIS predictor for model. Mean $PM2^{.5}$ annual average of 13.4 $\mu g/m^3$ with range of 11.90 to 21.90 $\mu g/m^3$	Effect of traffic-related air pollutants. $PM_{2.5}$ and NO_2 on respiratory health outcomes wheeze, cough, bronchitis, respiratory infections, and runny nose were evaluated using multiple logistic regression analyses of l, 756 children during the first and second year of life adjusting for potential confounding factors.	There was some indication of an association between $PM_{2.5}$ and symptoms of cough but not other outcomes. In the second year of life most effects were attenuated.	—
Latin America			
Calderón-Garcidueñas et al. (2000) Southwest Metropolitan Mexico City (SWMMC) winter of 1997 and summer of 1998.	Study of 59 SWMMC children to evaluate relationship between exposure to ambient pollutants (O_3 and PM_{10}) and chest x-ray abnormalities. Fishers exact test used to determine significance in a 2x2 task between hyperinflation and exposure to SWMMC pollutant atmosphere and to control, low-pollutant city atmosphere.	Bilateral symmetric mild lung hyperinflation was significantly associated with exposure to the SWMMC air pollution mixture ($p>0.0004$). This raises concern for development of chronic disease outcome in developing lungs.	—
Australia			
Lewis et al. (1998) Summary measures of PM_{10} and SO_2 estimated for each of 10 areas in steel cities of New South Wales. PM_{10} was measured using a high volume sampler with size-selective inlets.	Cross-sectional survey of children's health and home environment between Oct 1993 and Dec 1993 evaluated frequency of respiratory symptoms (night cough, chest colds, wheeze, and diagnosed asthma). Covariates included parental education and smoking, unflued gas heating, indoor cats, age, sex, and maternal allergy. Logistic regression analysis used allowing for clustering by GEE methods.	SO_2 was not related to differences in symptom rates, but adult indoor smoking was.	Night cough OR 1.34 (1.18, 1.53) Chest colds OR 1.43 (1.12, 1.82) Wheeze OR 1.13 (0.93, 1.38)
Asia			
Wong et al. (1999b) Hong Kong, 1989 to 1991 Sulfate concentrations in respirable particles fell by 38% after implementing legislation reducing fuel sulfur levels.	3405 nonsmoking, women (mean age 36.5 yr; SD ± 3.0) in a polluted district and a less polluted district were studied for six respiratory symptoms via self-completed questionnaires. Binary latent variable modeling used.	Comparison was by district; no PM measurements reported. Results suggest control regulation may have had some (but not statistically significant) impact.	—

TABLE 8B-8 (cont'd). LONG-TERM PARTICULATE MATTER EXPOSURE RESPIRATORY HEALTH INDICATORS: RESPIRATORY SYMPTOM, LUNG FUNCTION

Reference citation, location, duration, type of study, sample size, pollutants measured, summary of values	Health outcomes measured, analysis design, covariates included, analysis problems	Results and Comments Effects of co-pollutants	Effect estimates as reported by study authors. Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest effects of PM
Asia (cont'd)			
Wang et al. (1999) Kaohsiung and Panting, Taiwan October 1995 to June 1996 TSP measured at 11 stations, PM_{10} at 16 stations. PM_{10} annual mean ranged from 19.4 to 112.81 $\mu g/m^3$ (median = 91.00 $\mu g/m^3$) TSP ranged from 112.81 to 237.82 $\mu g/m^3$ (median = 181.00). CO, NO_2, SO_2, hydrocarbons and O_3 also measured.	Relationship between asthma and air pollution examined in cross-sectional study among 165,173 high school students (11- 16 yr). Evaluated wheeze, cough and asthma diagnosed by doctor. Video determined if student displayed signs of asthma. Only 155,283 students met all requirements for study analyses and, of these, 117,080 were covered by air monitoring stations. Multiple logistic regression analysis used to determine independent effects of risk factors for asthma after adjusting for age, gender, ETS, parents education, area resident, and home incense use.	Asthma significantly related to high levels of TSP, NO_2, CO, O_3 and airborne dust. However PM_{10} and SO_2 not associated with asthma. The lifetime prevalence of asthma was 18.5% and the 1-year prevalence was 12.5%.	Adjusted OR PM_{10} 1.00 (0.96–1.05) TSP 1.29 (1.24–1.34)
Guo et al. (1999) Taiwan, October 1955 and May 1996 PM_{10} measured by beta-gauge. Also monitoring for SO_2, NO_2, O_3, CO. PM_{10} ranged from 40 to 110 $\mu g/m^3$ with a mean of 69.	Study of asthma prevalence and air pollutants. Survey for respiratory disease and symptoms in middle-school students age < 13 to ≥ 15 yr. Total of 1,018,031 (89.3%) students and their parents responded satisfactorily to the questionnaire. Schools located with 2 km of 55 monitoring sites. Logistic regression analysis conducted, controlling for age, hx eczema, parents education.	Because of close correlation among air pollutants, not possible to separate effects of individual ones. Factor analysis used to group into two classes (traffic-related and stationary fossil fuel-related). No association found between lifetime asthma prevalence and nontraffic related air pollutants (SO_2, PM_{10}).	—
Wang et al. (1999) Chongqing, China April to July 1995 Dichot samplers used to measure $PM_{2.5}$. Mean $PM_{2.5}$ level high in both urban (143 $\mu g/m^3$) and suburban (139 $\mu g/m^3$) area. SO_2 also measured	Study examined relationship between PFT and air pollution. Pulmonary function testing performed on 1,075 adults (35 - 60 yr) who had never smoked and did not use coal stoves for cooking. Generalized additive model used to estimate difference, between two areas for FEV_1, FVC, and FEV_1/FVC% with adjustment for confounding factors (gender; age, height, education, passive smoking, and occupational exposures).	Mean SO_2 concentration in the urban and suburban area highly statistically significant different (213 and 103 $\mu g/m^3$ respectfully). $PM_{2.5}$ difference was small, while levels high in both areas. Estimated effects on FEV1 statistically different between the two areas.	Difference between urban and suburban area excluding occupational exposures: FEV_1: B – 119.79, SE 28.17, t – 4.25, $p < 0.01$ FVC: B – 57.89, SE 30.80, t – 1.88, $p < 0.05$

TABLE 8B-8 (cont'd). LONG-TERM PARTICULATE MATTER EXPOSURE RESPIRATORY HEALTH INDICATORS: RESPIRATORY SYMPTOM, LUNG FUNCTION

Reference citation, location, duration, type of study, sample size, pollutants measured, summary of values	Health outcomes measured, analysis design, covariates included, analysis problems	Results and Comments Effects of co-pollutants	Effect estimates as reported by study authors. Negative coefficients for lung function and ORs greater than 1 for other endpoints suggest effects of PM
Asia (cont'd)			
Zhang et al. (1999) 4 areas of 3 Chinese Cities (1985 - 1988) TSP levels ranged from an annual arithmetic mean 137 $\mu g/m^3$ to 1250 $\mu g/m^3$ using gravimetric methods.	A pilot study of 4 districts of 3 Chinese cities for the years 1985-1988, TSP levels and respiratory health outcomes studied. 4,108 adults (< 49 yrs) examined by questionnaires for couth, phlegm, wheeze, asthma, and bronchitis. Categorical logistic—regression model used to calculate odds ratio. SO_2 and NO_2 were also examined. Other potential confounding factors (age, education level, indoor ventilation, and occupation) examined in the multiple logistic regression model.	Results suggested that the OR's for cough, phlegm, persistent cough and phlegm and wheeze increased as outdoor TSP concentrations did. .	Wheeze produced largest OR for both mothers and fathers in all locations.
Qian et al. (2000) 3 China cities (1985-1988) The 4 year average TSP means were 191, 296, 406, and 1067 $\mu g/m^3$. SO_2 and NO_2 measurements were also available. TSP was measured gavimetrically.	Pilot cross-sectional survey of 2789 elementary school children in four Chinese communities chosen for their PM gradient. Frequency of respiratory symptoms (cough, phlegm, wheeze, and diagnosed asthma, bronchitis, or pneumonia) assessed by questionnaire. Covariates included parental occupation, education and smoking. The analysis used logistic regression, controlling for age, sex, parental smoking, use of coal in home, and home ventilation.	Results not directly related to pollution levels, but symptom rates were highest in highest pollution area for cough, phlegm, hospitalization for respiratory disease, bronchitis, and pneumonia. No gradient correlating with pollution levels found for the three lower exposure communities.	—
Shima et al. (2002) 8 communities in Japan, a prospective cohort study (1989-1992).	Respiratory symptoms of 3049 school children were evaluated by questionnaires every year from the 1st through the 6th grades. PM_{10} measured continuously by beta attenuation.	Incidence rates of asthma were associated significantly with ambient levels of NO_2. PM_{10} was also associated but not significantly (OR 2.84; 95% CI 0.84-9.58).	—

9. INTEGRATIVE SYNTHESIS

9.1 INTRODUCTION

This chapter integrates key information from the preceding chapters to provide coherent frameworks for assessment of human health and welfare risks posed by ambient particulate matter (PM) in the United States. Rather than simply resummarizing information from earlier chapters, the focus here is on integrating newly available scientific information with that available from the last review so as to address a set of issues central to EPA's assessment of scientific information upon which the PM NAAQS review is to be based.

In particular, this chapter provides an updated synthesis of the scientific information that is intended to facilitate consideration of the key policy-related NAAQS issues to be addressed in the PM Staff Paper, prepared by EPA's Office of Air Quality Planning and Standards (OAQPS) staff. These policy-related issues include selection of appropriate indicators, averaging times, forms, and levels for primary and secondary PM NAAQS in the United States. Ultimately, EPA's consideration of these issues will be informed not only by the scientific information and integrative assessment presented here and throughout this document, but also by additional policy evaluations of scientific and technical information to be included in the PM Staff Paper. As such, the PM Staff Paper serves to "bridge the gap" between scientific assessments and the judgments required of the EPA Administrator in deciding whether to retain or revise the existing PM NAAQS.

While this synthesis focuses on what has been learned since the last PM NAAQS review, it also highlights important uncertainties that remain and recognizes the value of continuing PM research efforts in a number of key areas. Although detailed delineation of research needs is beyond the scope of this document, such recommendations are to be discussed in later PM research needs documents and/or research plans to be prepared by EPA.

9.1.1 Chapter Organization

As part of this opening introduction, Section 9.1.2 first summarizes important information on U.S. PM air quality trends and current ambient concentrations, to provide the context for ensuing discussions of ambient PM characteristics, exposures, and effects.

In considering PM-related health effects information, Section 9.2 then builds specifically upon the integrative synthesis presented in Chapter 13 of the 1996 PM AQCD (U.S. Environmental Protection Agency, 1996). The Section 9.2 synthesis of PM-related health effects information is organized around five key issues: (1) consideration of fine and coarse thoracic particles as separate subclasses of PM pollution, taking into account atmospheric science, exposure, and dosimetric information; (2) assessment of strengths and limitations of the epidemiological evidence for associations between health effects and fine and coarse thoracic PM within the mix of ambient air pollutants; (3) integration of epidemiologic and experimental (e.g., dosimetric and toxicologic) evidence supporting judgments about the extent to which causal inferences can be made about observed associations between health endpoints and various indicators or constituents of ambient PM, acting alone and/or in combination with other pollutants; (4) characterization of susceptible and vulnerable subpopulations potentially at increased risk for PM-related health effects; and (5) discussion of potential public health impacts (including newly emerging evidence for adverse cardiovascular effects) of human exposures to ambient PM in the United States.

Building upon information presented in the 1996 PM AQCD where possible, Section 9.3 addresses the major PM-related welfare effects of importance for decision-making for secondary standards. This includes drawing upon key findings and conclusions on visibility and climate effects from Chapter 8 and on damage to manmade materials from Chapter 9 of the 1996 document, as well as consideration of new findings discussed in Chapter 4 of this document. Since PM-related effects on vegetation and ecosystems were not addressed in the 1996 PM AQCD, the present discussion is based entirely on findings characterized in Chapter 4 of this document.

9.1.2 Trends in United States PM Air Quality

PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ Concentrations and Trends

The nationwide average concentration of PM_{10} decreased from about 28 $\mu g/m^3$ to 24 $\mu g/m^3$ from 1992 through 2001 (U.S. Environmental Protection Agency, 2003). Most of this decrease occurred during the first half of that time period. There was considerable variability in the trends

for various geographic subregions, with the largest decreases being found in the northwest (~9.6 $\mu g/m^3$) and the smallest in the south-central United States (~1.3 $\mu g/m^3$). These trends reflect the continuation of longer-term declines in U.S. PM concentrations. For example, Lipfert (1998) estimated that total suspended particulate (TSP) concentrations may have declined by two- to three-fold in urban areas between 1950 and 1980. Data for quantifying nationwide trends in $PM_{2.5}$ concentrations are not available over this period. However, it may be surmised that notable declines in $PM_{2.5}$ concentrations also likely occurred over the same period. The consistent reductions in PM_{10} concentrations found in a wide variety of environments may have resulted from common controls that affected $PM_{2.5}$ more strongly than $PM_{10-2.5}$ particles (Darlington et al., 1997). These considerations suggest that $PM_{10-2.5}$ concentrations likely decreased to a smaller extent over this period.

Annual mean $PM_{2.5}$ concentrations in the United States currently average about 13 $\mu g/m^3$, based on data collected from 1999 through 2001. Such fine particle concentrations can be less than a few $\mu g/m^3$ in many remote areas in the western United States and in many urban areas immediately after it has rained. However, 24-h $PM_{2.5}$ concentrations on individual days can also exceed 100 $\mu g/m^3$ at certain locations, especially if there are events such as wild fires or dust storms. These values indicate a high degree of spatial and temporal variability in $PM_{2.5}$ concentrations. $PM_{2.5}$ concentrations observed in a number of urban areas across the United States are characterized in Chapter 3; see Section 3.2 and Appendices 3A (for urban areas) and 3E (for relatively remote areas).

It should be noted that the mean $PM_{2.5}$ concentrations given above are considerably lower than those obtained and used in many air pollution-health outcome studies conducted during the 1980s. Lipfert (1998) has estimated that $PM_{2.5}$ concentrations decreased by about 4 to 5% per year from 1970 to 1990; some of that change may be attributable to use of different monitoring methods during earlier versus later years.

The Composition of $PM_{2.5}$ and $PM_{10-2.5}$ Particles

Data for $PM_{2.5}$, $PM_{10-2.5}$ and PM_{10} from earlier monitoring studies, spanning the time period from the late 1970s to the mid 1990s, were presented in Appendix 6A of the 1996 PM AQCD. The data from such studies were summarized in Appendix 6A as pie charts showing the gross

composition of the three size fractions for the eastern, central, and western United States. The chemical composition of particles in the $PM_{2.5}$ size range, as determined most recently by the speciation network in 13 urban areas across the United States during 2001 to 2002 is summarized in Chapter 3.

As summarized in Chapter 3 (Section 3.2 and Appendix 3B), sulfate and organic carbon compounds constitute the major identified components of fine-particle the aerosol in the eastern and central United States. In the western United States, organic compounds and nitrate and/or sulfate constitute the major identified $PM_{2.5}$ aerosol components. Other important components are: elemental carbon, ammonium and crustal materials. Even though total organic compounds constitute 10 to 70% of $PM_{2.5}$, only about 10 to 20% of organic compounds in ambient samples can be quantified due to analytical limitations resulting largely from the polar nature of some organic compounds and the presence of oligomeric or polymeric substances (i.e., biopolymers and humic-like substances). Results of studies characterizing the composition of organic compounds in ambient particles are summarized in Appendix 3C. The attribution of organic carbon to primary or secondary sources is still under study in different regions of the country. Three mechanisms have been identified for the formation of secondary organic components in ambient PM: (1) condensation of oxidized end- products of photochemical reactions (e.g., ketones, aldehydes, organic acids, and hydroperoxides), (2) adsorption of semivolatile organic compounds (e.g., polycyclic aromatic compounds) onto existing particles, and (3) dissolution of soluble gases (e.g., aldehydes) that can undergo reactions in particle bound water (PBW). Primary biological particles (or bioaerosols) are also usually lumped into the broad category of organic compounds. In addition to soluble organic compounds, soluble oxidants (e.g., H_2O_2) can be taken up or formed in PBW, as discussed further below. As will be seen later, these considerations have implications for the delivery of these and other soluble components to lower respiratory tract regions.

Trace metals typically constitute a much smaller fraction of PM than the components given above. Typically, their average combined air concentrations constitute less than 1% of $PM_{2.5}$ levels (or on the order of 0.1 $\mu g/m^3$ or less), as shown in Appendix 3B. There are exceptions to this general pattern in industrial cities (e.g., St. Louis, MO), where metals can constitute closer to 2% of $PM_{2.5}$. However, maximum concentrations of Fe, typically the most abundant trace metal,

can be on the order of several tenths of a $\mu g/m^3$ in any of the urban areas characterized. Prior to the phaseout of leaded gasoline, Pb was often found to be the most abundant trace metal in urban atmospheres (Tables 6A2a-c, PM AQCD 1996) at quarterly-average concentrations in the range of 0.1 to 1.0 $\mu g/m^3$. Currently, ambient air Pb concentrations for most U.S. urban areas are in the range of several ng/m^3. The second most abundant trace metal, Zn, is typically present at < 0.1 $\mu g/m^3$, whereas other transition elements (e.g., Ni, V) are typically < 10 ng/m^3. Many transition elements are currently nondetectable in most U.S. 24-h ambient air filter samples, using X-ray fluorescence spectrometry.

The composition of $PM_{10-2.5}$ particles has not been characterized to the same extent as for $PM_{2.5}$. In general, the inorganic composition of $PM_{10-2.5}$ particles is dominated by crustal particles; and, at times, there is also some evidence of combustion-related PM in some U.S. locations. Photomicrographs obtained by scanning electron microscopy also indicate that large numbers of biologic particles, such as pollen spores, are often present among coarse ($PM_{10-2.5}$) ambient air particles. The contributions of organic compounds and elemental carbon to $PM_{10-2.5}$ particles are poorly known.

9.2 SYNTHESIS OF AVAILABLE INFORMATION ON PM-RELATED HEALTH EFFECTS

The integrative synthesis of the latest available information on PM-related health effects poses especially large challenges in view of:

- The unprecedented amount of new information generated since the 1996 PM AQCD, which adds greatly to the complexity of any integrative assessment;
- Extensive new information available from epidemiologic studies, which reflects much progress in addressing many research recommendations from the last review, but also raises new issues or resurfaces issues earlier thought to have been adequately addressed but which remain important in interpreting the body of epidemiologic evidence and the characterization of its strengths and limitations;
- Much new information from dosimetric and toxicologic studies, which makes notable progress toward identifying and exploring potential mechanisms of action and characteristics of PM that may underlie health effects observed in experimental studies, but still leaving open many issues to be more fully addressed in the future.

Thus, despite substantial progress, challenges remain in integrating these different types of evidence into a coherent synthesis.

As discussed in Section 8.1.4, concepts underlying an integrative assessment of statistical associations reported in epidemiologic public health studies have been discussed in numerous publications, from the historic publication by Hill (1965) to the most recent report by the U.S. Surgeon General on the health consequences of smoking (Centers for Disease Control and Prevention, 2004). All such discussions recognize that making causal inferences based on such associations requires expert judgment, and criteria to aid such judgments generally derive from those put forward earlier by Hill. Such criteria are not intended to serve as a checklist or a set of rigid rules of evidence, but rather as a means of organizing an evaluation of the evidence to facilitate reaching such judgments and conclusions. The criteria used in this assessment are generally consistent with those defined in the Surgeon General's report and include the following:

- *Strength of association*, which includes "the magnitude of the association and its statistical strength."
- *Consistency*, which refers to the "persistent finding of an association between exposure and outcome in multiple studies of adequate power, and in different persons, places, circumstances, and times." This criterion serves to address issues related to potential confounding, which in this assessment are separately considered in a discussion of the *robustness* of the associations to the inclusion of potential confounding factors.
- *Temporality,* which most simply refers to "the occurrence of a cause before its purported effect." In this assessment, temporality is more broadly defined to include consideration of lag periods between exposure and effect.
- *Biologic gradient*, or concentration-response relationships, which refers to "the finding of an increment in effect with an increase in the strength of the possible cause. . . ."
- *Experiment*, which refers to "situations where natural conditions might plausibly be thought to imitate conditions of a randomized experiment, producing a 'natural experiment' whose results might have the force of a true experiment."
- *Coherence and plausibility*, which in combination address the idea "that a proposed causal relationship not violate known scientific principles, and that it be consistent with experimentally demonstrated biologic mechanisms and other relevant data . . . ." (Centers for Disease Control and Prevention, 2004, pp. 21-23).

Section 9.2 is organized so as to first address the question of whether there is continued support for considering fine and coarse thoracic PM as separate subclasses of PM based on atmospheric science, air quality, exposure, and dosimetric information. Next, the strengths and limitations of epidemiologic evidence are evaluated, taking into account the criteria outlined above, including the strength and robustness of the reported associations; assessment of the consistency or general concordance of study results and consideration of potential reasons for observed differences; information related to lags and concentration-response relationships; and information from so-called intervention studies of "natural" or "found" experiments. Looking beyond the epidemiologic evidence, consideration is then also given to toxicological and other information bearing on the biological plausibility and coherence of the PM-effects associations observed in the epidemiologic studies to make causal inferences with regard to different categories of health effects (cardiovascular, respiratory, etc.) and to reach conclusions regarding the extent to which observed effects can be attributed to ambient fine and coarse thoracic PM, acting alone and in combination with other pollutants. This is followed by discussion of evidence regarding various risk factors (e.g., pre-existing disease and age-related factors) to reach conclusions as to which susceptible and vulnerable subpopulations are most likely to be at risk for health effects related to fine and coarse thoracic PM. Finally, information on the magnitude of susceptible subpopulations is discussed, to provide context for the consideration of potential public health impacts of exposures to ambient fine and coarse thoracic PM in the U.S.

9.2.1 Fine and Coarse Particles as Separate Subclasses of PM Pollution

The question of whether fine and coarse particles should continue to be considered as separate subclasses of ambient PM is addressed below, drawing upon information and assessments found primarily in Chapters 2, 3, 5, and 6 of this document related to the physics and chemistry of particle pollution, the measurement of airborne particles, relationships between ambient PM concentrations and population exposure, and PM dosimetry. The focus here is on whether the newly available science in these areas continues to support consideration of fine and coarse thoracic PM separately in the context of the Agency's periodic review of the PM NAAQS, and if so, on appropriate indicators for these subclasses of PM.

The primary focus in the last review was on thoracic particles (with PM_{10} defined as the index for regulatory purposes) and on the question of whether fine and coarse thoracic particles should be addressed by separate standards with different indicators. The 1996 PM AQCD noted that the PM_{10} indicator was established as a result of the 1987 PM NAAQS review, which concluded that the indicator for primary standards should represent those particles small enough to penetrate to the thoracic region (including the tracheobronchial and pulmonary regions) of the lower respiratory tract and should generally exclude particles that deposit only in the extrathoracic region (the latter being particles previously included in the original TSP indicator). The PM_{10} cut-point closely matches the definition for thoracic PM given by the American Conference of Government and Industrial Hygienists (1994), as shown in Chapter 2 (Figure 2-6).

As discussed in the 1996 PM AQCD, the natural division of ambient PM into fine particles and coarse particles is based on the recognition that "the fine and coarse modes originate separately, are transformed separately, are removed separately, and are usually chemically different . . . ." (Whitby, 1978). Consistent with this distinction, the 1996 PM AQCD stated that the evidence indicates that "it would be appropriate to consider fine and coarse particles as separate subclasses" of PM pollution. This conclusion was based on various considerations:

- Differences in formation processes and sources of fine and coarse thoracic particles, as well as differences in chemical and physical properties, atmospheric residence times and distances transported in the atmosphere;
- Resulting differences in patterns of ambient population exposures to fine and coarse thoracic particles;
- Evidence from dosimetric studies showing differences in the fractions inhaled, deposited, and/or retained in various regions of the respiratory tract for fine versus coarse thoracic particles; and
- Evidence from health studies leading to conclusions that fine particles are more strongly associated with more serious health effects and that chemical components likely to have higher relative toxicity occur primarily in the fine fraction.

The evidence available in the last review strongly focused on particle size as the basis for distinguishing between these essentially different classes of PM pollution. A cut point of 2.5 μm was chosen for use in a new dichotomous sampler in the mid-1970s, when it was recognized that within the range of about 1 to 3 μm there was no unambiguous definition of the appropriate cut

point for the separation of the overlapping fine and coarse particle modes. Subsequent epidemiologic studies of fine particles available in the last review, e.g., the Harvard Six City Study and the American Cancer Society (ACS) cohort study, were based on the continued use of the 2.5 μm cut point. During the last review, EPA gave consideration to a cut point of 1 μm as an alternative to the 2.5 μm cut point as a basis for a fine particle standard. In so doing, EPA took into account published size distributions that showed considerable variability in the intermodal range of about 1 to 3 μm, including, for example, distributions from Philadelphia, Phoenix, and Los Angeles (shown in Figure 2-9). Very little mass is seen in the intermodal region in Philadelphia; in Phoenix, the coarse mode can be seen to extend to below 1 μm; and in Los Angeles, a droplet mode, comprising the upper end of the fine mode, occurs under high relative humidity conditions (usually associated with very high fine particle concentrations) and extends above 2.5 μm.

EPA's decision to select a nominal cut-point of 2.5 μm in the last review reflected a number of considerations. Available epidemiologic studies of fine particles were-based largely on $PM_{2.5}$ since PM_1 had not been widely monitored. Further, while it was recognized that using PM_1 as an indicator of fine particles would exclude the tail of the coarse mode in some locations, in other locations it would miss a portion of the fine PM, especially under high humidity conditions, that would result in falsely low fine PM measurements on days with some of the highest fine PM concentrations. The selection of a 2.5 μm cut point reflects the regulatory importance that was placed on defining an indicator for fine particle standards that would more completely capture fine particles under all conditions likely to be encountered across the United States, especially when fine particle concentrations are likely to be high, while recognizing that some small coarse-mode particles would also be captured by $PM_{2.5}$ monitoring.

In selecting an indicator for coarse thoracic particles in the last review, EPA concluded that the available dosimetric evidence continued to support the use of the same nominal upper cut-point of 10 μm that had previously been selected as the basis for the standards set in 1987. While recognizing that this cut point is on a part of the size distribution curve where the concentration is changing rapidly, such that the amount of PM collected is sensitive to small changes in the effective cut point of the sampler, it still represents the most appropriate cut point to be used as the basis for an indicator of thoracic particles. EPA's decision in the last review to

retain PM_{10} as an indicator for standards to address coarse particles, rather than an indicator that would generally exclude fine particles (e.g., $PM_{10-2.5}$), was based largely on the limited epidemiologic studies and air quality data specifically available for coarse thoracic particles beyond that which could be inferred or derived from PM_{10} studies in areas dominated by coarse particles.[1]

As a consequence of these decisions made by EPA in the last PM NAAQS review, a national $PM_{2.5}$ monitoring network was established that has provided extensive air quality data on $PM_{2.5}$ and, by difference between co-located PM_{10} and PM_{25} monitors, more limited data on $PM_{10-2.5}$. The availability of such air quality data has prompted the increased use of $PM_{2.5}$ and, to a lesser degree, $PM_{10-2.5}$ as indicators in new epidemiologic studies, as well as increasing focus on these PM size fractions in other types of studies (exposure, dosimetry, toxicology, etc.).

In considering the distinctions between fine and coarse thoracic particles based on currently available information, the following discussion builds upon the most salient key findings from the previous PM NAAQS reviews, while updating and integrating key findings and conclusions from the newly available studies assessed in earlier chapters of this document.

9.2.1.1 Physics and Chemistry Considerations

Since the last PM NAAQS review, the physical and chemical properties of fine and coarse particles have become better understood. Nonetheless, the fundamental concept of the natural division of thoracic particles into somewhat overlapping ranges of fine and coarse particles, with a minimum in the mass distribution between 1 and 3 μm, as illustrated by the idealized distribution shown in Figure 9-1, remains unchanged. Improved measurement techniques have provided additional information that refines the general characterization of particles below ~0.1 μm diameter (i.e., ultrafine particles) from a single mode to a bi-modal structure. Thus, fine particles are now divided into three modes: a nucleation mode, an Aitken mode, and an accumulation mode. Nucleation mode applies to newly formed particles that have had little chance to grow by condensation or coagulation. Aitken mode particles are also recently formed

[1] As discussed in Chapter 1, subsequent litigation resulted in the court finding the use of PM_{10} as an indicator for coarse-mode particles (in conjunction with $PM_{2.5}$ standards) to be arbitrary, since PM_{10} includes all fine particles; the court remanded this aspect of EPA's 1997 decision to the Agency for further consideration.

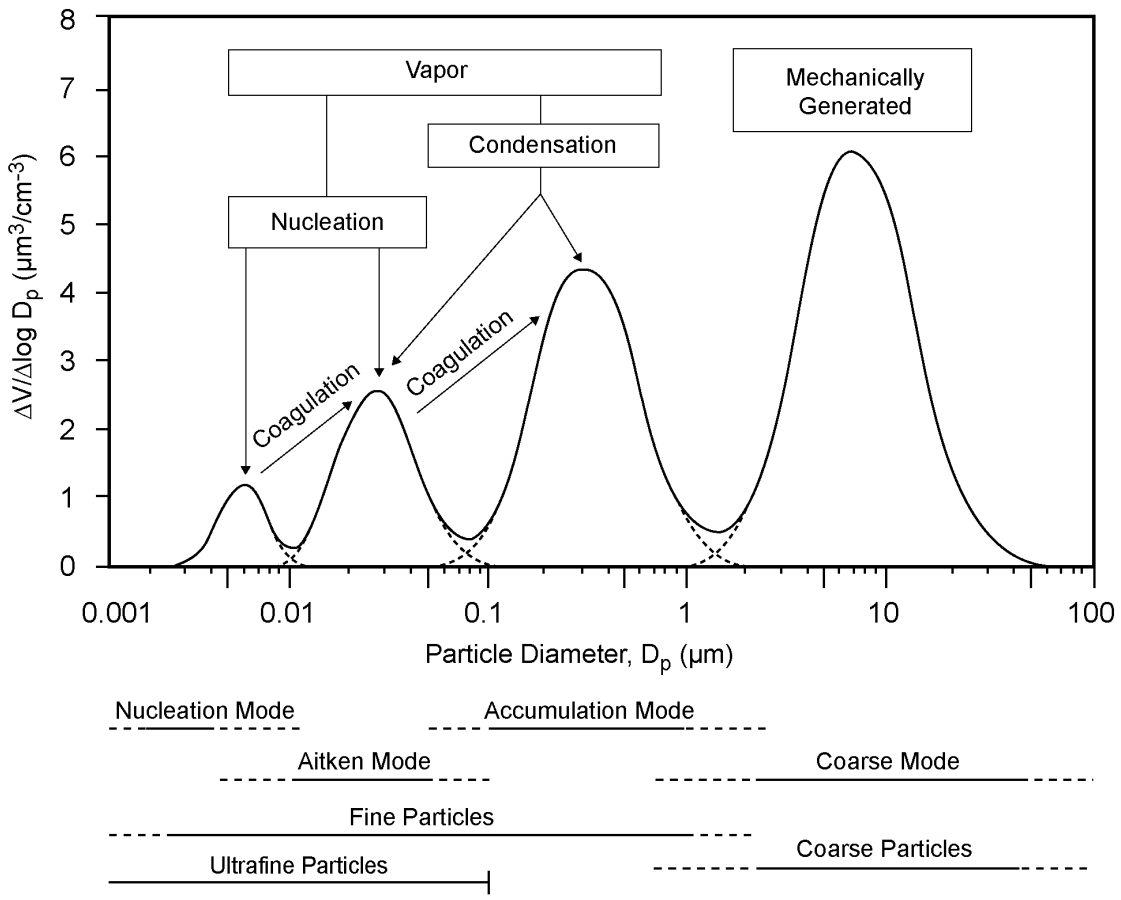

Figure 9-1. An idealized size distribution, as might be observed in traffic, showing fine and coarse particles and the nucleation, Aitken, and accumulation modes that comprise fine particles. Also shown are the major formation and growth mechanisms of the four modes of atmospheric particles.

particles that are still actively undergoing coagulation but have grown to larger sizes. The accumulation mode applies to the final stage, as particles originally formed as nuclei grow to a point where growth slows down, such that accumulation-mode particles normally do not grow into the coarse particle size range. However, during conditions of high relative humidity, hygroscopic accumulation mode particles grow in size, increasing the overlap of fine and coarse particles. The accumulation mode may split into a hygroscopic droplet mode and a nonhygroscopic condensation mode. In addition, gas-phase pollutants may dissolve and react in the particle-bound water (PBW) of hygroscopic particles, e.g., forming more sulfate or nitrate,

leading to particle growth beyond the original size even after removal of PBW. These three modes, which comprise fine particles (sometimes called fine-mode particles), are formed primarily by combustion or chemical reactions of gases that yield products with low saturated vapor pressures. Fine particles include primary PM (metals, black or elemental carbon, and organic compounds) and secondary PM (sulfate, nitrate, ammonium and hydrogen ions, and organic compounds).

The coarse mode refers to particles formed by mechanical breakdown of minerals, crustal material, and organic debris. The composition includes primary minerals and organic material. The coarse mode may also include sea salt, nitrate formed from the reaction of nitric acid with sodium chloride, and sulfate formed from the reaction of sulfur dioxide with basic particles. The accumulation mode and the coarse mode overlap in the region between 1 and 3 μm (and occasionally over an even larger range). In this intermodal region, the chemical composition of individual particles can usually, but not always, allow identification of a source or formation mechanism and so permit identification of a particle as belonging to the accumulation or coarse mode.

Since the 1996 PM AQCD, several studies have sought to better characterize particles present in the intermodal region (e.g., indexed by $PM_{2.5}$ - PM_1) and to assess the importance of coarse mode particles present in the intermodal region on associations reported in epidemiologic studies. For example, studies conducted in Phoenix suggested that inclusion of such particles would not likely affect reported associations with $PM_{2.5}$. Studies using Salt Lake City data suggest that coarse particles due to windblown dust are less toxic than PM_{10} present during non-windblown dust events. Studies in Spokane show that windblown dust contributes to $PM_{2.5}$ but not to PM_1. Thus, the inclusion of days with high windblown dust events could obscure associations with fine particles if $PM_{2.5}$ were used as the indicator.

Natural processes, such as the suspension of soil dust by wind, produce few particles below 1 μm in diameter. However, studies now suggest that biological material, although originally in the coarse mode, may deteriorate or fragment and produce particles in the fine-particle size range. Thus, fragments of pollen, endotoxins, and other biological material may be found in the fine-particle size range. Progress has also been made in understanding the semivolatile components of PM (particle-bound water, ammonium nitrate, and semivolatile organic

compounds) and new techniques have been developed to measure the semivolatile components of mass, either separately or included with the nonvolatile component. The many organic compounds formed in the atmospheric reactions of biogenic and anthropogenic hydrocarbons, including condensible species that form organic particles, are now better understood, and progress has been made in measurement of carbonaceous particles.

This progress has helped to enhance our understanding of ambient aerosol components and interrelationships among them that may contribute to ambient PM-related effects. Of much importance, for example, is emerging new evidence related to the role of PBW and associated submicron PM constituents serving as vectors by which water soluble gases (e.g., SO_2), short-lived reactive species (e.g., peroxides), and organic species (e.g., formaldehyde) present in atmospheric aerosol mixes can be delivered in enhanced proportions to lower regions of the respiratory tract. The importance of nonbiological ambient PM components serving as carriers or vectors enhancing deposition of bioaerosols (e.g., allergen-laden pollen fragments and endotoxins) in the lower respiratory tract has also been noted. It is notable that rather direct evidence has also been obtained which demonstrates adherence of allergen-laden pollen cytoplasm fragments to diesel particles, providing a likely mechanism by which diesel PM may act to concentrate bioaerosol materials and to increase their focal accumulation in lower regions of the respiratory tract.

The 1996 PM AQCD listed properties of fine and coarse particles. Because of the increasing interest in ultrafine particles and additional information on their properties, this current document provides new information on the chemical and physical properties of ultrafine and accumulation-mode fine particles and coarse particles, as shown in Table 9-1. As shown, ultrafine and accumulation-mode particles share similar formation processes and mechanisms, sources, and compositions. However, their fate and transport are quite dissimilar. In the atmosphere, ultrafine particles are removed largely by coagulation with other ultrafine particles (or accumulation-mode particles) and growth into the accumulation mode. Accumulation-mode particles are removed largely by serving as cloud-condensation nuclei that form cloud droplets and rain out, and to a lesser extent, by dry deposition. Coarse particles, however, are removed from the atmosphere rather rapidly by gravitational settling. With regard to the volume or mass of ambient PM, accumulation-mode and coarse particles both contribute appreciably in most

TABLE 9-1. COMPARISON OF AMBIENT PARTICLES, FINE PARTICLES (ultrafine plus accumulation-mode) AND COARSE PARTICLES

	Fine		
	Ultrafine	**Accumulation**	**Coarse**
Formation Processes:	Combustion, high-temperature processes, and atmospheric reactions		Break-up of large solids/droplets
Formed by:	Nucleation Condensation Coagulation	Condensation Coagulation Reactions of gases in or on particles Evaporation of fog and cloud droplets in which gases have dissolved and reacted	Mechanical disruption (crushing, grinding, abrasion of surfaces) Evaporation of sprays Suspension of dusts Reactions of gases in or on particles
Composed of:	Sulfate Elemental carbon Metal compounds Organic compounds with very low saturation vapor pressure at ambient temperature	Sulfate, nitrate, ammonium, and hydrogen ions Elemental carbon Large variety of organic compounds Metals: compounds of Pb, Cd, V, Ni, Cu, Zn, Mn, Fe, etc. Particle-bound water	Suspended soil or street dust Fly ash from uncontrolled combustion of coal, oil, and wood Nitrates/chlorides/sulfates from HNO_3/HCl/SO_2 reactions with coarse particles. Oxides of crustal elements (Si, Al, Ti, Fe) $CaCO_3$, $CaSO_4$, NaCl, sea salt Pollen, mold, fungal spores Plant and animal fragments Tire, brake pad, and road wear debris
Solubility:	Probably less soluble than accumulation mode	Largely soluble, hygroscopic, and deliquescent	Largely insoluble and nonhygroscopic
Sources:	Combustion Atmospheric transformation of SO_2 and some organic compounds High temperature processes	Combustion of coal, oil, gasoline, diesel fuel, wood Atmospheric transformation products of NO_x, SO_2, and organic compounds, including biogenic organic species (e.g., terpenes) High-temperature processes, smelters, steel mills, etc.	Resuspension of industrial dust and soil tracked onto roads and streets Suspension from disturbed soil (e.g., farming, mining, unpaved roads) Construction and demolition Uncontrolled coal and oil combustion Ocean spray Biological sources
Atmospheric half-life:	Minutes to hours	Days to weeks	Minutes to hours
Removal Processes:	Grows into accumulation mode Diffuses to raindrops	Forms cloud droplets and rains out Dry deposition	Dry deposition by fallout Scavenging by falling rain drops
Travel distance:	< 1 to 10s of km	100s to 1000s of km	< 1 to 10s of km (small size tail, 100s to 1000s in dust storms)

Source: Adapted from Wilson and Suh (1997).

areas, with very little contribution from ultrafine particles. With regard to particle surface area, however, ultrafine and accumulation-mode particles both contribute appreciably, with very little contribution from coarse particles. To the extent that inhaled PM may carry chemicals or reactive species on their surfaces, these smaller size fractions may have an additional dimension to their toxicity (in terms of surface chemical bioavailability) that is not found with coarse PM.

Ultrafine, accumulation mode, and coarse particles also behave differently with regard to exposure and dosimetric considerations, as discussed below, as well as in toxicologic and epidemiologic studies, as discussed in subsequent sections of this chapter.

9.2.1.2 Exposure-Related Considerations

The critical relationship to be considered is that between ambient PM *concentrations* and *personal exposures* to ambient PM (ambient PM refers to that PM measured at a community monitoring site, or the average over several such sites). It is convenient to consider two aspects of this relationship. One important aspect is the relationship between the ambient concentration measured at one or more monitoring sites and the distribution of outdoor concentrations across an area (e.g., outside homes and other microenvironments). This relationship will depend in part on the uniformity with which the PM indicator of interest is distributed across the community. For time-series epidemiologic analyses of associations between 24-h concentrations of ambient PM and health endpoints, the relevant measurement of this relationship is the day-to-day correlation of 24-h concentration values at various monitoring sites in the community. For long-term epidemiologic analyses, the variation in the seasonal or yearly average at various sites in the community is the relevant parameter. Much new information on the distribution of $PM_{2.5}$ and $PM_{10-2.5}$ concentrations across cities is available from the new monitoring networks and is presented in detail in Chapter 3. In general, $PM_{2.5}$ is more evenly distributed than $PM_{10-2.5}$ in terms of both daily/seasonal/yearly averages and day-to-day correlations, although there are significant differences among cities. Little is known about the spatial distribution of ultrafine particle concentrations, except that their concentrations are highest in and near heavy traffic areas and rapidly fall off with distance from traffic due to coagulation and dispersion. Because of their rapid growth into the accumulation mode, their concentrations are probably highest near

sources such as traffic. Thus, they likely have a more heterogeneous distribution across a community than accumulation-mode particles.

The second aspect is the relationship between the concentration of PM outdoors and the concentration of that outdoor PM which has infiltrated into the home or other microenvironment, characterized by an infiltration factor which is a function of particle size. Personal exposure includes a nonambient component due to PM generated indoors or by personal activities, a component which does not appear to correlate well with outdoor ambient PM concentrations. As shown in Figure 9-2, the infiltration factor depends on the air exchange rate, but for a given ventilation condition, the infiltration rate is high for accumulation-mode particles and decreases to low levels with decreasing size within the ultrafine range and with increasing size within the coarse-mode range. Exposure-related relationships for the three particle size classes are summarized in Table 9-2.

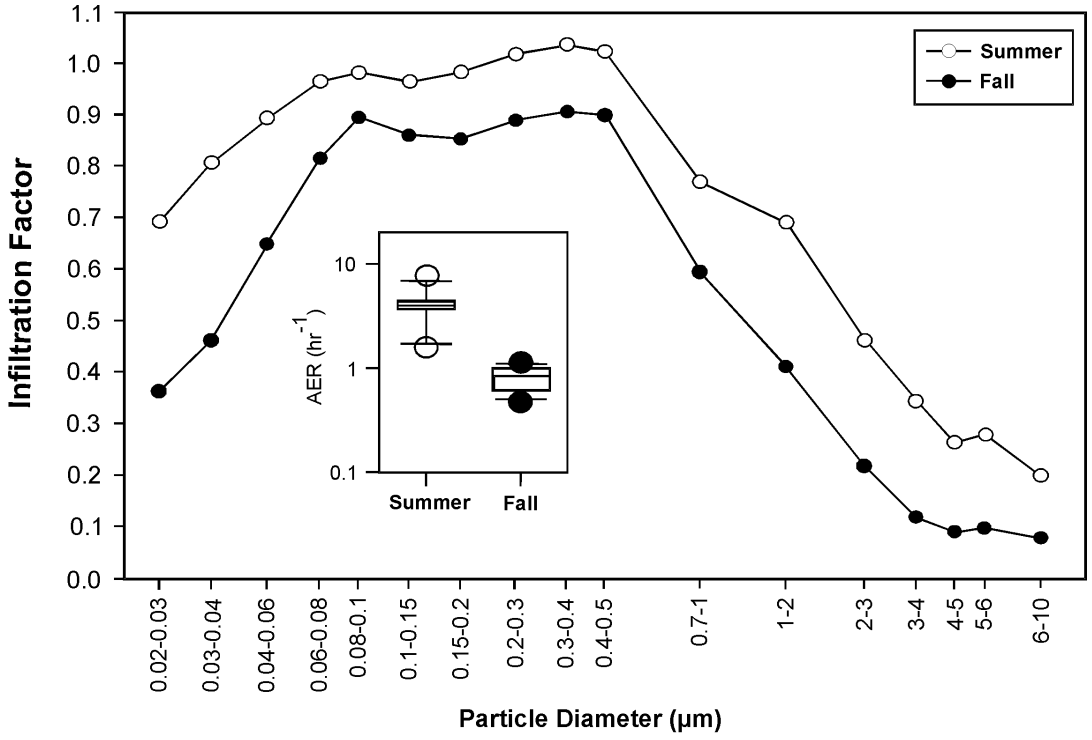

Figure 9-2. Geometric mean infiltration factor (indoor/outdoor ratio) for hourly nighttime, nonsource data for two seasons. Box plots of air exchange rates are shown as inserts for each plot (Boston, 1998).

Source: Long et al. (2001).

TABLE 9-2. EXPOSURE-RELATED RELATIONSHIPS FOR PARTICLE SIZE FRACTIONS

	Ultrafine	Accumulation-Mode	Thoracic-Coarse
Even distribution across city	Probably not	Frequently	Seldom
Site-to-site correlation	Probably low	Frequently high	Frequently low
Infiltration factor (for a given exchange rate)	Decreasing from high to low as particle size decreases from 0.1 μm	High	Lower than accumulation mode and decreasing with increasing size

In most community time-series studies and long-term cohort studies, the ambient concentration is used as a surrogate for personal exposure to ambient PM (ambient exposure). For the ambient concentration to be a satisfactory surrogate, there must be a reasonable correlation between ambient concentration and ambient exposure, as appears to be the case for fine particles ($PM_{2.5}$). However, because of the lower and more variable infiltration factors for ultrafine and coarse particles and their less even distribution and lower site-to-site correlations across the community, it is likely that their ambient concentrations will be a somewhat poorer surrogate for their ambient exposures than is the case for $PM_{2.5}$. Nonambient PM may also be responsible for health effects. However, since the ambient and nonambient components of personal exposure are independent, the health effects due to nonambient PM exposures generally will not bias the risk estimated for ambient PM exposures.

9.2.1.3 Dosimetric Considerations

The fraction of inhaled particles that are deposited in the various regions of the lung depends on the particle size, the breathing route (nasal or oral), the breathing frequency (breaths per minute), the volume of air inhaled (tidal volume), the anatomy of the respiratory tract of the individual, and deposition mechanisms (diffusion, sedimentation, impaction) which affect different-sized particles to varying extents. Because of differing effects of all the above-noted factors, calculated fractional deposition patterns in various respiratory tract regions can vary considerably for particles in different size ranges. The fractional depositions in the extrathoracic

(ET), tracheobronchial (TB), and gas exchange or alveolar (A) regions of the respiratory tract are shown as a function of particle size in Figure 9-3 for nasal and oral breathing at two levels of activity (resting and light exercise). Particles in the accumulation-mode size range generally have very low deposition fractions, especially in the ET and TB regions, that are relatively insensitive to breathing pattern or exercise. However, for nose breathing the deposition of larger accumulation-mode particles in the ET region does increase with exertion. Thus, most accumulation mode particles that enter the lungs are exhaled rather than deposited.

Ultrafine particles generally have much higher fractional depositions than accumulation mode particles. However, the smaller nucleation-mode (< 0.01 μm) ultrafine particles behave differently from the larger Aitken-mode (~0.01 to ~0.1 μm) ultrafine particles. As particle size decreases below 0.1 μm, the total deposition of particles increases, and the pattern of deposition within the respiratory tract slowly moves proximally, i.e., toward the ET region. This shift in the pattern of deposition is quite obvious for decreases in particle size below 0.01 μm where A deposition fractions rapidly decline and the ET deposition fractions correspondingly increase. The TB deposition fraction increases to a maximum near 3 nm. For the Aitken mode particles, the deposition fraction for the A region increases with exertion whereas in the TB region it decreases. Deposition fractions in the A region for particles less than ~1 μm are relatively insensitive to route of breathing.

The fractional deposition for coarse particles is even more complex. For both the A and TB regions, the deposition fraction increases with particle diameter above ~1 μm, reaches a peak before the diameter reaches 10 μm, and then declines. The deposition fractions for the A and TB regions are lower during nasal breathing because a large fraction of the coarse particles deposit within the nose. For mouth breathing, the A and TB deposition fractions are higher than during nasal breathing but not as high as those for the ultrafine mode during mouth breathing. For mouth breathing, the deposition fractions for both the A and the TB regions are greater for coarse particles than for accumulation-mode particles. Even for nose breathing, some coarse particles, of a specific size, will have higher A and TB deposition fractions than accumulation mode particles.

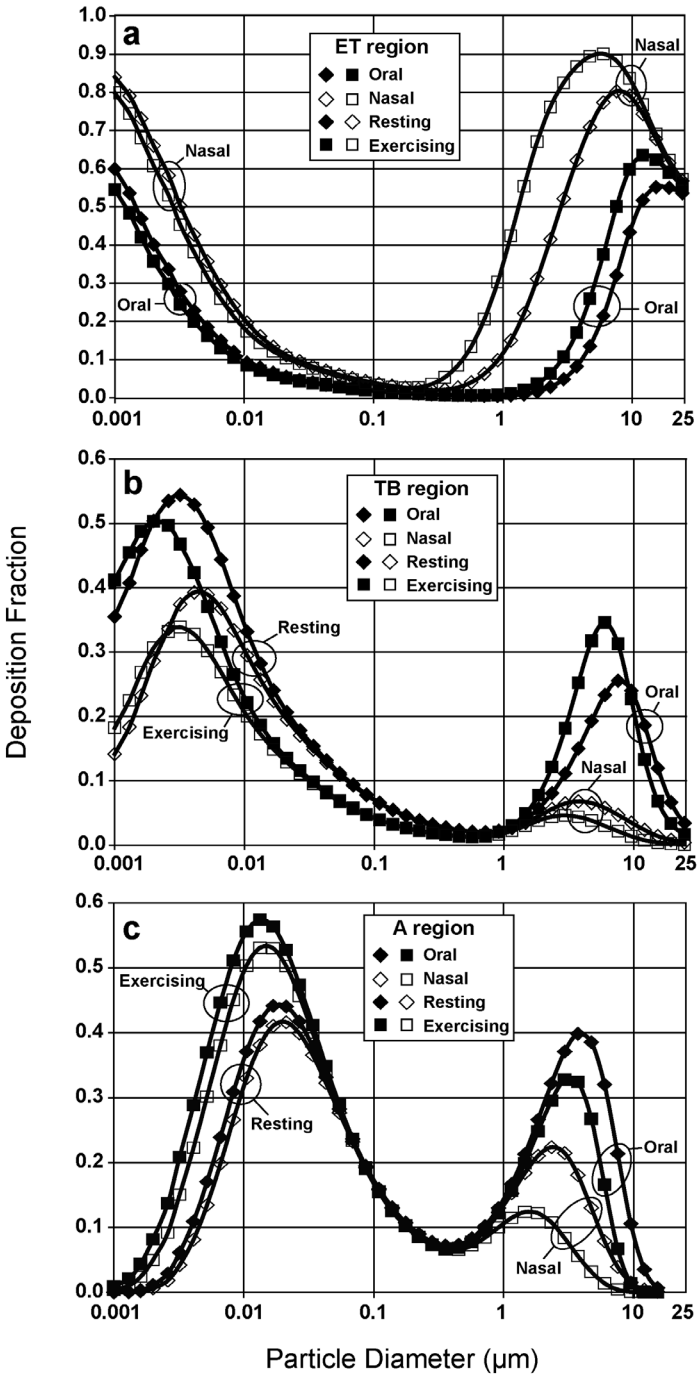

Figure 9-3. Deposition fraction as a function of particle size for nasal and oral breathing during rest and exercise: (a) extrathoracic (ET), (b) tracheobronchial (TB), and (c) alveolar (A) regions. Deposition estimates shown here were calculated with the ICRP model and were also shown in Figures 6-16 and 6-17 along with similar results from the MPPD model. The estimates below 0.01 μm are uncertain but are shown to indicate trends. Note the different scale for the ET region.

In general, given these complex deposition patterns, there are no sharp cut points that clearly distinguish between particle size ranges with relatively high versus relatively low fractional deposition rates. For example, in the ET region, particles ranging in size from roughly 0.01 μm on up to ~1 μm (for nasal breathing) to over 3 μm (for oral breathing) exhibit relatively low fractional deposition rates. For the TB region, relatively low rates are exhibited by particles ranging in size from roughly 0.05 μm up to ~2 μm (for oral breathing) to over 10 μm (for nasal breathing). For the A region, relatively low rates are exhibited not only by particles from ~0.1 to ~1 μm but also for particles in the low end of the ultrafine size range and as well as for particles in the upper end of the coarse-mode range. Thus, while differences in dosimetric properties continue to support the general division of ambient particles into fine and coarse fractions, dosimetric considerations now also suggest that further distinctions can be made between subclasses (ultrafine, accumulation-mode) within the range of fine particles.

9.2.1.4 Summary and Conclusions

The distinctions articulated in the last review between fine and coarse ambient particles (as indicators of of fundamentally different sources and composition, formation mechanisms, transport, and fate) remain generally unchanged. However, some important advances have been made in our understanding of such distinctions, especially with regard to characteristics of particles below ~0.1 μm in diameter (ultrafine particles). In particular, whereas fine particles were previously characterized in two modes, they are now characterized in terms of three modes, with two modes, nucleation and Aiken, observed in the ultrafine particle size range. Distinctions among these modes allow for more differentiation in characterizing properties of fine particles. Also, progress has been made in better understanding the size distribution of biological materials. While previously understood mainly to be present in the coarse particle size range, newly available information indicates that such particles (e.g., pollen grains, endotoxins) may fragment or deteriorate into the fine particle size range. This information expands our understanding of the types of particles that can occur in particular within the intermodal size range of ~1 to ~3 μm. New information indicates that atmospheric particles may carry components of biological particles (allergens and endotoxin) to the lower respiratory tract and

confirms earlier suggestions that water soluble gases can dissolve in particle-bound water and be delivered in enhanced proportions to the lower respiratory tract.

Data now available from the new national $PM_{2.5}$ monitoring network and speciation sites have allowed for better assessments of exposure-related considerations which broaden but do not fundamentally change our understanding of the substantial differences between fine particles in the accumulation mode and coarse particles. Relationships between ambient PM concentrations and personal exposure to ambient PM are now better understood, primarily for fine particles, but also to a more limited degree for coarse particles. For example, new data reinforce our earlier understanding that ambient concentrations of fine particle mass (measured as $PM_{2.5}$) are typically more highly correlated and/or are more uniform across community monitors within an urban area than are coarse particle mass concentrations (measured as $PM_{10-2.5}$), although in some areas the differences are much less pronounced than in others. More limited data and knowledge of the behavior of ultrafine particles suggest that spatial distributions of their concentrations (which decrease quickly from peak levels around major highways) are more variable than those of accumulation mode particles. Concentrations of coarse particles (which decrease quickly from peak levels around primary sources) are also more variable spatially than accumulation-mode particles. Further, new studies reinforce our earlier understanding that, for a given ventilation condition, fine particles generally infiltrate indoors much better than do either coarse or ultrafine particles. Thus, central site ambient concentration measurements are a better surrogate for population exposure to accumulation-mode fine particles, measured as $PM_{2.5}$, than for either coarse or ultrafine particles, although there may be large differences in $PM_{2.5}$ concentrations across many urban areas. These observations about the behavior of ultrafine particles and coarse particles are based on far more limited data, highlighting a need for further research on these particle size ranges.

Newly available dosimetry information continues to reinforce important distinctions between fine and coarse particles, and submodes within fine particles, with regard to deposition patterns within the respiratory tract. In general, while deposition patterns within the major respiratory tract regions as a function of particle size are complex and dependent in varying degrees on breathing route and ventilation levels, accumulation-mode particles exhibit distinctly lower fractional deposition rates in any of the major respiratory tract regions than do ultrafine or

coarse particles on average. The factional deposition of ultrafine, accumulation-mode, and coarse thoracic particles in the ET, TB, and A regions show complex variations with increasing levels of activity, associated increases in breathing rate, and associated increased oral nasal/oral breathing. Thus, it is difficult to characterize more specific size fractions within the range of thoracic particles that would clearly delineate ranges of relatively high and relatively low fractional deposition across all respiratory tract regions.

Overall, then, the above considerations reinforce the recommendation made in the 1996 PM AQCD that fine and coarse particles be considered as separate subclasses of PM pollution. Advances in our understanding of the characteristics of fine and coarse particles continue to support the use of particle size as an appropriate basis for distinguishing between these subclasses, even as progress is being made in understanding their composition. The considerations that led to the selection of a nominal upper cut point of 2.5 μm in the last review remain relevant, and lead again to the conclusion that an upper cut point of 2.5 μm remains appropriate as the basis for a regulatory indicator of fine particles, in conjunction with a regulatory indicator of coarse particles defined by a nominal lower cut point of 2.5 and a nominal upper cut point of 10 μm.

9.2.2 Assessment of Epidemiologic Evidence

Based on the PM epidemiologic evidence available at the time, the 1996 PM AQCD, arrived at the following overall conclusions:

> "The evidence for PM-related effects from epidemiologic studies is fairly strong, with most studies showing increases in mortality, hospital admissions, respiratory symptoms, and pulmonary function decrements associated with several PM indices. These epidemiologic findings cannot be wholly attributed to inappropriate or incorrect statistical methods, misspecification of concentration-effect models, biases in study design or implementation, measurement errors in health endpoint, pollution exposure, weather, or other variables, nor confounding of PM effects with effects of other factors. While the results of the epidemiology studies should be interpreted cautiously, they nonetheless provide ample reason to be concerned that there are detectable human health effects attributable to PM at levels below the current NAAQS." (U.S. Environmental Protection Agency, 1996, p. 13-92).

The 1996 PM AQCD went on to state further that, while the epidemiological studies indicate increased health risks associated with exposure to PM, alone or in combination with

other air pollutants, the role of PM as an independent causal factor has not been completely resolved, based on the available studies using multiple air pollutants as predictors of health outcomes (U.S. Environmental Protection Agency, 1996, p. 13-92).

In assessing the strengths and limitations of the extensive body of new epidemiologic evidence of associations between health effects and fine and coarse thoracic PM, information discussed in this section is drawn primarily from Chapter 8, as well as from Chapter 5 of this document. The information is considered here in relation to several criteria noted at the outset of Section 9.2: (1) the *strength* of reported associations, in terms of magnitude, statistical significance, and statistical power/precision of effects estimates; (2) the *robustness* of reported associations to the use of alternative model specifications, potential confounding by co-pollutants, and exposure misclassification related to measurement error; (3) the *consistency* or general concordance of findings in multiple studies of adequate power, and in different persons, places, circumstances and times; (4) *temporality*, in terms of lag periods between exposure and observed effects; (5) the nature of *concentration-response* relationships; and (6) information from so-called *natural experiments* or intervention studies as to the extent to which reductions in PM-related air pollution have been observed to be associated with improvements in health measures. The body of epidemiologic evidence is further considered in the following section in terms of its coherence within itself and in relation to toxicologic findings derived from controlled exposure studies which, overall, provide insights on the plausibility of reported PM-related health effects reflecting causal relationships.

Many recent epidemiologic studies have built upon what was previously known, showing statistically significant associations of various ambient PM indicators with a variety of cardiovascular and respiratory health endpoints, including mortality, hospital admissions, emergency department visits, other medical visits, respiratory illness and symptoms, physiological or biochemical changes related to the cardiovascular system, and physiologic changes in pulmonary function. Associations have been consistently observed between short-term PM exposures to certain PM size fractions and one or more of these endpoints; and long-term PM exposures have been associated with increased risk of mortality, development of respiratory disease, and changes in lung function. As summarized in Chapter 8, Appendices 8A and 8B, epidemiologic studies have been conducted in areas across the U.S. and Canada, as well

as in Mexico and South America, Europe, Asia and Australia; and various methods have been used to measure ambient PM concentrations. Considering the evidence from the full body of epidemiologic studies using various PM indicators, the available findings demonstrate well that human health outcomes are associated with ambient PM. Discussions in the following sections focus primarily on studies conducted in the U.S. and Canada using various mass measurements of thoracic particles (e.g., PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$) and source-oriented PM analyses.

9.2.2.1 Strength of Epidemiologic Associations

As quoted above, the 1996 PM AQCD concluded that the epidemiologic evidence for cardiorespiratory effects was "fairly strong" considering both magnitude and statistical significance of results available at that time. At that time, it was recognized that the relative risk estimates from time-series studies were generally small in magnitude. Since then, however, the results of recent reanalyses to address GAM-related issues has led to smaller effect estimates in some cases (as discussed in Chapter 8). In contrast with the marked increase in health effects observed during historic episodes of very high air pollution levels, relatively small effect estimates would generally be expected with current ambient PM concentrations in the United States. The etiology of most air pollution-related health outcomes is multifactorial, and the impact of ambient air pollution exposure on these outcomes may be small in comparison to that of other risk factors (e.g., smoking, diet).

9.2.2.1.1 Short-Term Exposure Studies

Many new epidemiologic studies have built upon what was available in the 1996 PM AQCD. These include several multicity studies that can provide more precise estimates of effects than individual city studies, offer consistency in data handling and modeling, allow for systematic evaluation of geographic patterns in effects, and clearly do not suffer from potential omission of negative findings due to "publication bias." In addition, there are studies of new health indices (e.g., physician visits) and cardiovascular health outcomes, analyses that provide insight into the sensitivity of PM effects to alternative statistical modeling, new assessments on the potential for confounding by gaseous co-pollutants, and new evidence from "found experiments" that evaluate improvements in health seen with reductions in air pollution levels.

The results from key United States and Canadian studies on short-term PM exposure for several commonly-used health outcomes — mortality, hospitalization and medical visits — are depicted in Figures 9-4 and 9-5. While recognizing that epidemiologic studies of short-term air pollution exposures have also evaluated other health outcomes (e.g., respiratory symptoms, cardiovascular health indicators, lung function changes), these figures illustrate results for a few major health outcome categories commonly used in PM time-series epidemiologic analyses. It should be noted that, while nearly all effect estimates shown in Figure 9-4 and 9-5 were derived from single-city time-series analyses, a few (among those with the narrowest 95% confidence intervals) represent results aggregated across multiple cities. See pertinent references (indicated by bold font in the figure captions) and discussion of such studies presented in Chapter 8 for more details on them.

It should also be noted that the results are drawn from studies using one or more of the three major PM mass indicators (PM_{10}, $PM_{2.5}$, or $PM_{10-2.5}$) that either did not use GAM or were reanalyzed to address GAM-related questions. Single-pollutant (PM only) results are presented here for purposes of comparison across studies, and it is noted that multipollutant model results are presented and discussed in Chapter 8 (see especially Section 8.4.3). The results of models using different lag periods from time-series epidemiologic studies are also presented and discussed in Chapter 8 (see Section 8.4.4). For each health outcome, the results are presented in Figures 9-4 and 9-5 in order (from left to right) of decreasing study power, using as an indicator the product of the number of study days and number of health events per day.

To be consistent with the rest of this document, the effect estimates are presented in Figures 9-4 and 9-5 using standardized PM increments to allow for comparison across studies. As described in Section 8.1.1, current air quality data distributions were used to select increments of 50 $\mu g/m^3$ for PM_{10} and 25 $\mu g/m^3$ for both $PM_{2.5}$ and $PM_{10-2.5}$ as representative of realistic high-to-low ranges of concentrations for most U.S. communities. Alternatively, if the effect estimates were presented per unit mass for each PM indicator, the estimates for $PM_{2.5}$ and $PM_{10-2.5}$, relative to those for PM_{10}, would be twice as large as those depicted in these figures. On a unit mass basis, the effect estimates for both $PM_{2.5}$ and $PM_{10-2.5}$ are generally larger than those for PM_{10}, which is consistent with $PM_{2.5}$ and $PM_{10-2.5}$ having independent effects.

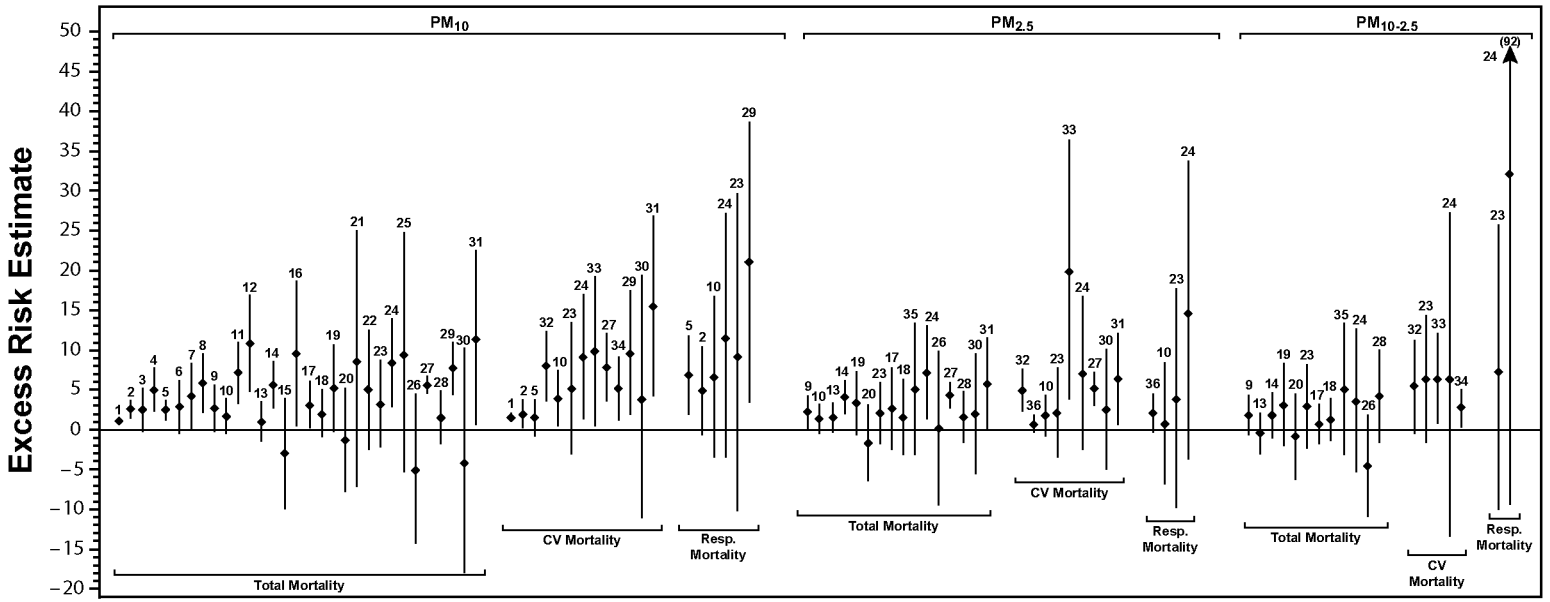

Figure 9-4. Excess risk estimates for total nonaccidental, cardiovascular, and respiratory mortality in single-pollutant models for U.S. and Canadian studies, including aggregate results from two multicity studies (denoted in bold print below). PM increments: 50 μg/m^3 for PM_{10} and 25 μg/m^3 for $PM_{2.5}$ and $PM_{10-2.5}$. Results presented from time-series studies that did not use GAM or were reanalyzed using GLM.

1. **Dominici et al. (2003a), 90 U.S. cities**
2. Moolgavkar (2003), Cook County
3. Kinney et al. (1995), Los Angeles
4. Schwartz (2003), Chicago
5. Ito and Thurston (1996), Cook County
6. Schwartz (2003), Pittsburgh
7. Styer et al. (1995), Cook County
8. Schwartz (2003), Detroit
9. **Burnett and Goldberg (2003), 8 Canadian cities**
10. Moolgavkar (2003), Los Angeles
11. Schwartz (2003), Seattle
12. Schwartz (2003), Minneapolis
13. Klemm and Mason (2003), St. Louis
14. Klemm and Mason (2003), Boston
15. Schwartz (2003), Birmingham
16. Schwartz (2003), New Haven
17. Chock et al. (2000), Pittsburgh (< 75 y.o.)
18. Chock et al. (2000), Pittsburgh (75+ y.o.)
19. Klemm and Mason (2003), Kingston-Harriman
20. Klemm and Mason (2003), Portage
21. Schwartz (2003), Canton
22. Schwartz (2003), Spokane
23. Ito (2003), Detroit
24. Fairley (2003), Santa Clara County
25. Schwartz (2003), Colorado Springs
26. Klemm and Mason (2003), Topeka
27. Tsai et al. (2000), Newark
28. Klemm and Mason (2003), Steubenville
29. Pope et al. (1992), Utah Valley
30. Tsai et al. (2000), Elizabeth
31. Tsai et al (2000), Camden
32. Lipfert et al. (2000), Philadelphia
33. Mar et al. (2003), Phoenix
34. Ostro et al. (2003), Coachella Valley
35. Klemm and Mason (2000), Atlanta
36. Ostro et al. (1995), Southern California

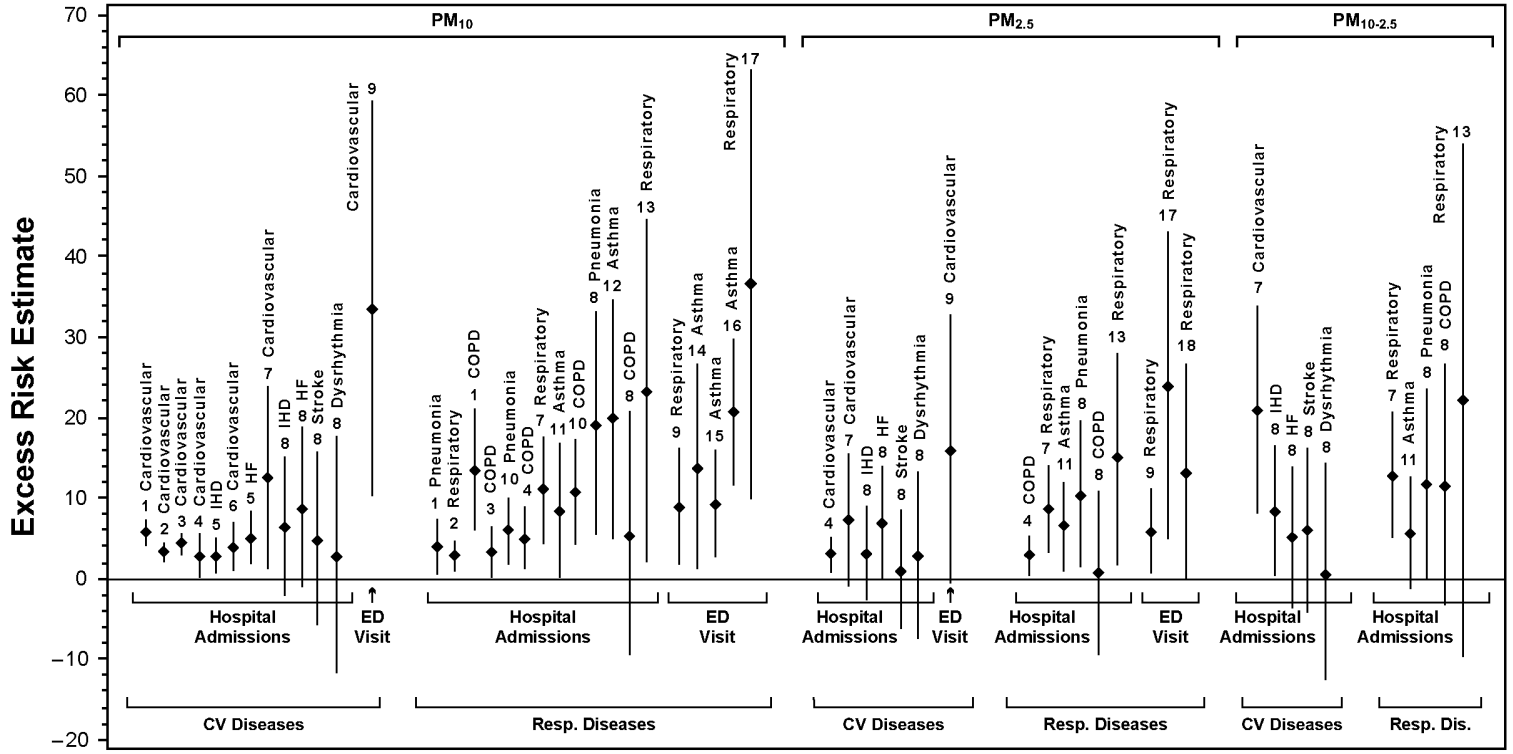

Figure 9-5. Excess risk estimates for hospital admissions and emergency department visits for cardiovascular and respiratory diseases in single-pollutant models from U.S. and Canadian studies, including aggregate results from one multicity study (as denoted in bold below). PM increments: 50 µg/m^3 for PM_{10} and 25 µg/m^3 for $PM_{2.5}$ and $PM_{10-2.5}$. Results presented from time-series studies that did not use GAM or were reanalyzed using GLM. PM effect size estimate (± 95% confidence intervals) are depicted for the studies listed below.

1. **Zanobetti and Schwartz (2003) U.S. 14 cities**
2. Linn et al. (2000), Los Angeles
3. Moolgavkar (2003), Cook County
4. Moolgavkar (2003), Los Angeles
5. Schwartz and Morris (1995), Detroit
6. Morris and Naumova (1998), Chicago
7. Burnett et al. (1997), Toronto
8. Ito (2003), Detroit
9. Stieb et al. (2000), St. John
10. Schwartz (1994), Detroit
11. Sheppard (2003), Seattle
12. Nauenberg and Basu (1999), Los Angeles
13. Thurston et al. (1994), Toronto
14. Tolbert et al. (2000), Atlanta
15. Lipsett et al. (1997), Santa Clara County
16. Choudhury et al. (1997), Montreal
17. Delfino et al. (1997), Montreal
18. Delfino et al. (1998), Montreal

In Figure 9-4, effect estimates for associations between mortality and PM are grouped both by PM indicator (PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$) and by mortality category (total nonaccidental, cardiovascular or cardiorespiratory, and respiratory). Looking across the results with particular focus on the more precise estimates, some general observations can be made:

- Almost all of the associations between PM_{10} and total mortality are positive and over half are statistically significant, including most all of those with more precise estimates. All associations reported between PM_{10} and cardiovascular and respiratory mortality are positive. Most of the cardiovascular mortality associations are also statistically significant, whereas most of the respiratory associations are generally larger in size but less precise and not statistically significant; less precision would be expected since respiratory deaths comprise only a small portion of total nonaccidental mortality. The more precise effect estimates range from ~1 to 8% increased risk of mortality per 50 $\mu g/m^3$ PM_{10}; for the multicity studies, effect estimates ranged from ~1.0 to 3.5% per 50 $\mu g/m^3$ PM_{10}.

- A similar pattern can be seen for $PM_{2.5}$, though fewer studies are available; and the effects estimates are generally somewhat less precise and less frequently statistically significant. In particular, almost all of the $PM_{2.5}$ associations with total mortality are positive, although less than half are statistically significant. All $PM_{2.5}$ associations with cardiovascular and respiratory mortality are positive; and about half of the cardiovascular associations, but none of the respiratory associations, are statistically significant. The more precise effect estimates range from about 2 to 6% increased risk of mortality per 25 $\mu g/m^3$ $PM_{2.5}$ and ~1 to 3.5% per 25 $\mu g/m^3$ $PM_{2.5}$ in multicity studies.

- Still fewer studies have used $PM_{10-2.5}$ measurements. The effect estimates are almost all positive and similar in magnitude to those reported for $PM_{2.5}$ and PM_{10}, but few reach statistical significance. Measurement error likely contributes to greater uncertainty, reflected by wider confidence intervals, in effect estimates for $PM_{10-2.5}$ than for $PM_{2.5}$ and PM_{10}.

The results for U.S. and Canadian studies are generally consistent with those presented in Chapter 8 based on all available epidemiologic studies world wide. These results indicate that there is substantial strength in the epidemiological evidence for association between PM_{10} and $PM_{2.5}$ and mortality, especially for total and cardiovascular mortality, but also for respiratory mortality. For $PM_{10-2.5}$, the evidence for associations with mortality is more limited and clearly not as strong, although it is important in interpreting these results to consider issues such as exposure error (which could cause the calculated effects to be lower and less significant than the true values).

In Figure 9-5, the effect estimates presented for associations between morbidity and ambient PM are grouped by PM indicator (PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$), general health outcome category (cardiovascular and respiratory), and more specific outcome measures (hospital admissions and medical visits). Several general observations can be made:

- All associations between PM_{10} and hospitalization for cardiovascular and respiratory diseases are positive and most are statistically significant, including all of the more precise estimates. Almost all PM_{10} associations with emergency department (ED) visits for cardiovascular and respiratory diseases are positive, and most respiratory (but not cardiovascular) associations are statistically significant. The more precise effect estimates range from about 2 to 6% increased risk per 50 $\mu g/m^3$ PM_{10} for cardiovascular diseases and 2 to 12% increased risk per 50 $\mu g/m^3$ PM_{10} for respiratory diseases, with some effect estimates for respiratory medical visits ranging up to about 30% per 50 $\mu g/m^3$ PM_{10}.

- For $PM_{2.5}$, all associations with hospitalization for cardiovascular and respiratory diseases are positive and many are statistically significant, especially for respiratory diseases. All $PM_{2.5}$ associations with ED visits for cardiovascular and respiratory diseases are positive, and about half are statistically significant. The more precise effect estimates range from about 1 to 10% increased risk per 25 $\mu g/m^3$ $PM_{2.5}$ for cardiovascular diseases, and 1 to 12% increased risk per 25 $\mu g/m^3$ $PM_{2.5}$ for respiratory diseases.

- Associations between $PM_{10-2.5}$ and hospitalization for cardiovascular and respiratory diseases are positive, and the effect estimates are of the same general magnitude as for PM_{10} and $PM_{2.5}$. In general, as was the case for mortality, the confidence intervals for the $PM_{10-2.5}$ estimates are broader than those for associations with PM_{10} or $PM_{2.5}$ and some, but not all, of the associations are statistically significant.

- For all PM indicators, associations with medical visits tend to be less precise than those for hospital admissions. As was noted in Section 8.3.2.4, many of the medical/physician visits effect estimates are larger in magnitude than those for hospital admissions.

These figures include effect estimates from both recent studies and those available in the previous PM NAAQS review, and it can be seen that the results fall within similar ranges. For example, in the 1996 PM AQCD, a 50 $\mu g/m^3$ increase in PM_{10} was associated with a 2.5 to 5% increase in mortality risk, and results of the Six Cities analysis showed a 3% excess risk per 25 $\mu g/m^3$ $PM_{2.5}$. The effect estimates from the more recent mortality studies, especially those with greater statistical power, can be seen to fall in the same ranges. It is expected that results of

multicity studies would more accurately reflect the magnitude of PM-health associations, and it is important to note that the effect estimates from the new multicity studies, such as NMMAPS, are at the low end of the effect estimate ranges; these results are, however, statistically significant and the precision of the multicity estimates is notably greater than for single-city studies.

For both mortality and morbidity outcomes, many more epidemiologic studies have used PM_{10} than have used $PM_{2.5}$ and $PM_{10-2.5}$ measurements, since there is a much more extensive set of air quality monitoring data available for PM_{10}. The few studies that have tested multipollutant models that include both $PM_{2.5}$ and $PM_{10-2.5}$ have reported that the two PM size fractions have independent outcomes (e.g., Lippmann et al., 2000; Ito, 2003). Thus, it is difficult to assess the implications of associations with PM_{10} for effects of fine and coarse fraction particles, since they are likely to be representing separate effects of $PM_{2.5}$ and $PM_{10-2.5}$. An association reported with PM_{10} is not simply a sum of the effects from the two particle size classes, but may represent the influence of either fine or coarse fraction particles, or some combination of the two, depending on the type of effect. PM_{10}, to the extent it is correlated with PM_{10} and $PM_{10-2.5}$, will capture some of the effects of both $PM_{2.5}$ and $PM_{10-2.5}$. However, since the correlation will be less than 1.0, the size of effects captured by PM_{10} will be less than that found for $PM_{2.5}$ and $PM_{10-2.5}$ for a given concentration increment (e.g., per 10 $\mu g/m^3$).

As discussed in more detail in Section 8.2.2.5 and summarized in Table 9-3, various PM components or characteristics, including ultrafine particles, have been associated with various health outcomes. In general, evidence for associations have been reported for most components that have been studied; and at least one new study has reported associations between ultrafine particles and mortality or respiratory morbidity. However, many PM components are correlated with each other and also with PM mass, making it difficult to distinguish effects of the various components. Also, different PM components or characteristics would be expected to be more closely linked with different health outcomes.

One new approach used to evaluate effects associated with various PM components is to conduct a source apportionment analysis of the composition data base and to use the resulting daily source factors as surrogates for exposure in an epidemiologic analysis. Motor vehicles, or

TABLE 9-3. PARTICULATE MATTER CHARACTERISTICS, COMPONENTS, OR SOURCE CATEGORIES SHOWN TO BE ASSOCIATED WITH MORTALITY IN U.S., CANADIAN, OR EUROPEAN EPIDEMIOLOGIC STUDIES [1,2]

PM Size Fractions	Ions/Elements	Carbon/Organic Fractions	Source Categories (Tracers) [3]
Mass fractions:	Sulfate ($SO_4^=$)	TC (Total Carbon)	Motor Vehicles (CO, Pb)
TSP	Nitrate (NO_3^-)	BC (Black Carbon)	Motor Vehicles plus resuspended road dust (CO, NO_2, EC, OC, Mn, Fe, Zn, Pb)
PM_{10}	Ammonium (NH_4^-)	EC (Elemental Carbon)	
Thoracic coarse PM (e.g., $PM_{10-2.5}$)	Transition metals (e.g., Cd, Cu, Fe, Ni, Mn, Zn)	COH (Coefficient of Haze)	Fuel oil combustion (Ni, V)
Fine PM (e.g., $PM_{2.5}$)		OC (Organic Carbon)	Coal burning (Se)
Ultrafine PM ($PM_{0.1}$)	Other toxic metals (e.g., Pb)	CX (Cyclohexene-extractable Carbon)	Sulfate or regional sulfate (S)
Particle number	Strong Acid (H^+)	Organic PM compounds	Industrial (Zn, Cd)

[1] Components measured in $PM_{2.5}$ unless otherwise specified.
[2] Organic PM compounds extracted by three techniques.
[3] Source: Laden et al. (2000); reanalyzed in Schwartz et al. (2003); Mar et al. (2000, 2003); Tsai et al. (2000).

more precisely particles associated with vehicular traffic, stand out clearly as a source category associated with mortality in all three studies that used this approach[2]. A regional sulfate source category was also identified as being associated with mortality in all three studies (although regional sulfate may be acting as a surrogate for $PM_{2.5}$, given the high correlation between the two); however, particles of crustal origin in $PM_{2.5}$ were not significantly associated with mortality. Also, associations were reported with an oil combustion factor and a source category related to vegetative burning. These studies suggest that many different chemical components of fine particles and a variety of different types of source categories are all associated with, and probably contribute to, mortality, either independently or in combinations.

[2] Multivariate techniques such as factor analyses and principal component analyses were used with speciation data to determine PM contributions from source categories (Section 8.2.2.5.3, Table 8-4). For example, factors used as indicators of particles from motor vehicle emissions in studies using older air quality data were Pb (Laden et al., 2000; Schwartz et al., 2003) or Pb and CO (Tsai et al., 2000), but in a study with more recent air quality data, the source category included several metals, OC, EC, CO and NO_2 (Mar et al., 2000, 2003).

One key research question that has not been addressed in epidemiologic studies is the relationship between sources or composition of thoracic coarse particles and health outcomes. The studies described above used source apportionment based on components of fine particles or PM_{15} in an area dominated by fine particles. Some limited information is available from air quality analyses that may help inform the assessment of epidemiological evidence for thoracic coarse fraction particles; however, no studies are available to indicate potential differences in thoracic coarse particle composition in relation to morbidity (for which there appears to be more epidemiologic evidence suggesting coarse particle effects). As summarized in Chapter 3, crustal material is an important contributor to thoracic coarse particles. Based on studies described above, crustal components of $PM_{2.5}$ have not been found to be important contributors to associations with mortality, although it is possible that particles of crustal origin may contribute to morbidity. Thoracic coarse fraction particles also include substantial contributions from metals and biological constituents, both of which may be linked to adverse health outcomes.

In summary, considering results from studies conducted both within and outside the U.S. and Canada, the epidemiological evidence is strong for associations between PM_{10} and $PM_{2.5}$ and mortality, especially for total and cardiovascular mortality. The magnitudes of the associations are relatively small, especially for the multicity studies. However, there is a pattern of positive and often statistically significant associations across studies for cardiovascular and respiratory health outcomes, including mortality and hospitalization and medical visits for cardiovascular and respiratory diseases, with PM_{10} and $PM_{2.5}$. The few available $PM_{10-2.5}$ studies also provide some evidence for associations between hospitalization for cardiovascular and respiratory diseases with $PM_{10-2.5}$. $PM_{10-2.5}$-hospitalization effect estimates were similar in magnitude to those for PM_{10} and $PM_{2.5}$, but with less precision. For $PM_{10-2.5}$, the evidence for associations with mortality is more limited; the magnitude of the effect estimates is very similar to those for $PM_{2.5}$ and PM_{10}, but in terms of precision, the evidence is not as strong. While there is some new epidemiological evidence suggesting possible associations between health outcomes and ultrafine particles and other fine particle components and sources, the data are as yet too sparse to characterize the relative toxicities of these various components or indicators of fine particles for different health outcomes.

9.2.2.1.2 Long-Term Exposure Studies

In the 1996 PM AQCD, results of prospective cohort studies linked long-term exposure to fine particles and mortality, and there was limited evidence indicating that long-term PM exposure was linked with chronic respiratory morbidity, such as the development of bronchitis. More recent long-term exposure studies have built upon these findings and provide further evidence for associations with both mortality and respiratory morbidity.

A series of analyses using data from the ACS cohort have shown significant associations of total and cardiopulmonary mortality with fine particles or sulfates, and the most recent analyses have also reported significant associations with lung cancer mortality. The Six Cities study found significant associations of total and cardiopulmonary (but not lung cancer) mortality with $PM_{2.5}$, but not with coarse particle indicators. The results most recently reported for the Adventist Health Study on Smog (AHSMOG), reported some significant associations between PM_{10} and total mortality and deaths with contributing respiratory causes. In further investigation of the results found for PM_{10} among males, the associations with $PM_{2.5}$ had larger effect estimates than those for $PM_{10-2.5}$ for males in the AHSMOG cohort, although none reached statistical significance. For the VA study, indices of long-term exposures to PM_{10}, $PM_{2.5}$, or $PM_{10-2.5}$ were not associated with mortality.

Based on several factors – the larger study population in the ACS study, better characterization of exposure in the Six Cities study, the more generally representative study populations used in the Six Cities and ACS studies, and the fact that these studies have undergone extensive reanalyses – the greatest weight is placed here on the results of the ACS and Six Cities cohort studies in assessing relationships between long-term $PM_{2.5}$ exposure and mortality. The results of these studies, including the reanalyses results for the Six Cities and ACS studies and the results of the ACS study extension, provide substantial evidence for positive associations between long-term ambient (especially fine) PM exposure and mortality.

For morbidity, results of studies in a cohort of children in Southern California have built upon the limited evidence available in 1996 PM AQCD to indicate that long-term exposure to fine particles is associated with development of chronic respiratory disease and reduced lung function growth. Long-term exposure to $PM_{2.5}$ was associated with significant decreases in lung function growth among a cohort of Southern California school children, but the earlier

cross-sectional analysis for the same cohort found no relationship between respiratory symptoms and annual average PM_{10} levels. These findings support the results of the cross-sectional study in 24 U.S. and Canadian cities from the1996 PM AQCD, in which long-term PM exposure was associated with some effects on respiratory function changes and respiratory illness.

As was true in the 1996 PM AQCD, it is more difficult to assess strength of evidence for long-term exposure studies, since there are fewer studies available. For mortality, reanalyses and extended analyses of cohort studies provide strong evidence for the link between mortality and long-term exposure to fine particles; however, the available studies have provided no evidence for associations between long-term exposure to coarse fraction particles and mortality. In addition, prospective cohort and cross-sectional analyses have reported associations between respiratory morbidity and PM_{10}, and sometimes also $PM_{2.5}$, providing fairly strong evidence for effects of long-term fine particle exposures on respiratory morbidity. The morbidity studies have not generally included $PM_{10-2.5}$ data; so no conclusions can be drawn regarding long-term exposure to coarse fraction particles and morbidity. Nor can any conclusions yet be drawn regarding possible effects of long-term exposures to ultrafine particles, given the lack of relevant data.

9.2.2.2 Robustness of Epidemiologic Associations

Many epidemiologic studies have also included assessment of whether the associations were robust to such factors as model specification and potential confounding by co-pollutants. Another factor that is relevant to robustness of epidemiologic findings is exposure error. Chapter 8 includes detailed discussions on each of these topics, and the following discussion focuses on the extent to which the current epidemiologic findings can be considered robust.

9.2.2.2.1 Model Specification

The 1996 PM AQCD included considerable discussion of issues regarding model specification for time-series epidemiologic studies, including results of reanalyses using several data sets, with a special focus on the large data set available from Philadelphia, PA. In this set of reanalyses, results reported with the use of alternative modeling strategies were not substantially different from the original investigators' findings. Also, at the time of completion of the 1996

PM AQCD, it appeared that issues related to model specifications used to control for weather effects in daily time-series analyses of ambient PM relationships to mortality/morbidity had largely been resolved. Based on two major studies extensively evaluating a number of different approaches to adjust for weather effects (including evaluations using synoptic weather patterns), it was concluded that significant PM-mortality associations were robust and verifiable via a variety of model specifications controlling for weather.

More recently, the influence of using default parameters and too low a standard error in a widely used software package for GAM on epidemiologic study results has been investigated and, in this process, the question of appropriate adjustment for weather, temporal trends, and other covariates in time-series models was reopened. Numerous study findings were reanalyzed to test the effect of using more stringent convergence criteria in the GAM program, as well as alternative modeling methods such as GLM while provide correct standard errors. The results from the GAM reanalysis studies indicate that PM risk estimates from GAM models were often, but not always, reduced when more stringent convergence criteria were used, although the extent of the reduction was not substantial in most cases. Also, the extent of downward bias in standard errors reported for these data (a few percent to ~15%) appears not to be very substantial, especially when compared to the range of standard errors across studies due to differences in population size and numbers of observation days available.

Thus, as stated in the HEI reanalysis report (Health Effects Institute, 2003), revised analyses using GAM with more stringent convergence criteria or GLM with natural splines and the use of alternative modeling strategies tended to reduce the PM effect estimate size for all PM indices, but did not change the overall findings and qualitative conclusions of epidemiologic studies showing associations between PM and both mortality and morbidity. In general, PM effect estimates were more sensitive to different controls for time-varying (e.g., weather or seasonal) effects. In some studies, with use of different methods or degrees of control for temporal variables, PM effects estimates were largely unchanged, whereas in several other studies the changes were enough to alter study conclusions. While it is clear that there will not be one "correct" model or approach for covariate adjustment, further research can help inform modeling strategies to adjust for temporal trends and weather variables in time-series epidemiology studies.

9.2.2.2.2 Assessment of Confounding by Co-Pollutants

Airborne particles are found among a complex mixture of atmospheric pollutants, only some of which are widely measured (e.g., gaseous criteria co-pollutants O_3, CO, NO_2, SO_2). Because many of the pollutants are closely correlated due to emission by common sources and dispersion by common meteorological factors, and some are in the pathway of formation of other pollutants (e.g., NO → NO_2 → HNO_3 → particulate nitrates), it is generally difficult to disentangle their effects. In addition, as described in Section 8.1.3.2, co-pollutants could possibly act as effect modifiers; for example, exposure to one pollutant could result in greater sensitivity to another pollutant. Potential effect modification between pollutants has been investigated in some toxicological or controlled human exposure studies (Section 7.9.3), but little evidence is available from epidemiologic studies to characterize any such effects.

The potential for co-pollutant confounding in the epidemiologic time-series studies was assessed in some detail in Section 8.4.3. Multipollutant modeling is the most common method used to test for potential confounding in epidemiologic studies; however, interpretation of the results of multipollutant models is complicated by the correlations that often exist between air pollutants. In interpreting the results of any of these studies, it is important to consider factors such as the biological plausibility of associations between the pollutants and health outcomes, as well as questions related to model specification and exposure error. For example, some new studies described in Section 5.3.3.4 have reported that ambient $PM_{2.5}$ concentrations are well correlated with personal $PM_{2.5}$ exposure measurements; in contrast, that is generally not the case for O_3, SO_2, and NO_2 .

Multipollutant modeling results for associations of a range of health outcomes with PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ and gaseous pollutants in single-city studies are presented in Section 8.4.3 (Figures 8-16 through 8-19). For most studies, there was little change in coefficients for all three indices between single-pollutant and multipollutant models; however, in some cases, the PM effect estimate was markedly reduced in size and lost statistical significance in models that included one or more gaseous pollutants. Key results are also available from the NMMAPS evaluation of associations across many U.S. cities with varying climates and mixes of pollutants; the NMMAPS associations between PM_{10} and both mortality and morbidity were not changed with adjustment for gaseous pollutant concentrations. Thus, for the most part, effect estimates

for the three PM indices were not substantially changed when gaseous co-pollutants were included in the models. Often, PM and the gaseous co-pollutants were highly correlated, especially for fine particles and CO, SO_2 and NO_2, and it was generally the case that high correlations existed between pollutants where PM effect estimates were reduced in size with the inclusion of gaseous co-pollutants.

In the prospective cohort and cross-sectional studies, the potential for confounding by co-pollutants has been assessed in some studies of mortality, but little studied for morbidity. The reanalysis of data from the ACS cohort indicated that the relationships with fine particles and sulfates were reduced in size in co-pollutant models including SO_2, but not the other gaseous pollutants. SO_2 is a precursor for fine particle sulfates, thus complicating the interpretation of multipollutant models (i.e., making it difficult to distinguish effects due to fine particles or to SO_2 for this study). The authors concluded that their results suggested that mortality may be associated with more than one component of the ambient air pollutant mix and that there were robust associations of mortality with fine particles and sulfates.

In summary, ambient PM exposure usually is accompanied by exposure to many other pollutants, and PM itself is composed of numerous physical/chemical components. Assessment of the health outcomes attributable to ambient PM and its constituents within an already subtle total air pollution effect is, therefore, very challenging, even with well-designed studies. Indeed, statistical partitioning of separate pollutant effects is not likely to characterize fully the effects that actually depend on simultaneous exposure to multiple air pollutants. Overall, the newly available epidemiologic evidence, especially for the more numerous time-series studies, substantiates that associations for various PM indices with mortality or morbidity are robust to confounding by co-pollutants.

9.2.2.2.3 Exposure Error

Numerous analyses of the potential influence of measurement error on time-series epidemiologic study results are discussed in Section 8.4.5. One consideration in comparing epidemiologic findings for different pollutants is the relative precision with which the pollutants are measured. If two pollutants have effects and there is correlation between both the pollutants, the effect estimate of the pollutant that is less precisely measured may be attenuated when the

pollutants are considered in a model together. One would expect that $PM_{2.5}$, CO, and NO_2 would often have a high positive correlation due to common activity patterns, weather, and source emissions. $PM_{10-2.5}$ is generally less precisely measured than $PM_{2.5}$, but the two are not generally highly correlated. Several recent studies have focused on this question, and reported that for most situations, it is unlikely that differential measurement error would result in shifting apparent effects from one pollutant to another. The most extreme case, complete transfer of apparently causal effects from one pollutant to another, required very high correlation between the covariates, no error in measurement of the "false" covariate and moderate error in measurement of the "true" predictor. The results of these analyses indicate that it is unlikely that effects attributed to PM (generally focusing on PM_{10} or $PM_{2.5}$) are falsely transferred from other less-precisely measured pollutants.

Another facet of exposure error is the degree to which the measurements made at community monitoring sites reflect population exposures to ambient PM. As discussed in Section 5.2, further analysis of the PTEAM study has shown that ambient PM_{10} concentrations were well correlated with temporal changes in personal exposures to ambient PM_{10}. However, it should be noted that (a) the spatial variability across a city is generally much greater for $PM_{10-2.5}$ than for $PM_{2.5}$ and (b) there may still be substantial variability in $PM_{2.5}$ concentrations across some urban areas, as discussed in Chapter 3. In addition, the infiltration factors for $PM_{10-2.5}$ and a number of gases (e.g., O_3, SO_2) are lower and more variable than that of $PM_{2.5}$, likely leading to a lower correlation between ambient concentration (used as an exposure surrogate in community time-series studies) and personal exposure to the ambient pollutant for $PM_{10-2.5}$ and these gases. Also, studies which included subjects limited to those living near the air monitoring site (and, therefore, presumably have lower exposure error due to spatial heterogeneity of $PM_{2.5}$ concentrations) tend to yield higher effect estimates. Thus, exposure studies indicate that particle measurements at central monitoring sites are better indicators of personal exposures to ambient $PM_{2.5}$ than $PM_{10-2.5}$ for time-series studies. Exposure relationships for $PM_{10-2.5}$ have been less well studied, but exposure error and measurement error would be expected to have greater influence for associations with $PM_{10-2.5}$ than for $PM_{2.5}$; this likely contributes to larger confidence intervals around $PM_{10-2.5}$ effect estimates.

9.2.2.3 Consistency of Findings Across Epidemiologic Studies

In the 1996 PM AQCD, it was observed that PM was associated with mortality and morbidity in studies conducted in numerous locations in the United States as well as in other countries. The expanded body of studies available in this review includes studies conducted in a wider range of locations; as described above, many of those studies, especially those with greater statistical power, report statistically significant associations. Magnitudes and significance levels of observed air pollution-related effects estimates would be expected to vary somewhat from place to place, if the observed epidemiologic associations denote actual effects, because (a) not only would the complex mixture of PM vary from place to place, but also (b) affected populations may differ in characteristics that increase susceptibility to air pollution health effects, and (c) areas may differ in factors that affect population exposures to ambient pollutants.

Multicity studies conducted in the United States, Canada, and Europe have included quantitative assessments of heterogeneity in PM effect estimates. The city-specific and regional PM_{10}-mortality associations presented in NMMAPS results suggested greater variability in effect estimates than had been observed in the studies available in the 1996 PM AQCD. However, statistical analyses indicated that there was no significant heterogeneity in mortality effect estimates for 90 U.S. cities (Samet et al., 2000; Dominici et al., 2003). For eight Canadian cities, no evidence of heterogeneity was reported in the initial analysis, but in reanalysis to address GAM issues, there appeared to be greater heterogeneity in the PM-mortality associations (Burnett and Goldberg, 2003). Finally, initial analyses of mortality associations for 29 European cities indicated differences between eastern and western cities, but these differences were less clear with reanalysis to address GAM questions (Katsouyanni et al., 2003).

There are a number of reasons to expect variation in PM-health outcome associations for different geographic regions. Regional differences can include differences in PM sources or composition, differences in population exposures, and differences in potentially susceptible groups. In the European multicity study, APHEA, PM-mortality associations were found to be larger in areas with higher average NO_2 levels (considered an indicator of traffic pollution), and warmer climates (possibly due to more open windows resulting in better exposure estimation). In NMMAPS, no apparent associations were found between PM-mortality associations and

either/or $PM_{2.5}/PM_{10}$ ratios or socioeconomic indicators, but there was also no statistically significant measure of heterogeneity in this study. However, for hospital admissions in the NMMAPS, the PM_{10} admissions associations were greater in areas with less use of central air conditioning (possibly an indicator of increased exposure to ambient pollutants) and with larger contributions of PM_{10} emissions from vehicle emissions and oil combustion.

Variability in PM concentrations across study areas could influence epidemiologic study results. For larger metropolitan areas, including monitors in outlying areas may bias the exposure estimate and reduce the correlation between the averaged concentration and the true population exposure. From among those U.S. cities in which epidemiological studies have been conducted, areas with more uniformity in $PM_{2.5}$ concentrations include Chicago and Detroit, whereas areas with more spatial variability include Seattle and Los Angeles. There are a number of factors that could influence spatial variability of PM concentrations, including topography, location of major PM sources, and weather patterns. Greater spatial variability in PM levels would be expected to increase exposure error, potentially affecting epidemiologic study results in those areas.

One factor unrelated to geographic location that would likely affect the consistency of results across studies is the amount of data available for analysis. For time-series studies, the number of days with measurements is one important indicator of study size, or statistical power. In Figure 9-4, the PM-mortality associations are plotted in order of decreasing statistical power, using the product of daily death rate and number of PM measurement days as the indicator. For single-city mortality studies, the number of PM measurement days ranges from about 150 (Tsai et al., 2000) to over 2,000 days (e.g., Ito and Thurston, 1996). Multicity studies included ranges of about 500 to 900 days for eight Canadian cities (Burnett and Goldberg, 2003), about 200 to 3,000 days for 90 U.S. cities (Dominici et al., 2003), and 1,500 to 3,000 days for 10 U.S. cities (Schwartz, 2003). For several studies, more data are available for PM_{10} than for $PM_{2.5}$ or $PM_{10-2.5}$; Fairley (2003), as an example, used a data set with approximately 800 days of PM_{10} measurements and 400 days for $PM_{2.5}$ and $PM_{10-2.5}$. In the 1996 PM AQCD, studies conducted in the United States had about 300 to 4,000 days of PM measurements, and a clear correlation between t-ratio and number of monitoring days could be seen (Figure 12-17, Table 12-25).

Similarly, Figures 9-4 and 9-5 show a tendency for larger studies to have more consistent effect estimates that are more likely statistically significant. A number of the newer studies, however, particularly those using $PM_{2.5}$ and $PM_{10-2.5}$ data, are somewhat smaller in size than those available in the 1996 PM AQCD. This would be expected to result in decreased precision and more variability in effect estimate size for the smaller studies.

In addition, while many single-city epidemiologic studies have used availability of everyday monitoring data as a criterion for selecting study locations, a number of the newer studies have used $PM_{2.5}$ and $PM_{10-2.5}$ data measured every sixth day. Beyond limiting the number of days of data available, the use of 1-in-6 day data may also complicate time-series analyses. As discussed in Section 8.4.5.2, one analysis of data from Chicago first used data from an everyday monitor and then six 1-in-6 day data sets were created from the same data. Whereas the resulting analysis using all the daily data showed clearly statistically significant positive PM_{10}-mortality associations, the results for the analyses using 1-in-6 day data sets were quite inconsistent. Hence, the use of air quality data with many missing days adds uncertainty to results for PM-health outcome associations.

Thus, there are numerous reasons to expect study results to vary across cities, based on different topographies, distribution of sources or emissions, mixes of pollutants, and population characteristics. The new multicity studies have provided some initial evidence for some of these factors that may affect the magnitude or significance of PM-health associations. Effect estimates reported for sets of studies of the same location generally fall well within the range of the confidence intervals of all studies. With multicity studies, statistical tests for heterogeneity among effect estimates have been conducted with inconsistent findings. It seems likely that some apparent variation in effect estimate size is simply statistical variability, while factors such as differential exposures based on housing characteristics or population characteristics may contribute to real variations in effects between locations. Overall, the epidemiological studies indicate that, in numerous locations across the United States, there are associations between PM_{10} and $PM_{2.5}$ and mortality from cardiorespiratory diseases and between PM_{10}, $PM_{2.5}$ and $PM_{10-2.5}$ and hospitalization for respiratory or cardiovascular causes.

9.2.2.4 Temporality and the Question of Lags

As discussed in Section 8.4.4, differing lag periods are likely appropriate for different health outcome-pollutant associations. For example, the time-series studies of cardiovascular hospital admissions or emergency department visits suggest that PM effects for all PM indices are stronger with same day PM concentrations, with some effects also linked with PM from the previous day. In a few studies of cardiac physiological changes, the strongest associations were reported for some outcomes with 1- to 2-hour lag periods, indicating that for certain health outcomes very short-term fluctuations in pollution are most important. In panel studies of respiratory symptoms and in several studies of asthma hospitalization or emergency department visits, longer moving average lag periods (up to 5- to 7-day moving averages) yielded larger PM effect estimates, suggesting that these health responses may have a longer and more extended latency period than indicated by single day lag analyses.

Where results are presented for a series of lag days, it is important to consider the pattern of results that is seen across the series of lag periods. When there is a pattern of effects across lag periods, selecting any one of the single-day lag effect estimates is likely to underestimate the overall effect size, since the largest single-lag day results do not fully capture the risk also distributed over adjacent days. Even if there is a jumbled pattern of results across the different lags, then the single-day lag with the largest effect is likely biased low. In these cases, a distributed lag model should more correctly capture the effect size.

Studies of long-term exposure have included less evaluation of temporal relationships between PM exposure and health outcome. The prospective cohort studies have used air quality measurements made over a period of years as an indicator of long-term exposure to air pollution. The associations reported in these studies are for relationships with PM across various levels of exposure, not as a measure of latency of effect. However, some new studies have included some assessment of temporal relationships between PM exposure and mortality. In the reanalysis of the Six City Study, the decline in fine particle levels over the monitoring period was included as a time-dependent variable, to assess the effect of changing PM concentrations over time on the association with mortality. The association between total mortality and fine particles was reduced in size, though still statistically significant, as compared with the model not allowing for

temporal change in pollution level. This is likely indicative of the effectiveness of control measures in reducing source emissions importantly contributing to the toxicity of ambient particles in cities where PM levels were substantially decreased over time.

The VA study analysis tested associations between different subsets of long-term exposure to pollution and mortality data. While the associations found between PM (PM_{10}, $PM_{2.5}$, and coarse fraction particles) and mortality varied and were often negative and generally not statistically significant, it was observed that the associations were larger and more likely to be statistically significant with the air quality data from the earliest time periods, as well as the average across all data. Further study is needed to evaluate the relationship between health outcomes and long-term PM exposure where PM concentrations are changing over time.

In summary, for time-series studies, it is likely that the most appropriate lag period for a study will vary depending on the health outcome and the specific pollutant under study. Where effects are found for a series of lag periods, the effect estimate for any one lag period will likely underestimate the effect size and a distributed lag model will more accurately characterize the effect estimate size. Caution should be used in selecting results for single lag periods if the pattern of results across lag periods is highly variable. For effects associated with chronic exposure, less is known about the importance of different time windows for exposure, and some recent studies indicate that further investigation is needed.

9.2.2.5 Concentration-Response Relationships

In the 1996 PM AQCD, the limitations of identifying possible "thresholds" in the concentration-response relationships in observational studies were discussed. It was observed that detection of threshold levels in population-based epidemiological studies would be very difficult on several bases, including difficulties related to the low data density in the lower PM concentration range, the small number of quantile indicators often used, and the possible influence of measurement error. Few studies had quantitatively assessed the form of PM-effect concentration-response functions and the potential for a threshold level.

A threshold for a population, as opposed to a threshold for an individual, has some conceptual issues that should be noted. For example, since individual thresholds vary from

person to person due to individual differences in genetic-level susceptibility and pre-existing disease conditions (and even can vary from one time to another for a given person), it is extremely difficult mathematically to demonstrate convincingly that a clear threshold exists in the population studies. This is especially true if the most sensitive members of a population are unusually sensitive even down to very low concentrations. The person-to-person difference in the relationship between personal exposure to PM of ambient origin and the concentration observed at a monitor may also add to the variability in observed exposure-response relationships, possibly obscuring otherwise more evident thresholds. Since one cannot directly measure but can only compute or estimate a population threshold, it would be difficult to interpret an observed population threshold biologically, without pertinent collateral dosimetric/toxicologic information.

Recognizing these difficulties, several epidemiologic studies have evaluated potential thresholds in time-series mortality analyses. Analyses using NMMAPS data for 90 U.S. cities showed that, for total and cardiorespiratory mortality, it was difficult to discern any threshold level for PM_{10}, with statistical tests indicating that a linear concentration-response model was preferred over the spline and the threshold models. In this study, the likelihood of a threshold occurring above 24-h PM_{10} levels of ~25 $\mu g/m^3$ seems to be essentially zero (see Figure 8-31); but there was increasing probability of a threshold occurring at levels below 25 $\mu g/m^3$. In some single-city analyses, there were indications of potential population thresholds for associations between mortality and 24-h PM_{10} in the range of 80 $\mu g/m^3$ to 100 $\mu g/m^3$ and, with 24-h $PM_{2.5}$, in the range of 20-25 $\mu g/m^3$. However, other single-city analyses reported no evidence of a threshold for PM-mortality associations for PM_{10}, $PM_{2.5}$ or $PM_{10-2.5}$. One group of researchers who did not find evidence for thresholds in the PM_{10}-mortality relationship using various statistical methods observed it to be "highly likely" that the statistical methods could detect a threshold if a threshold existed in this population-based study.

In summary, the available evidence does not either support or refute the existence of thresholds for the effects of PM on mortality across the range of concentrations in the studies. In the multicity and most single-city studies, statistical tests comparing linear and various nonlinear or threshold models have not shown statistically significant distinctions between them.

Where potential threshold levels have been suggested in single-city studies, they are at fairly low levels. In epidemiological analyses of complex health endpoints (such as total nonaccidental mortality) in populations where individuals differ in susceptibility and exposures, it is likely to be extremely difficult to detect threshold levels. Also, it must be recognized that dose-response relationships observed for one or another PM indicator (e.g., PM_{10}) do not necessarily apply to other PM indicators (e.g., $PM_{2.5}$ or $PM_{10-2.5}$).

9.2.2.6 Natural Experiment Studies

Although many studies have reported short-term associations between PM indices and mortality, a largely unaddressed question remains as to the extent to which reductions in ambient PM actually lead to reductions in health effects attributable to PM. This question is not only important in terms of "accountability" from the regulatory point of view, but it is also a scientific question that challenges the predictive validity of statistical models and their underlying assumptions used thus far to estimate excess mortality due to ambient PM.

The opportunities to address this question are rare. However, at the time of the 1996 PM AQCD, results were available from epidemiologic studies of a "natural" or "found experiment" in the Utah Valley, where respiratory hospital admissions were found to decrease during the time a major PM source was closed. Newly available controlled human exposure and animal toxicology studies, using particle extracts from ambient community PM_{10} sampling filters from the Utah Valley, have also shown reduced effects with exposure to extracts of particles collected during the time period when the source was not operating. A recent epidemiologic study in Dublin, Ireland also provides evidence for reductions in ambient PM (measured as British smoke) being associated with reductions in mortality rates. Other "found experiments" also provide evidence for decreases in mortality and/or morbidity being associated with notable declines in different indices of PM (and/or gases such as SO_2) as the result of interventions aimed at reducing air pollution.

By providing evidence for improvement in community health following reduction in air pollutant emissions, these studies add further support to the results of the hundreds of other epidemiologic studies linking ambient PM exposure to an array of health effects. Such studies showing improvements in health with reductions in emissions of ambient PM and/or gaseous

co-pollutants provide strong evidence that reducing emissions of PM and gaseous pollutants has beneficial public health impacts.

9.2.2.7 Summary and Conclusions

Epidemiological evidence can help to inform judgments about causality. The present discussion evaluated the epidemiologic evidence in relation to the first five criteria listed in the beginning of Section 9.2, including key considerations with regard to criteria such as the strength (magnitude, precision) and robustness of reported associations. Information related to last of the six criteria (coherence and biological plausibility of the evidence) is discussed in the following section.

Overall, there is strong epidemiological evidence linking (a) short-term (hours, days) exposures to $PM_{2.5}$ with cardiovascular and respiratory mortality and morbidity, and (b) long-term (years, decades) $PM_{2.5}$ exposure with cardiovascular and lung cancer mortality and respiratory morbidity. The associations between $PM_{2.5}$ and these various health endpoints are positive and often statistically significant. There are fewer studies available for $PM_{10-2.5}$ and the magnitude of the effect estimates for associations with mortality and morbidity effects (especially respiratory morbidity) is similar to that for $PM_{2.5}$, but the lesser precision reduces the strength of the evidence for $PM_{10-2.5}$ effects. Little evidence is available to allow conclusions to be drawn about long-term $PM_{10-2.5}$ exposures and morbidity. There is also extensive and convincing evidence for associations between short-term exposures to PM_{10} and both mortality and morbidity, as was reported in the previous review.

With regard to the robustness of the associations, research questions remain on modeling issues with time-varying variables, but extensive reanalyses conducted for both time-series and prospective cohort studies provide further support for the results of the original analyses. Recent reanalyses of a number of time-series studies found that results were little changed with adjustments to deal with GAM-related issues, but some results were sensitive to different adjustment for time-varying factors such as weather. However, the recent studies, using a variety of approaches to control for weather effects, still appear to demonstrate increased PM-related mortality and morbidity risks beyond those attributable to weather influences alone.

Much progress has been made in sorting out contributions of ambient PM_{10} and its components to observed health effects relative to other co-pollutants. Despite continuing uncertainties, the evidence overall tends to support the above conclusions that ambient PM_{10} and $PM_{2.5}$ are most clearly associated with mortality/morbidity effects, acting either alone or in combination with other covarying gaseous pollutants, with more limited support being available with regard to $PM_{10-2.5}$. Likely contributing to this is the fact that greater measurement error associated with exposure estimates for a given pollutant or indicator will result in less precise effect size estimates that are less robust in multipollutant models. Of importance here, directly measured PM_{10} and $PM_{2.5}$ values likely have less measurement error than $PM_{10-2.5}$ values derived by subtracting $PM_{2.5}$ values from PM_{10} concentrations, especially if obtained from non-collocated PM_{10} and $PM_{2.5}$ monitors at different locations in a given urban area. Thus, the current paucity of statistical significance for a pattern of positive associations with $PM_{10-2.5}$ may reflect measurement imprecision, not necessarily lack of effects.

Focusing on the studies with the most precision, it can be concluded that there is much consistency in epidemiological evidence regarding associations between short-term and long-term exposures to fine particles and cardiopulmonary mortality and morbidity. For coarse fraction particles, there is also some consistency in effect estimates for hospitalization for cardiovascular and respiratory causes based on the few studies available for several locations across the United States. Some variability in effect estimate size can be seen across locations, especially in the recent multicity studies. Factors likely contributing to this variability include geographic differences in air pollution mixtures, composition of ambient PM components, and personal and sociodemographic factors potentially affecting PM exposure (e.g., use of air conditioning), as well as differences in PM mass concentration.

Temporality, or the occurrence of the health outcome following the exposure, has been found to hold well for the time-series epidemiological studies. The length of the lag period for exposure and effect varies for different health outcomes, with short acute exposures of an hour or more seemingly more important for some cardiovascular health endpoints and longer average exposures or distributed lag exposure windows being more closely associated with other health endpoints. For long-term exposures, the existing studies generally use spatial variation in

concentrations to estimate exposure changes, thus temporality is not directly tested, but some new evidence suggests that changes in pollutant mix over time may influence relationships with health effects.

In conclusion, the epidemiological evidence continues to support likely causal associations between $PM_{2.5}$ and PM_{10} and both mortality and morbidity from cardiovascular and respiratory diseases, based on an assessment of strength, robustness, and consistency in results. For $PM_{10-2.5}$, less evidence is available, but the studies using short-term exposures have reported results that are of the same magnitude as those for PM_{10} and $PM_{2.5}$, though less often statistically significant and thus having less strength, and the associations are generally robust to alternative modeling strategies or consideration of potential confounding by co-pollutants. This evidence is suggestive of associations for morbidity with short-term changes in $PM_{10-2.5}$. Epidemiologic studies suggest no evidence for clear thresholds in PM-mortality relationships within the range of ambient PM concentrations observed in these studies. Important new results from source apportionment studies and found experiments indicating that reductions in PM and other air pollutants result in improvements in community health lend support to the results of the other epidemiological studies.

9.2.3 Integration of Experimental and Epidemiologic Evidence

In more broadly assessing the extent to which the overall body of evidence supports the attribution of observed health effects to exposure to fine and coarse thoracic PM and related chemical constituents, one needs to look beyond just epidemiologic evidence to consider the implications of newly available dosimetric, toxicologic, and other evidence as well. More specifically, the following assessment (a) evaluates information pertaining to the biological plausibility of the types of health outcome associations observed in the epidemiologic studies, taking into account toxicologic findings and potential mechanisms of action; and (b) considers information about the coherence of the overall body of evidence relevant to PM-related health outcomes supporting conclusions regarding attribution of observed effects to ambient fine or coarse thoracic PM and related chemical constituents, acting alone and/or in combination with other pollutants.

The 1996 PM AQCD highlighted several key findings and conclusions concerning attribution of observed health outcomes to specific ambient PM size fractions or chemical compounds:

- "The likelihood of ambient fine mode particles being significant contributors to PM-related mortality and morbidity among [the] elderly population is bolstered by: (1) the more uniform distribution of fine particles across urban areas. . . ; (2) the penetration of ambient particles to indoor environments. . . ; and (3) the longer residence time of ambient fine particles in indoor air, enhancing the probability of indoor exposure to ambient fine particles more so than for indoor exposure to ambient coarse particles."

- The PM indices that have been "most consistently associated with health endpoints are fine particles (indexed by BS, COH, and $PM_{2.5}$), inhalable particles (PM_{10} or PM_{15}), and sulfate ($S0_4^=$)," whereas "[l]ess consistent relationships have been observed for TSP, strong acidity (H^+), and coarse PM ($PM_{10-2.5}$). . . . [and] none of these indices can completely be ruled out as a biologically relevant indicator of PM exposure."

- "Based on current evidence from epidemiologic, controlled human, human occupational, and laboratory animal studies, no conclusions can be reached regarding the specific chemical components of PM_{10} that may have the strongest biologic activity." Further, none of the various subclasses of PM [e.g., acid aerosols, bioaerosols, metals (including transition metals), and insoluble ultrafine particles] that have been considered "can be specifically implicated as the sole or even primary cause of specific morbidity and mortality effects." (U.S. Environmental Protection Agency, 1996, p. 13-93)

Hence, although at the time of the 1996 PM AQCD, the epidemiologic evidence was viewed as substantiating well PM_{10} or $PM_{2.5}$ associations with human mortality and morbidity, uncertainties remained with regard to (a) the contribution of specific PM constituents to PM toxicity and (b) the biological plausibility of the reported effects and/or the mechanisms of action underlying them.

Since the 1996 PM AQCD evaluations, progress has been made in (1) further substantiating and expanding epidemiologic findings indicative of ambient PM-health effect associations, (2) identifying possible constituents contributing to observed effects, and (3) obtaining evidence bearing on the biological plausibility of observed effects and possible mechanisms of action involved. Efforts to interpret the overall meaning of the epidemiologic findings and to evaluate their biological plausibility and pertinent mechanisms of action are

complicated by the fact that ambient PM exists as a component of a complex air pollution mixture that includes gaseous air pollutants. This section addresses these complexities by considering the extent of coherence observed among findings reported for specific PM components identified in epidemiologic studies for specific health outcome categories (cardiovascular; respiratory; lung cancer; fetal and infant development/mortality) and related toxicologic links to biologic changes observed in controlled exposure human, animal, and in vitro studies. Hypothesized potential mechanisms of actions and other supporting pieces of evidence are also summarized.

As discussed at the outset of Section 9.2, several criteria were listed as useful in evaluating scientific evidence as supporting conclusions regarding potential causal relationships between two variables. In addition to those criteria addressed in the preceding discussion of PM-related epidemiologic evidence, it is important to take into account still other information or criteria which combine consideration of biological plausibility and coherence, so as to help ensure: "that a proposed causal relationship not violate known scientific principles, and that it be consistent with experimentally demonstrated biologic mechanisms and other relevant data. . . ."

For the purposes of this assessment: the ensuing discussion of plausibility and coherence considers both: (a) the extent to which the available epidemiologic evidence (of adequate power) shows associations in the same location (urban area) with a range of logically linked health endpoints (i.e., endpoints within a "pyramid of effects" ranging from the most severe outcome, mortality, to physiological changes in the cardiovascular or respiratory systems, e.g., altered fibrinogen levels or lung function changes); and (b) the extent to which the available toxicologic evidence and mechanistic information provide support for the plausibility of the array of observed epidemiologic associations likely reflecting causal relationships.

Before embarking on the plausibility and coherence discussions in Section 9.2.3.2 for each of several health endpoints (cardiovascular, respiratory, etc.) evaluated as likely being impacted by ambient PM, the next section first provides important background information on three cross-cutting issues that help to place the ensuing discussions in context.

9.2.3.1 Background on Cross-Cutting Issues

Background information on several cross-cutting issues is provided here to help place the ensuing discussions in perspective. First, important considerations related to strengths and weaknesses of experimental approaches used to study PM health effects are summarized along with relevant caveats. Next, interspecies dosimetric comparisons are discussed and representative examples are provided for extrapolation of PM exposure/doses between rats and humans. Lastly, information on inhaled particles as carriers of other toxic agents and consequent potential implications are discussed.

9.2.3.1.1 Approaches to Experimental Evaluation of PM Health Effects

As discussed in Chapter 7, various experimental approaches have been used to evaluate PM health effects, including: studies of human volunteers exposed to PM under controlled conditions; in vivo studies of laboratory animals including nonhuman primates, dogs, and rodent species; and in vitro studies of tissue, cellular, genetic, and biochemical systems. A variety of exposure conditions have been used, including: whole body, mouth-only, and nose-only inhalation exposures to concentrated ambient particles (CAPs) or laboratory-generated particles; intratracheal, intrapulmonary, and intranasal instillation; and in vitro exposures to test materials in solution or suspension. These approaches have been used mainly to test hypotheses regarding the role of PM in producing the types of health effects identified by PM-related epidemiologic studies. Thus, most new toxicological studies have mainly addressed the question of biologic plausibility of epidemiologically-demonstrated effects and mechanisms of action, rather than attempting to delineate dose-response relationships.

Reflecting this, most of the toxicology studies have generally used exposure concentrations or doses that are relatively high compared to concentrations commonly observed in ambient air. One consideration underlying the use of such experimental exposure concentrations is the fact that healthy animals have most typically been used in many controlled-exposure toxicology studies, whereas epidemiologic findings often reflect ambient pollutant effects on compromised humans (e.g., those with one or another chronic disease) or other susceptible groups at increased risk due to other factors. Implicit in using relatively high concentrations in experimental studies of healthy subjects is the assumption that increasing the dose makes up for compromised

tissue/organ functions that may contribute to observed ambient PM effects, but this may not be so.

Recognizing this, there has been growing attention to the development and use of compromised animal models thought to mimic important characteristics contributing to increased human susceptibility to ambient PM effects. One example is the use of monocrotaline (MCT)-treated rats, in which the MCT-induced pulmonary vasculitis/hypertension is thought to render them at possible increased risk for PM effects. A limitation of this model is that pathology is induced acutely in rats to model a chronic illness in humans. Another example is a compromised animal model of chronic bronchitis (induced by repeated, prolonged exposure to SO_2 before exposure to PM). Partial coronary artery occlusion is yet another example of a compromised animal model, evaluated for increased cardiovascular risk. Possible PM exacerbation of respiratory infections has also been evaluated in animals intratracheally exposed to various bacteria. There is a need to search for relevant new animal models to better simulate human pathophysiology in PM exposure studies.

Given the relatively high concentrations used, caution is needed in attempting to interpret and extrapolate effects seen in these studies to provide insight into the biological plausibility and mechanisms of action underlying effects seen in humans under "real-world" exposure conditions. Some reported responses may only be seen at the higher concentrations (more typical of occupational exposures) and not necessarily at (usually much lower) ambient particle exposure levels. On the other hand, differences between humans and rodents with regard to the inhalability, deposition, clearance, and retention profiles for PM (see Chapter 6 for details) could in some instances make doses to some specific respiratory tract tissues from relatively high experimental exposures relatively similar to doses from human ambient exposures.

Since the 1996 PM AQCD, the effects of controlled exposures to ambient PM have been evaluated by use of urban air particles (UAP) collected from ambient samplers (e.g., impactors, diffusion denuders, etc.) and, more recently, by the use of aerosol concentrators. In the first type of study, particles from ambient air samplers are collected on filters or other media, then stored for varying time periods (hours to years or even decades) before later being resuspended in an aqueous medium and used in inhalation, instillation, or in vitro studies. Depending on the storage conditions for the filters (e.g., whether or not kept refrigerated or in the dark) varying

amounts of some originally collected materials (including highly biologically active semivolatile compounds) may be lost and their possible effects missed in UAP studies. Also of potential concern is the fact that prolonged storage of filters under inappropriate conditions may lead not only to volatilization of semivolatile material, but also to chemical alteration of reactive compounds and/or possible growth of mold, bacterial contamination, etc.

Particle concentrators allow exposure under controlled conditions of animals or humans by inhalation to concentrated "real-world" ambient particles (CAPs) at levels higher than typical ambient PM concentrations. However, CAPs studies cannot closely control the mass concentration and day-to-day variability in ambient particle composition; and they have sometimes lacked detailed characterization of variations in chemical composition from one CAPs exposure to another. Because the composition of CAPs varies across both time and location, thorough physical-chemical characterization is needed (but not always done or reported) to facilitate comparison of results between studies or even among exposures within studies, so as to better link specific particle composition to effects. Another limitation is the fact that concentrators used in many of the studies assessed here lose concentrating efficiency below 0.3 μm, and do not concentrate ambient particles in the ultrafine range ≤ 0.1 μm. Thus, it is possible that portions of potentially important combustion-generated particles (e.g, from diesel, gasoline vehicle, wood smoke, coal smoke, etc.) were present only at ambient (not higher concentrated) levels in most of the CAPs studies assessed here; and many other potentially toxic co-components (e.g., SO_2, O_3, peroxides, etc.) of the ambient aerosols may not have been concentrated or were excluded from the CAPs exposure mix as well. Newer versions of CAPs concentrators being used in ongoing research do allow for concentrating of particles ≤ 0.1 μm and for exposure to gaseous co-pollutants present in the ambient air along with the particles being concentrated. These improvements should enable CAPs exposures in ongoing and/or future research studies to more fully reflect potentially important interactive effects of overall "real-world" aerosol mixes.

Controlled human and laboratory animal exposures to particulate material obtained from combustion-source bag house filters or other combustion-source collection devices have also been used to evaluate the in vitro and in vivo respiratory toxicity of complex combustion-related PM. Residual oil fly ash (ROFA) collected from large industrial sources (e.g., oil-fired power

plants) has been extensively used, and, less often, domestic oil furnace ash (DOFA) or coal fly ash (CFA). The major disadvantage associated with the use of such materials derives from questions about the potential relevance of results obtained in understanding ambient PM exposure effects. Before extensive implementation of air pollution controls, ambient U.S. air contained mixtures of PM species (at higher than current concentrations) analogous to those in many of the source samples used in toxicologic studies during the past decade or so. However, it is unlikely that high concentrations of certain materials that typify such samples would be found or approached in ambient air PM samples from community monitoring sites in the United States, Canada, and much of western Europe that generated the aerometric data (collected during the past 20 to 30 years) that were used to estimate PM exposures in most PM epidemiology studies assessed here. Very high concentrations of metals (especially Ni and V, for example) typify most ROFA samples, and experimental exposures to such materials have generally resulted in exposures and doses orders of magnitude (100s of times) higher than for usual concentrations of such metals in ambient PM measured routinely since the 1970s at community monitoring sites across the United States. Thus, significant issues arise concerning the extent to which the effects of high concentrations of ROFA or other combustion-source particle mixes can be extrapolated to help interpret ambient air PM effects. However, these studies provide some insight into the relative toxicity of contributing sources or specific PM components.

Analogous issues arise with evaluation of the toxicity of PM emitted from mobile source combustion devices, e.g., diesel and gasoline vehicle engines. Complex combustion-related mixtures in such mobile source emissions include many different types of particles and gaseous compounds in high concentrations that are not necessarily representative of ambient PM derived from such sources after passage through particle traps, catalytic converters, exhaust pipes, etc. For example, ultrafine particles emitted from gasoline and diesel engines are reduced in numbers and concentrations as they agglomerate to form larger, accumulation-mode particles as they cool in passing through exhaust systems and/or as they undergo further physical and chemical transformation as they "age" in ambient air. Further complicating evaluation of the toxicity of mobile source emission components is: (1) the difficulty in separating out toxic effects attributable to particles versus those of gaseous components in automotive exhausts; and (2) the changing nature of those exhaust mixes as a function of variations in engine operating mode

(e.g., cold start versus warm start or "light" versus "heavy" load operation, etc.) and changes in engine technology (e.g., "old diesels" versus "new diesels").

The in vivo and in vitro PM exposure studies have almost exclusively used PM_{10} or $PM_{2.5}$ as particle size cutoffs for studying the effects of ambient PM. Collection and study of particles in these size fractions has been made easier by widespread availability of ambient sampling equipment for PM_{10} and $PM_{2.5}$. However, other important size fractions, such as the coarse fraction ($PM_{10-2.5}$) and $PM_{1.0}$, have largely been ignored; and only limited toxicology data are now available to assess effects of these particle sizes. Similarly, relatively little research has addressed mechanisms by which organic compounds may contribute to ambient PM-related effects.

9.2.3.1.2 Interspecies Comparisons of Experimental Results

Much of the new toxicologic data assessed in Chapter 7 and discussed here was derived from either: (a) in vivo exposures of human subjects or laboratory animals via inhalation exposures or instillation of PM materials; or (b) in vitro exposures of various (mostly respiratory tract) cells or tissues to diverse types of PM.

Of the three common experimental approaches for studying PM health effects, inhalation studies provide the most realistic exposure scenarios and physiologically best mimic biological reactions to ambient PM. However, because they are expensive, typically require large samples, are time consuming, and require specialized equipment and personnel, they are often supplemented by instillation and in vitro studies. Instillation studies, in which particles suspended in a carrier such as physiological saline are applied to the airways, have certain advantages over in vitro studies. The exposed cells have normal attachments to basement membranes and adjacent cells, circulatory support, surrounding cells and normal endocrine, exocrine, and neuronal relationships. Although the TB region is most heavily dosed in such studies, alveolar regions can also be exposed via instillation techniques. In vitro studies using live cells are cost-effective, allow for precise dose delivery, and provide a useful avenue by which to conduct rapid PM mechanistic and comparative toxicity studies. Often, initial information on the likely mechanisms of action of particles is obtained through in vitro

techniques. For PM toxicologic studies, dose selection is important to avoid overwhelming normal defense mechanisms.

As already noted, the experimental exposure conditions used in these studies are typically different from those experienced through inhalation of airborne PM by human populations in ambient environments. To help place the toxicologically relevant concentrations/doses into context in relation to ambient conditions, EPA carried out illustrative dosimetric/extrapolation modeling analyses (described in Appendix 7A) to provide comparisons between the high exposure doses typically used in toxicological studies and doses more typical of human exposures under ambient conditions. Building upon advances in dosimetric modeling discussed in Chapter 6, Appendix 7A provides analyses of relationships between rat and human lung doses predicted for various exposure scenarios ranging from ambient PM exposures to PM instillations into the lung. As noted in Appendix 7A, establishing firm linkages between exposure and dose requires consideration of particle characteristics and biological normalizing factors. These analyses and interpretation of their results provide context for exposure concentrations used and toxicological results assessed here.

It is difficult to compare particle deposition and clearance among different inhalation and instillation studies because of differences in experimental methods and in quantification of particle deposition and clearance. In brief, inhalation may result in deposition within the ET region, the extent of which depends on the size of the particles used; but intratracheal instillation bypasses this portion of the respiratory tract and delivers particles directly into the TB tree. Inhalation generally results in a fairly homogeneous distribution of particles throughout the lungs, relative to instillation, which is typified by heterogeneous distribution and high focal levels of particles. This disparity in distribution likely impacts clearance pathways, dose to cells and tissues, and systemic absorption. This is reflected, for example, by particle burdens within macrophages, those from animals inhaling particles being burdened more homogeneously and those with instilled particles showing some populations of cells with heavy burdens and others with no particles. Also, some studies have found greater percent retention of instilled than inhaled particles, at least up to 30 days postexposure, while others report similar clearance rates. Exposure method, thus, clearly influences dose distribution; and, possibly clearance, thus necessitating much caution in interpreting results from instillation studies.

In many studies, both toxicologic and epidemiologic, health endpoints are presented and analyzed as a function of exposure concentration. However, it is generally accepted that the dose to target cells or tissues, rather than exposure concentration per se, is responsible for adverse responses. Experimental exposure concentrations can be estimated that should result in the same tissue dose in a rat as received by a human exposed to various levels of ambient PM as a function of dose metric, normalizing factor, and level of human exertion. As no single dose metric nor normalizing factor appears to be appropriate for all situations, numerous potential exposure scenarios were considered in Appendix 7A. Optimally, the dose metrics and normalizing factors should be based on the biological mechanisms mediating an effect. For some effects, the mass of soluble PM depositing in a region of the lung may be an appropriate dose metric. For example, an appropriate normalizing factor for soluble PM could be the surface area of the airways for irritants, whereas body mass might be more suitable when considering systemic effects. The parameters chosen can dramatically affect the rat exposure concentration estimated to be required to provide a normalized dose equivalent to that occurring in a human, as illustrated in Tables 7A-7a through 7A-9b of Appendix 7A.

Representative dosimetric calculations provided in Appendix 7A indicate that higher PM concentration exposures in rats than in humans are needed under certain conditions in order to achieve nominally similar acute doses per lung tissue surface area in exercising humans exposed to ambient PM while undergoing moderate to high exertion. However, for resting or light exertion situations, lower rat exposure concentrations are adequate to produce equivalent lung tissue doses. Also, given that rats clear PM much faster than humans, Appendix 7A dosimetric modeling predicted that much higher exposure concentrations in the rat are required to simulate the retained burden of poorly soluble particles which builds up over years of human ambient PM exposure. In resuspended PM, used in some inhalation studies, the smaller particles found in the accumulation and Aitken modes of the original atmospheric aerosol are aggregated onto (or into) larger particles and are not fully disaggregated during the resuspension process. Thus, for dose metrics based on particle surface area or number, very high exposure concentration of resuspended PM for rats would be required to provide a dose equivalent to that received by humans exposed to ambient atmospheric aerosols.

The dose to the lung can be estimated for both animal and human inhalation studies. These analyses make it possible to compare biological responses as a function of dose rather than just exposure. Equal lung doses should not be assumed in comparing studies, even if PM mass concentrations, animal species, and exposure times are identical. Differences in the aerosol size distributions to which animals are exposed also affect dose delivered or retained. For example, in an Appendix 7A comparison of several CAPs studies, one study was estimated to have 1.7 times the alveolar dose of another study despite a 10% lower exposure concentration. Thus, to make accurate estimates of dose, it is essential to have accurate and complete information regarding exposure conditions, i.e., not only concentration and duration of exposure, but also the aerosol size distribution and the level of exertion (and hence breathing rates) for exposed subjects.

It was obviously not feasible, given the complexity involved, to attempt extrapolation modeling for more than a few illustrative health endpoints from among those evaluated in the vast array of studies assessed in Chapter 7. Such calculations require knowledge about the characteristics associated with the particles, the exposed subject and the environmental exposure scenario. Hence, each study can present a unique dosimetric analysis. In most cases, it is useful to know the relationship between the surface doses in instillation studies and realistic local surface doses that could occur in humans. However, providing some illustrative modeling results here should be of value in helping to provide a context by which to gauge the potential relevance of experimental results for ambient human exposure conditions.

PMN Influx as a Marker for Lung Inflammation

Various types of particulate materials have been shown to cause inflammation of the lung by migration of polymorphonuclear (PMN) cells (predominantly neutrophils) into the airways, as discussed in Chapter 7 and summarized below. Alveolar macrophages (AMs) and PMN cells, constitute an important lung defense mechanism triggered by invasion of PM, bacteria, and some other foreign matter. The PMN cells, once in the lung, ingest PM and may then degranulate, forming hydrogen peroxide and superoxide anions. Excessive quantities of PM in the lung can cause the lysosomal enzymes in PMN cells to enter the extracellular fluid, creating further

inflammatory responses. Also, PMN cells produce thromboxanes, leukotrienes, and prostaglandins.

Three new studies discussed in Chapter 7 and Appendix 7A provide data on PMN cell increases following CAPs exposure. Analysis of PMN data from exposures of rats and humans to CAPs in these studies confirm that rats exhibit analogous effects on PMN cells as seen in humans in response to CAPs exposures, although the varying composition of the CAPs materials from day-to-day or location-to-location and other considerations do not allow confident evaluation of whether healthy humans may be more or less susceptible to the inflammatory effects of CAPs than are rats based on currently available data.

Inhibition of Phagocytosis by PM Exposure

Phagocytosis is a form of endocytosis wherein bacteria, dead tissue, or other foreign material (e.g., inhaled ambient particles) are engulfed by phagocytic cells such as AMs, PMN cells, or monocytes (MO) as part of normal lung defense mechanisms. Increased numbers of these cells in lung tissue are an indicator of normal mobilization of lung defenses in response to infection or deposition of inhaled particles. Inhibition of phagocytosis signals interference with lung defense mechanisms. If an AM is overwhelmed by the amount or toxicity of ingested material, that material may be released along with the AM's digestive enzymes onto the alveolar surface and the numbers of AM or their phagocytic activities may decrease. Several in vitro studies discussed in Chapter 7 have shown that, in certain instances, one or another type of PM has caused an inhibition of phagocytosis. As with other endpoints affected by PM, this inhibitory effect is determined by the size and composition of the specific particle mixes tested.

Comparison in Chapter 7 of in vitro rodent and human data evaluating inhibition of phagocytosis suggest some important species differences. Human AMs demonstrated inhibition of phagocytosis at 0.05 ng/cell (Utah Valley PM) and 0.2 to 0.5 ng/cell (UAP and ROFA). A mouse AM cell line showed inhibition of phagocytosis at concentrations of 0.013 to 0.025 ng/cell of TiO_2 and carbon black. However, hamster AMs showed no inhibition of phagocytosis at doses up to 0.04 ng/cell CAPs and 0.4 ng/cell ROFA. Differences in inhibition may be attributed to interspecies variability in AM capacity, wherein rodent AMs are smaller, have less capacity for phagocytosis, and appear to be inhibited at a lower burden of PM per cell

than human AM. It must be noted that these in vitro exposures are at extremely high doses, exposing each cell to tens to hundreds of particles at physiologically improbable levels unlikely to be experienced as the result of human exposures to current U.S. ambient air PM (except possibly, under very extreme conditions).

9.2.3.1.3 Inhaled Particles as Carriers of Other Toxic Agents

In Chapter 2, it was noted that, although water vapor is not considered an air pollutant per se, particle bound water (PBW) may serve as a carrier for other toxic pollutants. Wilson (1995) proposed that water-soluble gases that are usually removed by deposition to wet surfaces in the upper (ET) regions of the respiratory tract may be dissolved in PBW and be carried into lower regions (TB, A) of the respiratory tract. Thus, PBW could be a vector by which certain toxic gases commonly found in polluted air masses may be delivered in enhanced proportions to deep lung regions, including water-soluble gases such as: oxidants (e.g., H_2O_2, organic peroxides); acid gases (e.g., SO_2, HCl, HONO, formic acid); and polar organic species.

Kao and Friedlander (1995) also noted that many short-lived chemical species in the gas or particle phase (such as free radicals) in ambient aerosols may not still be present in sampled materials when analyzed hours to weeks (or even longer) after collection on filters and being stored. Also, the unmeasured reactive but metastable species may be much more biochemically active than the resulting stable components collected or remaining on analyzed filters. They also noted that since inhalation toxicology studies often do not include the potential for metastable species and reactive intermediaries to be present, then such studies could greatly underestimate the effects seen in field or epidemiological studies. Friedlander and Yeh (1998) further noted that atmospheric submicron (< 1.0 μm) aerosols contain short-lived reaction intermediaries (e.g., hydrogen peroxides and other peroxides) formed in clouds and rain water. Also, they indicated that: (1) hydrogen peroxide particle phase concentrations fall in a toxicologic range capable of eliciting biochemical effects on respiratory tract airway epithelial cells; (2) this may help to explain epidemiologic results indicating health effects to be associated with sulfate or other fine particle aerosols; and (3) such aerosols may be surrogate indicators for hydrogen peroxide or other species.

Certain physical modeling of gas-particle-mucus heat and mass transport in human airways suggests that very soluble gases (e.g., H_2O_2, formaldehyde) may be largely evaporated from particles < 0.1 μm diameter before reaching A regions of the lung, but particles > ~0.3 μm can efficiently carry such gases into the air exchange region of the lung. Also one new toxicological study discussed in Chapter 7 (Section 7.9.1) evaluated whether certain commonly present hygroscopic components of ambient PM can transport H_2O_2 into the lower lung and thereby exert or enhance toxic effects. More specifically, rats exposed by inhalation to combinations of (NH_4) SO_4 (0.3 to 0.4 MMD) and H_2O_2 exhibited enhanced biochemical effects that were interpreted by the authors as showing that biological effects of inhaled PM are augmented by coexposure to sulfate and peroxide, including altered production of cytokine mediators by alveolar macrophages.

The information summarized above has important implications for interpreting and understanding epidemiologic and experimental toxicology results discussed in ensuing sections of this chapter. Also, of much importance is dosimetric information discussed in Chapter 6 which indicates that hygroscopicity affects particle deposition patterns in the respiratory tract, such that under high humidity conditions one can expect increased deposition of small nucleation (< 0.1 μm) ultrafine particles and larger accumulation-mode (≥ 0.5 μm) particles, the latter of which are able to grow to exceed 1.0 μm and both of which would contain enhanced amounts of PBW and other toxic agents (e.g., SO_2, peroxide, aldehydes, etc.). Also, to some extent, growth of ultrafine and accumulation mode particles under high humidity conditions would likely enhance particle "hot spot" deposition at airway branching points and increase PM doses to lung tissue at those points. Enhanced deposition and tissue doses would likely exacerbate PM respiratory effects in particularly susceptible population groups, e.g., asthmatics, COPD patients, and others with severe cardiopulmonary conditions.

In addition to recognition that particle-bound water may serve as a carrier of other toxic agents, there is growing recognition that bioaerosols likely have the potential to contribute to some ambient PM effects, in part, via their serving as carriers of toxic agents or via their attaching to and being carried by nonbiological particles. Bioaerosols, from sources such as plants, fungi, and microorganisms, range in size from 0.01 μm to > 20 μm. Although they

typically only comprise a small fraction of ambient PM, they likely contribute to some types of ambient PM-related health effects.

Intact pollen grains from plants, trees and grasses are most abundant during warm/humid spring/summer months. When they deposit in upper airways, they induce allergic rhinitis. However, allergen-laden cytoplasmic fragments (~0.1 to 0.4 μm in size) of pollen grains (which rupture under high moisture conditions) can enter the deep lung, where they can exacerbate asthma. Binding of allergen-laden pollen cytoplasmic fragments to ambient fine particles, e.g., diesel particulate matter (DPM) has also been observed; and synergistic interactions between pollen debris and other ambient PM, e.g., the polycyclic hydrocarbon component of diesel exhaust, may be a mechanism that increases incidence of asthma morbidity and mortality. Pollen granules can also act as vectors for binding of other bioaerosols (e.g., endotoxins, fungi or fungal fragments, glucans) and thereby enhance their inhalation and deposition in the respiratory tract, as well.

Fungal spores and fungal fragments are among the largest and most consistently present bioaerosols found outdoors (levels being higher during warm/humid months). Certain molds and other fungi cause allergic rhinitis and asthma, which is highly dependent on seasonal variations in concentration. Exposures have been linked in epidemiologic studies to asthma hospitalization and death. Some proliferate very effectively on wet cellulose materials (at times posing serious indoor contamination problems), thus raising the possibility that airborne cellulose-containing plant debris (which otherwise may be non-toxic when dry) may serve as effective vectors for proliferation of fungi and their delivery into the lung under high humidity ambient conditions. Exposures to other soil-dwelling fungi found in contaminated airborne soil particles entrained in windblown dust stirred up by natural or anthropogenic activities has been linked to increased risk of serious respiratory infections (Valley Fever) in endemic areas of California and the southwestern United States (see Appendix 7B).

Bacteria and viruses are also significant bioaerosols. Bacteria have endotoxins in their outer cell membrane, which trigger production of cytokines and a cascade of inflammation. Ambient airborne levels of endotoxins vary with seasons (being higher in warm/humid periods and low in colder months). Another cell wall component of bacteria and fungi, (1→3)-β-D-glucan, has also been shown to cause respiratory inflammation.

Based on the above, it appears that certain ambient bioaerosols (e.g., pollen, fungi, endotoxins, glucans) that become abundant during warm/humid weather have the potential to contribute to seasonal increases in PM-associated risk during spring/summer months in many U.S. areas, but not during colder winter months. In addition, the copresence of nonbiological particles, serving as vectors concentrating such bioaerosols and enhancing their delivery into the deep lung, also appears likely to be important. For example, airborne endotoxins have been shown to be associated with both fine and coarse thoracic ambient particles (albeit higher with the coarse PM); and cytoplasmic pollen fragments have been found attached to airborne diesel particles. It thusly appears that airborne anthropogenic particles (both in fine and coarse size ranges) as well as naturally-generated biological particles likely enhance the risk for bioaerosols-stimulated effects.

9.2.3.2 Biological Plausibility and Coherence of Evidence for Different Health Endpoint Categories

This section is organized to integrate epidemiologic, toxicologic, and mechanistic information for each of four major categories of health endpoints, i.e., (a) cardiovascular; (b) respiratory; (c) lung cancer; and (d) fetal/infant development and mortality, purported to be associated epidemiologically with either short- or long-term ambient PM exposures. Each subsection concisely summarizes pertinent key information and then arrives at conclusions as to the plausibility of effects being reasonably attributable to fine and coarse thoracic particles and/or subcomponents.

9.2.3.2.1 Cardiovascular-Related Health Endpoints

As noted in Section 9.2.2, a number of epidemiologic studies (a) show associations between short-term and/or chronic ambient PM exposures and increases in cardiac-related deaths and/or morbidity indicators and (b) indicate that the risk of PM-related cardiac effects may be as great or greater than those attributed to respiratory causes (see Chapter 8). Hypothesized mechanisms thought to be involved in cardiovascular responses to PM exposure (as discussed in Chapter 7) include: (a) effects on autonomic nervous system control of cardiovascular functions and (b) pathophysiologic effects on certain blood chemistry parameters involved in control of

blood clotting or otherwise impacting cardiovascular integrity. It should be noted that most new PM cardiovascular effects research has focused on exposure to fine particles; little evidence is available on the effects of coarse fraction particles.

With regard to autonomic nervous system control, the heart receives both parasympathetic and sympathetic inputs that decrease or increase heart rate, respectively. Vasoconstriction, possibly due to release of endothelin elicited by PM, could cause increased blood pressure and its detection by baroreceptors. Parasympathetic neural input may then be increased to the heart, slowing heart rate and decreasing cardiac output (which is sensed by aortic and carotid chemoreceptors). These, in turn, may stimulate a sympathetic response, manifested by increased heart rate and contractile force, thus increasing cardiac output. This arrhythmogenesis and altered cardiac output in either direction can be life-threatening to susceptible individuals.

Pathophysiological changes in cardiac function can be detected by electrocardiographic (ECG) recordings, with certain ECG parameters (e.g., heart rate variability or HRV) now often being used as indicators of PM-induced cardiac effects. HRV is a reflection of the overall autonomic control of the heart and can be divided into time and frequency measures. Frequency measures of variability help to resolve parasympathetic and sympathetic influences on the heart better than do time domain measurements. Under some circumstances (as discussed in Chapter 7), HRV provides insight into sympathetic nervous activity, but more commonly it is a good measure of parasympathetic modulation. Heart rate variability can be used to judge the relative influences of sympathetic and parasympathetic forces on the heart, but short-term spectral parameters (i.e., measures averaged over five minute intervals) can vary as much as 4-fold during the course of a 1-h period. Despite the inherent variability of short-term HRV measures during routine daily activity, long-term measures show excellent day-to-day reproducibility. Given the inherent variability in the minute-to-minute spectral measurements, much care is required in the design of studies using HRV techniques and in interpretation of HRV results. Still, studies utilizing measures of HRV can provide insight into relationships between perturbations of the internal or external environment and subsequent changes in the modulation of autonomic neural input to the heart.

Using both time and frequency domain parameters, HRV has been studied as a marker of medical prognosis in human clinical populations, most frequently in coronary artery disease

populations, particularly in the post-myocardial infarction (post-MI) population. Those variables most closely correlated with parasympathetic tone appear to have the strongest predictive value in heart disease populations. The altered HRV itself is not the causative agent, but rather altered HRV (including changes in HRV associated with exposure to PM) is simply a marker for enhanced risk of serious cardiac events (e.g., arrhythmia, sudden cardiac death).

Another route by which PM could exert deleterious cardiovascular effects may involve ambient PM effects on endothelial function. PM exposure may affect blood coagulation through endothelial injury that results in platelet activation. This then could initiate a cascade of effects (e.g., platelet activation and/or aggregation, increased blood fibrinogen and fibrin formation modulated by Factor VII, etc.), leading to increased formation of blood clots. Or PM taken up into the systemic circulation could possibly affect clot lysing events that normally terminate the blood coagulation cascade. Newly available studies have measured various blood substances to evaluate possible PM-induced effects on blood coagulation. Another significant effect of PM exposure could be vascular inflammation, which induces release of C-reactive proteins and cytokines that may cause further inflammatory responses which, on a chronic basis, can lead to atherosclerosis. In narrowed coronary arteries, clots formed by the aforementioned cascade may block blood flow, resulting in acute myocardial infarction.

Small prothrombotic changes in blood coagulation parameters in a large population can have substantial effects on the incidence and prevalence of cardiovascular disease events (Di Minno and Mancini, 1990; Braunwald, 1997; Lowe et al., 1997). Altered coagulation, for example, could increase heart attack risk through formation of clots on atherosclerotic plaques in coronary arteries that cut off blood supply to the myocardium or induce ischemic strokes via clots forming or lodging in the carotid arteries and blocking blood flow to the brain. Also, evidence exists for formation of small thrombi being common in persons with atherosclerosis (Meade et al., 1993); and whether such thrombi lead to more serious effects (heart attack, stroke) depends in part on the balance between thrombogenic factors underlying blood clot formation and fibrinolytic factors that lyse clots. Increased sympathetic activity is thought to cause prothrombotic changes in blood coagulation parameters such that even small, homeostatic modulations of coagulation within a normal range could translate into significant increased risk for heart attack.

Another possible effect of PM exposure could be plasma extravasation from post-capillary venules. The mechanisms by which this occurs are thought to include the release of peptides (such as neurokinin A, substance P, and calcitonin-gene-related peptide) from unmyelinated sensory nerves near to or on the blood vessels. These peptides bind to receptors on the endothelial cells of vessels and create gaps, allowing leakage of plasma, which is one component of neurogenic inflammation (Piedimonte et al., 1992; Baluk et al., 1992).

Thus, alterations in cardiovascular functions due to PM exposure could be signaled by small PM-related (a) changes in blood coagulation cascade indicators, e.g., altered blood platelet, fibrinogen, or Factor VII levels or decreased tissue plasminogen activator (TPA) levels; (b) increased C-reactive protein or cytokines, possibly contributing to increased atherosclerosis plaque formation and/or blood coagulation; (c) increased blood pressure; and/or (d) certain alterations in heart rate, heart rate variability, or other ECG indicators indicative of shifts in parasympathetic/sympathetic neural inputs to the heart or other underlying cardiac pertubations. These alterations, while not likely to have significant impact in healthy individuals, may be deleterious in susceptible individuals with underlying cardiopulmonary disease.

Coherence Between Epidemiologic and Experimental Evidence for Cardiovascular Effects

Considering first the evidence from epidemiologic studies conducted within a given location (e.g., the same urban area), recent studies have reported associations for PM with both mortality and hospital admissions for cardiovascular diseases in several U.S. cities. For example, in Chicago (Figure 8-24), associations were reported between PM_{10} and cardiovascular mortality and cardiovascular hospital admissions. In Los Angeles (Figure 8-25), associations were found between PM_{10} and cardiovascular mortality, cardiovascular hospital admissions, and admissions for specific categories of cardiovascular disease (e.g., myocardial infarction, congestive heart failure, cardiac arrhythmia, cerebrovascular and occlusive stroke); some studies included associations with $PM_{2.5}$. In addition, one recent study in a group of Los Angeles residents with COPD reported associations between PM_{10} and diastolic and systolic blood pressure, although no associations were reported for heart rhythm measures (Section 8.3.1.3.4). In Detroit (Figure 8-27), as well, associations were seen between PM_{10} and cardiovascular mortality, cardiovascular hospital admissions and admissions for specific categories of

cardiovascular disease (including ischemic heart disease, heart failure, dysrrhythmia, stroke); associations were also reported with $PM_{2.5}$ and $PM_{10-2.5}$.

More broadly, the fuller array of epidemiologic studies shows associations between various ambient PM indices and a range of cardiovascular health outcomes, from mortality and hospitalization for various cardiovascular diseases to recent evidence for associations with incidence of myocardial infarctions and physiological or biochemical indicators of cardiovascular health. The newer evidence includes epidemiologic panel studies reporting changes in blood characteristics (e.g., increased fibrinogen or C-reactive protein levels) related to increased risk of ischemic heart disease, and some indications of changes related to heart rhythm, including cardiac arrhythmia or changes in HRV that may be linked with more serious cardiac effects. While further research is needed to more firmly establish and understand links between particles and these more subtle endpoints, the newly available results provide suggestive evidence for a chain of endpoints linked to potential mechanisms for cardiac effects. These more recent studies have mainly found associations for PM_{10} and $PM_{2.5}$; only one study included $PM_{10-2.5}$ and reported no associations with HRV changes (Section 8.3.1.3.4). As for lags seen epidemiologically between PM exposure and observed effects, acute short-term ($\leq$ 24-h) exposures to ambient PM appear to exert cardiovascular/systemic effects rather quickly, with peak lags of 0-1 days being generally seen, and one study reporting myocardial infarction increases even as early as 2 h post exposure.

There were few toxicologic studies assessed in the 1996 PM AQCD that evaluated cardiovascular system effects of exposures to particulate matter. Since 1996, numerous studies have now become available that evaluated cardiovascular effects of exposures (via inhalation or instillation) of ambient PM, constituent components, complex mixtures from PM emission sources and/or exposures to single PM substances or binary/ternary combinations of particles of varying chemical composition. Whereas earlier studies tended to focus on healthy animals, the more recent studies have, in addition, begun to focus on evaluation of PM effects in animal models of disease states thought to mimic aspects of pathophysiologic states experienced by compromised humans at increased risk for PM effects.

A growing number of studies have used extracts of collected/stored ambient PM or real-time concentrated ambient particles (CAPs) drawn from various airsheds (e.g., Boston, New

York City, etc.) to evaluate cardiovascular and other systemic effects of PM. Most of this research has focused, again, on fine particles. A number of new animal studies have also used residual oil fly ash (ROFA) as one type of combustion source particle mix and others have used other combustion source materials, e.g., domestic oil fly ash (DOFA), coal fly ash (CFA), or diesel exhaust (DE).

The ensuing discussion focuses mainly on those toxicology studies using ambient or near-ambient PM concentrations thought to be most relevant to ambient PM exposure situations in the United States. Controlled human exposure studies have yielded some limited evidence for ambient PM effects on cardiac physiological function (as indexed by ECG readings) or systemic endpoints (as indexed by vasopressor control, blood coagulation control, etc.) linked to more serious cardiovascular events. Blood coagulation effects of inhaled PM were also observed with CAPs, UAP, and ROFA. Probably of most note, two controlled human exposure CAPs studies found evidence that ambient levels (~50 to 300 $\mu g/m^3$) of inhaled $PM_{2.5}$ can produce biochemical changes (increased fibrinogen) in blood suggestive of PM-related increased risk for prothrombotic effects. Also, blood fibrinogen levels increased in both normal and compromised dogs at 69 to 828 $\mu g/m^3$; and decreased Factor VII levels were observed by other investigators in humans with 2-h CAPs exposure at ~174 $\mu g/m^3$, perhaps reflecting that enzyme being consumed in an ongoing coagulation process. On the other hand, the same and many other human and animal studies did not find significant changes in other factors (e.g., increased platelets or their aggregation) related to blood coagulation control. Additional other studies have shown no cardiovascular effects in rats and dogs with CAPs exposures of 3-360 $\mu g/m^3$.

One excellent example of linkage between cardiovascular results from epidemiological and toxicological studies is provided by a series of studies conducted in Boston. Recent epidemiological studies have linked daily or hourly changes in $PM_{2.5}$ with several cardiovascular health outcomes: incidence of myocardial infarction was increased in association with PM exposures 2 hours prior to the health event; increases in recorded discharges from implanted cardiovertex defibrillators (an indicator of cardiac arrhythmia) were positively associated with daily $PM_{2.5}$ concentrations; and decreases in HRV measures were reported (a) in young healthy boilermakers to be associated with personal $PM_{2.5}$ measurements and (b) in elderly residents of a retirement community with ambient $PM_{2.5}$ (Section 8.3.1.3.4). Results of toxicological studies in

Boston using $PM_{2.5}$ CAPs exposures in dogs are suggestive of changes in cardiac rhythm with $PM_{2.5}$ mass and changes in blood parameters with certain $PM_{2.5}$ components (Table 7-1). These findings in both humans and animals, using the same general mix of particles and co-pollutants, are suggestive of changes in cardiac rhythm and changes in blood parameters. Also, in addition to the epidemiologic studies conducted in Los Angeles, results from controlled human inhalation exposures (for 2 h) of healthy adult volunteers to Los Angeles $PM_{2.5}$ CAPs suggest effects on some cardiovascular outcomes (decreased Factor VII blood levels and some cardiac symptoms), but not with other cardiovascular indicator measures (such as changes in blood fibrinogen levels) (Table 7-1). More rigorous characterizations of dose-response relationships with environmentally relevant levels and species of PM will be necessary to evaluate more fully cardiovascular risks posed by ambient PM exposures.

Limited new evidence is available regarding the effects of different components or attributes of particles on the cardiovascular system. Recent epidemiological studies reported slight increases in blood viscosity with ultrafine particle exposures. Little or no evidence is available on cardiovascular effects of PM components, such as sulfates or acid aerosols. Particle constituents such as transition metals (e.g., Ni, V, Zn, Fe) have been shown to cause cell injury and inflammatory responses in toxicologic studies, that may possibly be linked with cardiovascular health outcomes. Since particles are complex mixtures, studies using factor analysis or source apportionment methods may be more relevant than studies of individual components, and the few studies available to date have linked cardiovascular mortality with several fine particle source categories (Table 9-3).

More limited evidence is available on cardiovascular effects of long-term exposure to particles. Epidemiologic studies indicate associations between fine particles and mortality from cardiovascular diseases, although no evidence is currently available regarding long-term PM exposure and cardiovascular morbidity. Toxicologic studies have not yet been conducted to investigate potential cardiovascular effects with chronic PM exposures.

Beyond the evidence of coherence and plausibility described above, it is useful to consider salient hypotheses that have been proposed to account for PM-related effects. The most salient hypotheses proposed to account for cardiovascular effects of PM are: alterations in coagulability (Seaton et al., 1995; Sjögren, 1997); cytokine effects on heart tissue (Killingsworth et al., 1997);

perturbations in both conductive and hypoxemic arrythmogenic mechanisms (Watkinson et al., 1998; Campen et al., 2000); altered endothelin levels (Vincent et al., 2001); and activation of neural reflexes (Veronesi and Oortgiesen, 2001). Only limited progress has been made in obtaining evidence bearing on such hypotheses; and, to date, the strongest evidence found thus far most clearly supports the plausibility of the first mechanism being involved. Both epidemiologic and toxicologic studies (largely using fine particles) have found evidence of ambient PM effects on blood fibrinogen and/or other measures indicative of increased blood coagulability within 2 to 24 hours following short-term ($\leq$ 24 h) exposures to ambient or near-ambient concentrations of urban PM aerosols, with most evidence being available for fine particles. Much future research using controlled exposures to PM of laboratory animals and human subjects will be needed, however, to test further such mechanistic hypotheses so as to more fully understand pathways by which low concentrations of inhaled ambient PM may be able to produce life-threatening cardiovascular/systemic changes, and a particular research need is for more research on cardiovascular effects of coarse fraction particles.

9.2.3.2.2 Respiratory-Related Health Endpoints

As noted in Section 9.2.2, a number of epidemiologic studies show associations between short-term and/or chronic ambient PM exposure and respiratory effects ranging from respiratory-related mortality to hospitalization or medical visits for respiratory diseases to increased respiratory symptoms or decreased lung function. Respiratory system effects of PM may be exerted via several different types of mechanisms of action, including involving direct pulmonary effects and others secondary to lung injury. Direct pulmonary effects include lung injury and inflammation; increased airway reactivity and exacerbation of asthma; and increased susceptibility to infection.

Numerous toxicological studies point towards lung injury and inflammation being associated with exposure of lung tissue to complex combustion-related PM materials. Important evidence pointing towards ambient PM causing lung injury and inflammation derives from the study of ambient PM (PM_{10} and TSP) materials on filter extracts collected from community air monitors before, during the temporary closing of a steel mill in Utah Valley, and after its reopening. Studies in animals and human volunteers reported greater lung inflammatory

responses with exposure to materials obtained before and after the temporary closing versus that collected during the plant closing. Further analyses suggested that the metal constituents of particles may be important contributors to the pulmonary toxicity observed in these studies. Rats with SO_2-induced bronchitis and monocrotaline-treated rats have been reported to have a greater inflammatory response to concentrated ambient PM than normal rats. The toxicologic studies suggest that exacerbation of respiratory disease by ambient PM may be caused in part by lung injury and inflammation.

Toxicologic studies have also indicated that PM exposure can affect pulmonary defense responses to microbial agents. Studies using combustion related particles, albeit at high doses, have shown effects such as increased inflammatory responses or mortality rate from respiratory infections, compared with animals exposed to infectious agents without PM exposure (as discussed in Section 7.5.4).

Finally, PM exposure may result in increased airway reactivity and exacerbation of asthma. The strongest evidence supporting this hypothesis is from studies on DPM, an example of fine PM. Diesel particulate matter has been shown to increase production of antigen-specific IgE in mice and humans (summarized in Section 7.2.1.2).

Coherence Between Epidemiologic and Experimental Evidence for Respiratory Effects

Recent time series epidemiologic studies have reported associations between short-term (24-h) PM exposures for various indices and respiratory-related mortality and hospital admissions for respiratory diseases in cities such as Chicago, Los Angeles and Detroit. These studies, and others in Seattle and Pittsburgh, have also reported associations between PM and hospitalization or emergency department visits for asthma, pneumonia and COPD, as well as physicians visits for respiratory diseases. In addition, new evidence exists for ambient PM associations with reductions in pulmonary function and/or increased respiratory symptoms, especially of note in relation to asthmatic or other chronic lung disease individuals. Respiratory effects typically exhibit somewhat longer and more extended lag periods, from 1 to 2 days on out to a week or so after PM exposure, than do cardiovascular effects.

Some epidemiologic studies also indicate associations between long-term (years to decades) exposures to ambient PM (especially fine particles) and mortality due to

cardiopulmonary causes, although other recent studies indicated that such fine PM associations may be more strongly linked to cardiovascular diseases than respiratory disease. Long-term exposure to PM has also been found to be associated with potential development of chronic respiratory diseases and reductions in lung function.

The respiratory effects of PM with varying physical and chemical characteristics have been extensively studied for more than 30 years using a wide range of techniques and with exposure durations ranging from brief periods to months. The most extensively studied materials have been sulfates and acid aerosols formed as secondary pollutants in the atmosphere. Fly ash from coal-fired power plants or other coal-combustion sources has been less extensively studied. Controlled exposures to crustal materials, e.g., those in Mt. St. Helens volcanic ash, have also been studied. The toxicological data available today provide little basis for concluding that these types of specific PM constituents have substantial respiratory effects at current U.S. ambient levels of exposure. Recently, ROFA, a very specific kind of PM derived from oil combustion, has been studied extensively and found to produce a range of respiratory effects, especially lung inflammation, mainly attributable to its very high metal content that is several orders of magnitude (100s of times) higher than ambient concentrations typically found in U.S. ambient air.

Probably of more direct relevance for present purposes, other recent studies evaluating controlled human exposures to CAPs from diverse locations (e.g., Boston, New York City , Los Angeles, Toronto, and Chapel Hill, NC) have found little or no effects on pulmonary function or respiratory symptoms in healthy human adults acutely exposed (for 2 h) by inhalation to CAPs at concentrations that ranged from about 25 up to about 300 $\mu g/m^3$. Some indications of mild lung inflammation were reported with such exposures in some of the studies, but not others. Analogous controlled exposures to CAPs of rats, hamsters, and dogs at concentrations varying across a range of ~100 to 1000 $\mu g/m^3$ for 1-6 h/day for 1 to 3 days yielded similar minimal effects on respiratory functions, but did yield some signs of mild inflammation in normal healthy animals and somewhat enhanced indications of lung inflammation in at least one compromised animal model of chronic bronchitis. Follow-up evaluations have produced new evidence implicating transition metal components of ambient PM from diverse locations and of ROFA as inducing inflammatory responses. Another

inhalation study found indications of some impairment of lung immune defense functions and exacerbation of bacterial infection with an acute (3 h) exposure of rats to New York City CAPs (at 100-350 $\mu g/m^3$). Although concentration ranges were reported in the above inhalation studies, it is difficult to discern the actual lowest concentrations at which effects were observed.

Also, CAPs, UAPs, and ROFA have all been used in in vitro experiments to demonstrate effects and explore mechanisms whereby PM causes effects. Approximately 0.02 to 0.2 ng PM/cell is the concentration range where in vitro effects (e.g., cytokine production, inhibition of phagocytosis, and oxidant formation) were observed, though these doses are extremely high and are unlikely to be approached with exposures to ambient levels of PM currently found in U.S. airsheds (except, possibly, under unusual circumstances, e.g., exposure to dense smoke from forest fires).

A set of epidemiologic, toxicologic and controlled human exposure studies on effects of particles from the Utah Valley area has linked PM_{10} with respiratory system effects or, more specifically, lung inflammation. A special feature of these studies was the closure of a steel mill, a major source of PM emissions in the area, for a 13-month period. An epidemiologic study reported that respiratory hospital admissions for children were reduced during the period when the source was not operating (see Chapter 8, Section 8.2.3.4). New toxicologic and human studies then used extracts of ambient particles collected on filters from ambient PM_{10} monitors operating during the time periods before, during and after steel mill closure. Intratracheal instillation of particle extracts in both human volunteers and animals resulted in greater lung inflammatory responses for materials obtained before and after the plant closure period (as discussed in Chapter 7, Section 7.3.1.2). The health responses were indicative of inflammatory changes in the lung, including increased levels of neutrophils, protein and inflammatory cytokines. However, consideration of dosimetric analyses (see Appendix 7A) indicates that the bolus instillation doses of particles used in these experiments resulted in a single-dose exposure comparable to the cumulative dose that would result from extended (for 6-9 weeks) continuous exposure to the higher-end of the range of concentrations of PM_{10} that the community might have experienced during wintertime inversions in the Utah Valley. In vitro studies using a human airway epithelial cell line and primary rat airway epithelial cells also showed evidence for inflammatory responses, such as increases in cytokine levels, indicators of oxidative response

in alveolar macrophages and some evidence of cytotoxicity (see Section 7.4.2). Additional evaluations indicate that the in vivo and in vitro inflammatory responses observed were attributable to elevated metal content present in the particle extracts during the periods when the steel mill was operating. This body of evidence provides coherent links between results of community epidemiologic studies reporting increases in respiratory hospitalization with toxicologic evidence of respiratory inflammation in humans and animals.

Some evidence is also available on respiratory effects of different components or attributes of particles, especially fine particles. A few epidemiologic studies have reported associations between ultrafine particles (measured as particle number) with respiratory symptoms or decreased lung function. In addition, toxicologic studies have used various types of ultrafine particles (e.g., carbon black), and reported greater inflammatory responses than those seen with fine particle mass for the same type of particles. The relative importance of differing composition or surface area for these effects remains to be determined.

Fine particulate sulfates and acid aerosols have been associated with respiratory hospitalization, symptoms or and decreased pulmonary function in epidemiological studies, in both short-term and long-term exposure studies. Toxicological studies, however, have reported pulmonary or inflammatory effects with acid aerosol or sulfate exposures only at fairly high concentrations (hundreds of $\mu g/m^3$). It appears likely that, in the epidemiological studies, sulfates are serving as an indicator of particle mixtures or sources of particles. Toxicological studies have also reported that transition metals in or on fine particles (e.g., Ni, V, Zn, Fe) cause cell injury and inflammatory responses and, so, they may contribute to associations with respiratory health outcomes reported in epidemiological studies. Also, recent studies also show that diesel exhaust particles may exacerbate allergic responses to inhaled antigens.

As summarized above (Section 9.2.3.3.1) and discussed in more detail in Chapter 7 (Section 7.3.6) biological constituents of particles (e.g., fungal spores, plant and insect fragments, airborne bacteria) have been clearly linked with allergic, pulmonary or inflammatory responses in toxicological studies, and with respiratory symptoms or lung function changes in epidemiologic studies. Though the 1996 PM AQCD had concluded that bioaerosols at ambient levels were unlikely to account for PM-related health effects, more recent findings suggest that biogenic materials in ambient air may be attached to either natural or anthropogenic particles and

be carried by them into the deep lung and concentrated at "hot spots", where enhanced doses to tissue may produce exacerbation of lung inflammatory and allergic responses to of the bioaerosols.

For the most part, information regarding components of particles has come from studies of fine particles. Some of these components, particularly biogenic material and metals, can also be important components of coarse fraction particles. More research involving the systematic conduct of studies of potential respiratory effects of major components of PM commonly found in different size fractions in the United States is needed, in recognition that PM of different composition and from different sources can vary markedly in its potency for producing respiratory toxicity. Of particular importance are studies that more systematically evaluate mixtures of ambient constituents found in various airsheds, including short-lived species, e.g., peroxides.

9.2.3.2.3 Lung Cancer

Historical evidence linking cancer with PM exposures includes epidemiological studies of lung cancer trends, studies of occupational groups, comparisons of urban and rural populations, and case-control and cohort studies using diverse exposure metrics. Numerous past ecological and case-control studies of PM and lung cancer have generally found lung cancer relative risks greater than 1.0 to be associated with living in areas having higher PM exposures despite possible problems with respect to potential measurement errors for exposure and other risk factors. The 1996 PM AQCD (Section 8.4.6.4) further noted certain recently published prospective cohort study results (e.g., those from the ACS study) which found positive, but not statistically significant, associations between $PM_{2.5}$ and lung cancer mortality—leading to a bottom line conclusion in that document that insufficient evidence then existed by which to link ambient PM exposures to increased risk of lung cancer.

More recent epidemiologic studies published since the 1996 PM AQCD have expanded upon and extended the earlier findings, including both (a) reported significant associations between long-term exposure to fine particles and lung cancer mortality in further analyses of data for the ACS and AHSMOG cohorts, and (b) suggestive evidence for PM-related increases in lung cancer incidence in analyses using AHSMOG cohort data (see Section 8.4.6.4,

Tables 8-10 and 8-12). The 2002 extended ACS analysis included additional mortality data from that cohort, inclusion of more recent air quality data , incorporation of statistical modeling advances, and additional data on potential confounders (such as dietary information); and it showed a 13% increase in lung cancer mortality per 10 $\mu g/m^3$ increase in $PM_{2.5}$. The AHSMOG analysis also included follow-up data from the AHSMOG cohort and yielded a significant association between PM_{10} and lung cancer mortality in males, but not in females. In further follow-up of the results in males only, positive but not statistically significant associations were reported with $PM_{2.5}$ and $PM_{10-2.5}$, and the authors observed that the association was larger in magnitude for $PM_{2.5}$ than for $PM_{10-2.5}$.

Toxicological studies have shown extensive evidence that certain types of particles are mutagenic or otherwise genotoxic in various types of bioassays, and several recent in vivo and in vitro studies have suggested that ambient particles are mutagenic. These latter studies have included exposures to ambient particles collected in Los Angeles, urban areas of Germany, and high traffic areas in the Netherlands (Section 7.8.1). In Germany, $PM_{2.5}$ extracts were found to have more mutagenicity than extracts of PM_{10} samples. Also, evidence of mutagenicity has been reported in studies using exposures to emissions from wood/biomass burning, coal combustion, and gasoline and diesel engine exhaust. Some of these studies identified polyaromatic hydrocarbons (PAHs) as well as some gaseous components of the emissions as being more mutagenic than other portions (Sections 7.8.2, 7.8.3). Such results appear to provide experimental evidence that adds some degree of plausibility for the reported epidemiologic findings of ambient PM associations with increased risk of lung cancer. However, this should be caveated by noting that some of the bioassay results were not indicative of particularly strong mutagenic responses to the PM sample extracts or components tested, nor is there necessarily a high degree of correspondence between some of the types of in-vitro genotoxic effects observed and demonstrated tumorigenic/cancer-causing potential across a broad array of different types of gaseous and particulate compounds tested over many years.

Thus, recent epidemiological studies support an association between long-term exposure to fine particles and lung cancer mortality; and the new toxicological studies provide credible evidence for the biological plausibility of these associations.

9.2.3.2.4 Fetal and Infant Development/Mortality

A few older cross-sectional studies reviewed in the 1996 PM AQCD reported findings suggestive of (a) possible TSP relationship to increased postnatal mortality among U.S. infants, children, and adolescents (aged 0-14 years) and (b) possible associations between early postnatal mortality among Czech infants (1-12 months). Several more recent studies conducted in the U.S. have focused on the possible effects of air pollution exposures during pregnancy on the occurrence of preterm or low birth weight births, both of these being risk factors for a myriad of later health problems (childhood morbidity/mortality; possible adult morbidity). One study found results suggestive of prenatal PM_{10} exposures during the 1st month of pregnancy or averaged over 6 weeks prior to birth being associated with increased risk of preterm birth, even in multipollutant models. However, another large scale U.S. study found little evidence indicative of prenatal PM_{10} exposures being related to increased risk of low birth weight, whereas a new Czech study did find evidence indicative of interuterine growth retardation (leading to low birth weight) being related to $PM_{2.5}$ exposures during the first gestational month. Similarly, analogously mixed results were reported for some new studies that evaluated ambient PM relationships to early postnatal mortality among U.S., Czech, and Mexican infants. These results, overall, highlight the need for more research to elucidate potential ambient PM effects on fetal development/mortality and for postnatal morbidity/mortality.

9.2.3.3 Summary and Conclusions

Consideration of the plausibility and coherence of PM-related effects involves the integration of the epidemiologic evidence with information derived from other types of studies (e.g., exposure, dosimetry, toxicology). As discussed in Section 9.2.2, consideration of epidemiologic evidence alone gave evidence supporting causality for associations between PM and a range of cardiovascular and respiratory health outcomes. In this section, evidence from both epidemiologic and toxicologic studies for health outcomes that are logically linked together was considered.

Epidemiologic studies have reported associations between ambient PM and cardiovascular effects across a range of endpoints, from cardiovascular mortality to more subtle effects, such as

changes in electrocardiographic markers of cardiac function, including evidence of cardiac arrhythmia and altered heart rate variability, or changes in blood characteristics (e.g., alterations in C-reactive protein levels, fibrinogen levels, blood viscosity, etc.) related to increased risk of ischemic heart disease. The new epidemiological findings for physiological changes suggest links to mechanistic pathways that could result in observed cardiovascular morbidity or mortality, but as described earlier, there are caveats to be considered in the interpretation of these studies. Important new evidence is available from toxicologic studies that builds support for plausibility of associations between particles, especially fine particles (or constituents) with physiological endpoints indicative of increased risk of ischemic heart disease, development or exacerbation of atherosclerosis or changes in cardiac rhythm. While many research questions remain, the convergence of evidence related to cardiac health from epidemiologic and toxicologic studies indicates both coherence and plausibility in this body of evidence.

For respiratory effects, notable new evidence from epidemiological studies substantiates positive associations between ambient PM concentrations and not only respiratory mortality, but (a) increased respiratory-related hospital admissions, emergency department, and other medical visits; (b) increased incidence of asthma and other respiratory symptoms; and (c) decrements in pulmonary functions. Of much interest are new findings tending to implicate not only fine particle components but also coarse thoracic (e.g., $PM_{10-2.5}$) particles as likely contributing to exacerbation of various respiratory conditions (e.g., asthma). Also of much interest are emerging new findings indicative of likely increased occurrence of chronic bronchitis in association with (especially chronic) PM exposure. The biological pathways underlying such effects can include inflammatory responses, increased airway responsiveness or altered responses to infectious agents. Toxicological studies have provided evidence that supports plausible biological pathways for respiratory effects of fine particles; little evidence is yet available on coarse fraction particles.

New epidemiological reanalyses or extensions of earlier prospective cohort studies of long-term ambient PM exposure also show substantial evidence for increased lung cancer risk being associated with such PM exposures, especially exposure to fine PM or specific fine particles subcomponents (e.g., sulfates) and/or associated precursors (e.g., SO_2). Toxicological evidence

of mutagenicity or genotoxicity in ambient or combustion-related particles supports the plausibility of a relationship between fine particles and lung cancer mortality.

PM-related health effects in infants and children are emerging as an area of more concern than in the 1996 PM AQCD; and ultimately, such health effects could have very substantial implications for life expectancy calculations. However, only very limited evidence currently exists about potential ambient PM relationships with some of the more serious pertinent health endpoints (low birth weight, preterm birth, neonatal and infant mortality, emergency hospital admissions, and mortality in older children). Most studies have used PM_{10} or other measures of thoracic particles; little evidence is available regarding $PM_{2.5}$ or $PM_{10-2.5}$. Also, little is yet known about involvement of PM exposure in the progression from less serious childhood conditions, such as asthma and respiratory symptoms, to more serious disease endpoints later in life.

Taken together, new evidence from mechanistic studies suggesting plausible biological response pathways, and the extensive body of epidemiology evidence on associations between short- and long-term exposures to ambient thoracic particles (typically indexed by PM_{10}) and a range of health effects, supports the general conclusion that ambient thoracic particles, acting alone and/or in combination with gaseous co-pollutants, are likely causally related to cardiovascular and respiratory mortality and morbidity. A growing body of evidence both from epidemiologic and toxicologic studies also supports the general conclusion that $PM_{2.5}$ (or one or more $PM_{2.5}$ components), acting alone and/or in combination with gaseous co-pollutants, are likely causally related to cardiovascular and respiratory mortality and morbidity. The strength of the evidence varies across such endpoints, with relatively stronger evidence of associations with cardiovascular than respiratory endpoints, potentially due to reduced statistical power where respiratory outcomes are seen less frequently than cardiovascular outcomes. In addition, mortality associations with long-term exposures to $PM_{2.5}$, in conjunction with evidence of associations with short-term exposures, provide strong evidence in support of a casual inference.

A much more limited body of evidence is suggestive of associations between short-term (but not long-term) exposures to ambient coarse-fraction thoracic particles (generally indexed by $PM_{10-2.5}$) and various mortality and morbidity effects observed at times in some locations.

This suggests that $PM_{10-2.5}$, or some constituent component(s) of $PM_{10-2.5}$, may contribute under some circumstances to increased human health risks. The strength of the evidence varies across endpoints, with somewhat stronger evidence for coarse-fraction particle associations with morbidity (especially respiratory) endpoints than for mortality. Reasons for differences among findings on coarse-particle health effects reported for different cities are still poorly understood, and much remains to be learned about the contribution of different sources or thoracic coarse particle components to different health outcomes. Reduced precision for $PM_{10-2.5}$ effect estimates may be heavily influenced by the increased error in $PM_{10-2.5}$ measurements obtained by subtraction, and exposure error related to greater spatial variability and reduced penetration indoors, as compared with $PM_{2.5}$.

There is also important new information highlighting potentially crucial roles that particle-bound water plays in serving as a carrier or vector by which other toxic agents (e.g., SO_2, peroxides, aldehydes) can be accumulated within inhalable PM and delivered in enhanced quantities into the deep lung. Water-soluble gases, which would be removed by deposition to wet surfaces in the upper respiratory system during inhalation, could dissolve in particle-bound water and be carried with the particles into the deep lung. Of much concern, particle-bound water appears to be a means by which dissolved hydrogen peroxide and other short-lived reactive oxygen species can be carried into lower respiratory tract regions and contribute to the induction of inflammatory responses. Also, certain other toxic species (e.g., nitric oxide [NO], nitrogen dioxide [NO_2], benzene, PAHs, nitro-PAHs, a variety of allergens) may be absorbed onto solid particles and carried into the lungs. Thus, ambient particles may play important roles not only in inducing direct health impacts of their constituent components but also in facilitating delivery of toxic gaseous pollutants or bioagents into the lung and may, thereby, serve as important mediators of health effects caused by the overall air pollutant mix.

The increased availability of certain bioaerosol materials (e.g., allergen-laded pollen fragments) in small (0.1 to 0.4 micrometers) fine particle sizes that deposit in TB and A regions of the lung (where they can exacerbate asthma effects) is also now recognized. Such bioagents have been found attached to nonbiologic particles of anthropogenic origin, as well as to natural biologic particles, which may serve to concentrate the biologic agents and enhance their delivery

into TB and A regions of the lung and to exacerbate consequent inflammatory and allergic asthmatic responses.

9.2.4 Potentially Susceptible and Vulnerable Subpopulations

The term *susceptibility* generally encompasses innate or acquired factors that make individuals more likely to experience effects with exposure to pollutants. Genetic or developmental factors can lead to innate susceptibility, while acquired susceptibility may result from age, from disease, or personal risk factors such as smoking, diet, or exercise; personal risk factors such as smoking, diet, or exercise habits are also associated with the development of heart and lung diseases. In addition, new attention has been paid to the concept of some population groups having increased *vulnerability* to pollution-related effects due to factors including socioeconomic status (e.g., reduced access to health care) or particularly elevated exposure levels.

The 1996 PM AQCD included only a relatively limited discussion of susceptible population groups potentially at increased risk for ambient PM effects, noting:

> "There is considerable agreement among different studies that the elderly are particularly susceptible to effects from both short-term and long-term exposures to PM, especially if they have underlying respiratory or cardiac disease. . . Children, especially those with respiratory diseases, may also be susceptible to pulmonary function decrements associated with exposure to PM or acid aerosols." (U.S. Environmental Protection Agency, 1996, p. 13-92)

New studies appearing since the 1996 PM AQCD provide additional evidence that substantiates the above-named groups as likely being at increased risk for ambient PM-related morbidity or mortality effects; and the evidence related to preexisting disease, age groups, and genetic susceptibility is summarized below. In addition, recent studies have explored potential new risk factors related to potential increased vulnerability for certain population groups, and evidence regarding factors such as socioeconomic status or exposure status are also discussed below.

9.2.4.1 Preexisting Disease as a Risk Factor

A number of time-series epidemiologic studies have reported increased risk in study subsets of individuals with preexisting heart or lung diseases. Several studies have suggested that people with diabetes are also susceptible to PM effects, possibly due to cardiovascular complications associated with diabetes. One study reported large relative risk estimates for total mortality in people with preexisting COPD living in Barcelona. Another study in Montreal showed larger effect sizes for total mortality in persons with cancer, diabetes, lower respiratory disease, cardiovascular disease, coronary artery disease, and congestive heart failure. In addition, an European study found significant effects in the subset of adults who had bronchial hyperreactivity or increased peak flow variability; and a Canadian study reported greater effects in a subset of children who had asthma.

Toxicologists have used several animal models of cardiopulmonary disease to evaluate PM susceptibility aspects. Such animal models include rats with monocrotaline-induced pulmonary vasculitis/hypertension, experimental coronary artery clockage, apo-E atherosclerosis-prone mice, SO_2-induced chronic bronchitis, spontaneously hypertensive rats, and animals infected with various viral or bacterial agents. As summarized in Section 7.5.1 of Chapter 7, increased magnitude or frequency of effects have been reported with PM exposure for these groups of animals relative to healthy animals. In addition, toxicologists have also studied effects of particles, including diesel exhaust particles, in animals with heightened allergic sensitivity and via in vitro studies (summarized in Section 7.5.2). Overall, the results from newly available toxicological studies provide evidence suggestive of enhanced susceptibility to inhaled PM in "compromised" hosts.

The underlying biology of lung diseases might also lead to heightened sensitivity to PM, but this attribute of disease remains hypothetical in the context of PM (see Section 7.4.9 of Chapter 7). The functional linkages with the cardiac system for maintenance of adequate gas exchange and fluid balance notwithstanding, the role of inflammation in the diseased respiratory tract (airways and alveoli) could be an important factor. There is sufficient basic biological data to hypothesize that the exudated fluids in the airspaces may either interact differently with deposited PM (e.g., to generate oxidants), to augment injury, or to predispose the lung (e.g., sensitize receptors) so as to enhance the response to a stereotypic PM stimulus through otherwise

normal pathways. Less appreciated is the loss of reserve (functional or biochemical), wherein the susceptible individual may be incapable of sufficient compensation (e.g., antioxidant responses). Any of these or related mechanisms may contribute to increased "susceptibility" and may indeed be a common factor possibly contributing to increased risk for various susceptible groups.

Studies with humans that might reveal more specific data have been limited both ethically, as well as by the absence of or limitations associated with biomarkers of response (such as interpretation of ECG indicators of cardiac function and disease). Measures of blood-gas saturation and lung function appear not to be sufficiently revealing or sensitive to mild physiologic changes in those with moderate disease conditions who might be amenable to participation in laboratory studies. In the field, assessing the degree of underlying disease and how that relates to responsiveness of these biomarkers is unclear. However, subjects with COPD and asthma have been studied under controlled conditions with inert aerosols for the purpose of assessing distribution of PM within the lung, and it is now quite clear that airways disease leads to very heterogeneous distribution of PM deposited within the lung. Studies have shown up to 10-fold higher than normal deposition at airway bifurcations, thus creating "hot-spots" that may well have biologic implications, especially if the individual already has diminished function or other debilitations due to the underlying disease, even cardiovascular disease (CVD).

9.2.4.2 Age-Related At-Risk Population Groups: the Elderly, Infants, and Children

The very young and the very old apparently constitute two other groups thought to be especially at risk for ambient PM air pollution health effects. Numerous epidemiological studies have reported health responses to PM and other pollutants for one or another specific age group.

These studies, as summarized in Section 8.4.9 of Chapter 8, tend to support previous findings that, depending on the effect under study, older adults and children may be more susceptible to certain PM-related effects. More specifically, older adults (aged 65+ years) appear to be most clearly at somewhat higher risk for PM exacerbation of cardiovascular-related disease effects and, perhaps, tend to experience higher PM-related total (nonaccidental) mortality risk, as well. On the other hand, more limited evidence points to children possibly being at somewhat higher risk for respiratory-related (especially asthma) PM effects than adults. Some

newly emerging studies provide suggestive evidence for increased neonatal mortality and adverse birth outcomes being associated with ambient PM exposures, but other new studies have found contradicting results.

A major factor in increased susceptibility to air pollution is the presence of a preexisting illness and susceptibility related to age group may well be closely linked with the potential for preexisting cardiopulmonary diseases. Cardiopulmonary diseases more common to the elderly contribute to the potentially higher risk within older age groups. Also, some recent studies have reported evidence suggestive of associations between ambient PM exposure and effects on total development or neonatal mortality (see Section 8.3.4 of Chapter 8). Although infection as a risk factor for PM has already been noted, it is important to emphasize that there are clear age differences in both the incidence and type of infections across age groups. Young children have the highest rates of respiratory illnesses related to infection (notably respiratory syncytial virus), while adults are affected by other infectious agents such as influenza that may also lend increased susceptibility to PM effects. Data to address fully the importance of these differences is incomplete, but some of the newly available toxicological studies provide evidence for ambient PM exposures affecting lung defense mechanisms so as to exacerbate preexisting respiratory infections.

In addition to their higher incidences of preexisting respiratory conditions, several other factors may render children and infants more susceptible or vulnerable to PM exposures, including more time spent outdoors, greater activity levels and ventilation, higher doses per body weight and lung surface area, and the potential for irreversible effects on the developing lung. The amount of air inhaled per kilogram body weight decreases dramatically with increasing age, due in part to ventilation differences (in cubic meters per kilogram a day) of a 10-year-old being roughly twice that of a 30-year-old person, even without the consideration of activity level. Child-adult dosage disparities are even greater when viewed on a per lung surface-area basis.

As to potential lung developmental impacts of PM, there exist both experimental and epidemiologic data, which although limited, suggest that the early post-neonatal period of lung development is a time of high susceptibility for lung damage by environmental toxicants. In experimental animals, for example, elevated neonatal susceptibility to lung-targeted toxicants has been reported at doses “well below the no-effects level for adults” (Plopper and Fanucchi,

2000); and acute injury to the lung during early postnatal development may impair normal repair processes, such as down-regulation of cellular proliferation (Smiley-Jewel et al., 2000, Fanucchi et al., 2000).

9.2.4.3 Genetic Susceptibility

A key issue in understanding adverse health effects of inhaled ambient PM is the identification of which classes of individuals are susceptible to PM. Although factors such as age and health status have been studied in both epidemiology and toxicology studies, some investigators have begun to examine the importance of genetic susceptibility in the response to inhaled particles because of evidence that genetic factors play a role in the response to inhaled pollutant gases. To accomplish this goal, toxicologists typically have sought to detect interstrain differences in responses to particles in rodents; little evidence is available from epidemiological studies at this time. The small group of newly-available toxicological studies have begun to demonstrate that genetic susceptibility can play a role in the response to inhaled particles (Section 7.5.2); for example, one research group has found a genetically-based difference in susceptibility to lung injury induced by instilled ROFA, using several strains of rats with varying genetic characteristics.

9.2.4.4 Gender

There are appear to be some gender differences in the regional efficiency of deposition as well as the deposition rate of particles. These differences derive from differences between males and females in body size, conductive airway size, and ventilatory parameters. Females have a somewhat greater deposition of coarse mode particles in the ET and TB regions, but lower deposition in the A region. This gender effect appears to be particle-size dependent, showing a greater fractional deposition in females for very small ultrafine and large coarse thoracic particles. Total fractional lung deposition for 0.04 and 0.06 μm particles also appears to be somewhat greater in females than males but only negligibly so for particles in the size range 0.8 to 1.0 μm. As the particle size increases (3 to 5 μm), total fractional deposition increases in females. While deposition appears to be more localized in females than males, deposition rate appears to be greater in males.

Little evidence is available from toxicology studies regarding gender differences in susceptibility to pollution effects. In the epidemiology studies that have included stratified analyses based on gender, there is no clear pattern of increased vulnerability for either males or females. Results from two of the prospective cohort studies evaluating long-term PM exposure effects have reported greater mortality (and cancer) risks in males than in females (e.g., Abbey et al., 1999; Pope et al., 2002), but a number of studies using long-term and short-term PM exposures report no clear pattern of differences in effects across genders (e.g., Linn et al., 2000; Ostro et al., 2001; Dockery et al., 1996; Raizenne et al., 1996; Krewski et al., 2000). Where differences in effects between males and females were reported in the time-series studies, they were generally not significantly different and the findings were not consistent. For example, from PM_{10}-mortality studies conducted in Chicago, Styer et al. (1995) report larger effect estimates for men, but Ito and Thurston (1996) report larger effect estimates for women. Thus, insufficient evidence exists overall to allow for any clear conclusions to be drawn as to potential gender differences with regard to PM health effects.

9.2.4.5 Factors Related to Enhanced Vulnerability

Epidemiological studies of long-term PM exposures have suggested that there is effect modification of PM-mortality associations due to socioeconomic factors. In the ACS and Six Cities cohort analyses on mortality risk with long-term exposure to $PM_{2.5}$, there was clear evidence of effect modification (though not confounding) by education level, with greater effects being reported in the cohort subgroups with lower education levels (Krewski et al., 2000; Pope et al., 2002).

Among the studies of short-term PM exposure (Chapter 8, Appendices 8A and 8B), the evidence is more mixed regarding potential influence of socioeconomic status on PM-related health risks. No evidence of effect modification for PM_{10}-mortality associations in 10 U.S. cities was found using four measures of social or economic status: greater percent of population living in poverty status; higher unemployment rate; greater percent of population with college degrees; or greater percent of the population being nonwhite. Similarly, in a study of hospital admissions in 10 U.S. cities, none of the four measures of social or economic status mentioned above significantly modified the relationship between PM_{10} and hospitalization for COPD or

pneumonia. However, for CVD admissions, PM_{10} effect estimates were greater in communities with greater percentages of the population being unemployed, nonwhite, or living in poverty. This may be a result of increased exposure, increased prevalence of predisposing diseases, or other factors. Also, one study in Atlanta found race (black versus white) and insurance (Medicaid versus non-Medicaid) to be effect modifiers for emergency department admissions for asthma in children, but no associations with interaction terms for these factors and PM_{10} or ozone. Another study analyzed associations between hospitalization for asthma with PM_{10} and ozone in Los Angeles for subsets of patients who were uninsured, insured by MediCal, or had other insurance. Significant associations with PM_{10} were reported only for the subset of patients using MediCal, not for the privately insured or uninsured; the authors speculate that the small sample size for uninsured patients may have precluded detection of an effect. However, a Seattle study reported no effect estimate differences for asthma hospitalization in children (< 18 years) when comparing the inner city area with the rest of Seattle.

Vulnerability to PM-related effects may also be increased in populations experiencing enhanced exposure to ambient aerosols in comparison to other groups. In some cases, e.g., proximity to roadways or other PM sources, there may be overlap with other factors (e.g., socioeconomic statuses).

As summarized in Chapter 8, in several reports from the Southern California children's study, larger effect estimates for reduced lung function or increased respiratory illness with long-term exposure to PM and other pollutants were reported for the subset of children spending a larger amount of time outdoors. Also, using data from 14 U.S. cities, other investigators found that effect estimates between PM_{10} and hospitalization for CVD and COPD increased with less air conditioning use in homes (such use being an indicator of decreased exposure due to less penetration of particles into the home). Increased vulnerability to the effects of pollution may come from living near a source of PM and other pollutants, such as a major roadway. Numerous recent studies have linked adverse health effects with indicators of traffic-related pollution and with residences near a major road.

In addition to the above factors contributing to increased vulnerability, exercise may also increase the potential health risks of inhaled particles, because exercise increases the rate of oxygen consumption and changes ventilatory parameters affecting airflow rate and breathing

patterns. The switch from nose breathing to mouth breathing, which occurs as exercise intensity increases, leads to an increase in fractional deposition of ultrafine and coarse thoracic particles in the tracheobronchial and alveolar regions. The higher breathing rate and larger tidal volume lead to a greater amount of deposition. Total lung deposition rate may be 3 to 4 times greater during exercise. The more rapid breathing of children also leads to a greater amount of deposition.

9.2.4.6 Summary and Conclusions

The existence of heart and lung disease is clearly linked with increased susceptibility to effects from PM exposure, based on epidemiological and toxicological studies and dosimetric evidence. The epidemiological evidence of susceptibility is primarily from studies of short-term exposure. Long-term exposure studies have suggested that PM exposure may result in chronic respiratory disease or decreased lung function growth, thus there is the potential that chronic PM exposure can also increase susceptibility to acute changes in PM. More recent studies also support considering older adults and children, including possibly infants, as susceptible groups, recognizing that there is likely overlap between age categories and preexistence of cardiopulmonary diseases. Some new evidence from toxicologic studies indicates that there may be populations who are genetically predisposed to PM-related effects. In addition, beyond consideration of innate or acquired factors related to susceptibility, some population groups can be considered to be more vulnerable to PM-related effects due to factors such as socioeconomic status or residing near roadways or other sources.

9.2.5 Potential Public Health Impacts in the United States

The 1996 PM AQCD highlighted the then considerable uncertainty related to estimating public health impact of ambient PM exposure, stating:

> "Efforts to quantify the number of deaths attributable to, and the years of life lost to, ambient PM exposure are currently subject to much uncertainty." (U.S. Environmental Protection Agency, 1996, p. 13-87). Nonetheless, while "PM-related increases in individual health risks are small," they are "likely significant from an overall public health perspective because of the large numbers of individuals in susceptible risk groups that are exposed to ambient PM." (U.S. Environmental Protection Agency, 1996, p. 1-21)

9.2.5.1 Magnitude of Susceptible Groups

As summarized in Section 9.2.4, numerous U.S. population groups may be identified as having increased susceptibility or vulnerability to adverse health effects from PM. Considering together the subpopulations of persons with preexisting cardiopulmonary disease, older adults, children, people of lower socioeconomic status and those with higher potential exposure levels as potentially susceptible or vulnerable, it is clear that the impact of PM on public health could be very extensive.

One consideration in the assessment of potential public health impacts is the size of various population groups that may be at increased risk for health effects associated with PM-related air pollution exposure. Table 9-4 summarizes information on the prevalence of chronic respiratory and circulatory conditions and diabetes in the U.S. population in 2000. It can be seen that people with preexisting cardiopulmonary disease constitute a fairly large proportion of the population, with tens of millions of people included in each disease category. For circulatory conditions, approximately 22 million people, or 11% of the U.S. adult population, have received a diagnosis of heart disease. Approximately 20% of the U.S. adult population has hypertension, with 6% reporting diagnoses of coronary heart disease. For respiratory conditions, approximately 9% of U.S. adults (and 11% of children) have been diagnosed with asthma, and 6% of adults diagnosed with conditions included in COPD. Table 9-5 provides further information on the number of various specific respiratory conditions per 100 persons by age among the U.S. population during the mid-1990s. In addition, approximately 6% of the U.S. adult population has diabetes. Both cardiovascular conditions and diabetes are more common among older age groups, while asthma prevalence is higher in children.

In addition, as discussed previously, subpopulations based on age group or socioeconomic status would also comprise substantial segments of the population that may be potentially more vulnerable to PM-related health impacts. Based on U.S. census data from 2000, about 26% of people in the U.S. are under 18 years of age, and 12% are 65 years of age or older. From among commonly-used indicators of socioeconomic status, about 12% of individuals and 9% of families are below the poverty level, and 20% of the U.S. population does not have a high school or higher level of education. Hence, large proportions of the U.S. population are included in groups that are thought likely to be at increased risk for ambient PM-related health effects.

TABLE 9-4. PREVALENCE OF SELECTED CARDIORESPIRATORY DISORDERS BY AGE GROUP AND BY GEOGRAPHIC REGION, 2000 (reported as percent or numbers of cases in millions)

			Age				Regional			
	Adults (18+)*		18-44	45-64	65-74	75+	NE	MW	S	W
Chronic Condition/Disease	Number ($\times 10^6$)	%	%	%	%	%	%	%	%	%
Respiratory conditions										
Asthma	18.7	9.3	9.8	8.7	8.7	8.1	8.9	9.3	9	10.3
*Asthma (<18 years)**	*8.92**	*12.4**								
COPD:										
Chronic bronchitis	9.36	4.6	3.6	5.5	6.4	6.6	3.9	4.6	5.4	4.1
Emphysema	3.13	1.6	0.2	1.9	4.7	5.9	1	1.7	2	1.2
Circulatory conditions										
All heart disease	21.99	10.9	4.2	12.5	26.4	35	10.4	11.5	11.5	9.5
Coronary heart disease	11.23	5.6	0.7	6.6	17.3	22.7	5.1	5.3	6.3	5
Hypertension	39.21	19.5	6.4	27.3	46.3	51.5	17.9	18.8	21.6	18.1
Stroke	4.36	2.2	0.3	2.1	6.5	10.5	1.6	2.1	2.6	2.1
Diabetes	11.86	5.9	1.9	8.4	15.9	13.4	5.5	5.6	6.4	5.9

Source: Pleis et al. (2003).

*All data are for adults except asthma prevalence data for children under 18 years of age, responding to "ever told had asthma"; source for data on children is Blackwell et al. (2003).

TABLE 9-5. NUMBER OF ACUTE RESPIRATORY CONDITIONS PER 100 PERSONS PER YEAR, BY AGE: UNITED STATES, 1996

Type of Acute Condition	All Ages	Under 5 Years	5-17 Years	18-24 Years	25-44 Years	45 Years and Over		
						Total	45-64 Years	65 Years and Over
Respiratory Conditions	78.9	129.4	101.5	86	76.9	53.3	55.9	49
Common Cold	23.6	48.6	33.8	23.8	18.7	16.1	16.4	15.7
Other Acute Upper Respiratory Infections	11.3	13.1	15	16.1	11.6	7	7.5	6.1
Influenza	36	53.7	44.3	40.5	38.1	23.3	26.1	18.6
Acute Bronchitis	4.6	*7.2	4.3	*3.9	5.1	3.8	3.5	*4.4
Pneumonia	1.8	*3.9	*1.7	*1.4	*1.3	*2.0	*0.9	*3.8
Other Respiratory Conditions	1.7	*2.9	*2.4	*0.4	*2.0	*1.1	*1.5	*0.5

Source: Adams et al. (1999).

The health statistics data also illustrate what is known as the "pyramid" of effects. At the top of the pyramid, there are approximately 2.5 millions deaths from all causes per year in the U.S. population, with about 900,000 deaths due to cardiovascular diseases and 100,000 from chronic lower respiratory diseases (Arias et al., 2003). For measures of cardiovascular disease morbidity, there are approximately 6 million hospital discharges per year (Hall and DeFrances, 2003), nearly 5 million emergency department visits (McCaig et al., 2004), to over 70 million ambulatory care visits for circulatory system disorders (Cherry et al., 2003). For chronic respiratory health diseases, there are over 3 million hospital discharges for respiratory diseases (Hall and DeFrances, 2003), nearly 13 million emergency department visits (McCaig et al., 2004), over 200 million ambulatory care visits per year for respiratory conditions (Cherry et al., 2003) and an estimated 700 million restricted activity days per year due to respiratory conditions (Adams et al., 1999). Combining small risk estimates with relatively large baseline estimates of health outcomes can result in quite large public health impacts. Thus, even a small percentage reduction in PM health impacts on cardiorespiratory-related diseases would reflect a large number of avoided cases.

Another key input for public health impact assessment is the range of concentration-response functions for various health outcomes. As described in Chapter 8, epidemiological studies have reported associations between short-term exposure to PM, especially PM_{10} and $PM_{2.5}$, with: mortality, hospitalization and medical visits for cardiovascular and respiratory diseases; changes in heartbeat rhythm or electrocardiographic markers of cardiac function; incidence of myocardial infarction; changes in blood characteristics (e.g., C-reactive protein, fibrinogen levels); incidence of respiratory symptoms; and reduced lung function. As discussed previously, the fewer studies using $PM_{10-2.5}$, measurements have reported evidence for associations with hospitalization for cardiovascular and respiratory causes, and increased respiratory symptoms, and suggestions of associations with cardiopulmonary mortality. Associations with long-term exposure to fine particles have been reported for cardiovascular and lung cancer mortality, increased incidence of respiratory disease and decreased lung function and lung function growth. The magnitude of the concentration-response function, measured or anticipated change in air concentration, and size of population group are three major components of a public health impact assessment.

Of concentration-response functions for PM-related effects, it can generally be said that the effect estimates are small in magnitude. In historical episodes with very high air pollution levels, risks on the order of 4-fold (400%) increases in mortality were estimated, but much smaller risk estimates have been reported from recent studies at current pollution levels.

Risk estimates from long-term exposure studies are often larger in magnitude than those for the same health outcome associated with short-term PM exposure. These estimates can reflect different responses — long-term exposure perhaps being linked with development of disease and short-term exposure with acute exacerbation of existing conditions — but there may also be some overlap in the effect estimates. Relative risk estimates for total mortality from the prospective cohort studies fall in the range of 7 to 13% increase per 10 $\mu g/m^3$ increase in $PM_{2.5}$; there are no significant associations with long-term exposure to $PM_{10-2.5}$. Risk estimates from the short-term exposure studies are considerably smaller in magnitude, on the order of 2 to 6% increase in mortality per 25 $\mu g/m^3$ increase in $PM_{2.5}$ and $PM_{10-2.5}$. Time-series studies using

distributed lag periods over more extended time periods (e.g., 40-60 days) partially bridge these results.

Effect estimates for morbidity responses to short-term changes in PM tend to be larger in magnitude than those for mortality; those for hospitalization generally range from 4-10% increases for cardiovascular diseases and 5-15% increases for respiratory diseases per 25 $\mu g/m^3$ increase in $PM_{2.5}$ and $PM_{10-2.5}$. From the more recent studies on visits to the emergency department or physicians' offices for respiratory conditions, effect estimate sizes have been somewhat larger, ranging up to about 35% per 25$\mu g/m^3$ increase in $PM_{2.5}$.

Other important considerations for public health impact assessment that have been discussed previously include questions about the concentration-response function form and potential identification of threshold levels, and attribution of risks for the varying health outcomes to PM, sources or components of particles, and co-pollutants. Taken together, however, it can be concluded that small incremental risks for large groups of the U.S. population would result in large public health impact estimates.

9.2.5.2 Impact on Life Expectancy

Conceptually, ambient PM exposures may be associated with both the long-term development of underlying health problems ("frailty") and with the short-term variations in timing of mortality among a susceptible population with some underlying health condition (Künzli et al., 2001). New evidence from toxicological studies have provided insights into potential mechanisms for PM-related health effects, but this evidence is not sufficient to allow direct conclusions to be drawn regarding specific effects linked with short-term or long-term PM exposures. Epidemiologic studies of the mortality effects of short-term exposure to PM using time-series studies can only capture PM's association with short-term variations in mortality and, therefore, must systematically underestimate the proportion of total mortality attributable to PM.

Finally, as discussed in Section 8.4.10 of Chapter 8, there appears to be no strong evidence to suggest that PM exposures are shortening life by only a few days (i.e., for "harvesting"). To the contrary, the 1996 PM AQCD noted that results from the Harvard Six City Study

suggested that long-term exposure to $PM_{2.5}$ was associated with ~2 year loss of life expectancy. More recent investigations of the public health implications of effect estimates for long-term PM exposures were also reviewed in Chapter 8. Using results from prospective cohort studies of mortality in adults, it has been estimated that loss of population life expectancy may be substantial (on the order of a year or so) with long-term exposure to PM; however, further research is needed on this question. Further research is also needed to build upon currently only very limited evidence about potential PM-related health endpoints in infants and children, which may ultimately significantly increase estimates of the extent of life shortening due to PM-related premature mortality.

It is also useful to highlight the newer results of the extension of the ACS study analyses (that include more years of participant follow-up and address previous criticisms of the earlier ACS analyses), which indicate that long-term ambient PM exposures are associated with increased risk of lung cancer. That increased risk appears to be in about the same range as that seen for a nonsmoker residing with a smoker, with any consequent life-shortening due to lung cancer.

Lastly, new epidemiologic studies of a broader array of health endpoints indicate ambient PM associations with increased nonhospital medical visits (physician visits) and asthma effects. Such new findings suggest likely much larger health impacts and costs to society due to ambient PM than just those indexed either by just hospital admissions/visits and/or mortality.

9.3 SYNTHESIS OF AVAILABLE INFORMATION ON PM-RELATED WELFARE EFFECTS

The synthesis of available information on PM-related welfare effects presented in this section focuses on four types of effects, i.e., PM-related effects on: visibility, vegetation and ecosystems, climate change processes, and man-made materials. The resulting synthesis of information and conclusions are intended to provide the scientific bases for options to be considered by the EPA Administrator as to whether currently available scientific information supports retention or revision of existing secondary PM NAAQS.

9.3.1 Airborne Particle Effects on Visibility

The following discussion of the effects of airborne particles on visibility is drawn primarily from information in Chapter 4 of this document, which itself is supplementary to several other significant reviews of the science of visibility. These reviews include reports of the National Acid Precipitation Assessment Program (1991, 1998), the National Research Council (1993) report on Protecting Visibility in National Parks and Wilderness Areas, and U.S. EPA's Interim Findings on the Status of Visibility Research (U.S. Environmental Protection Agency, 1995). The focus here is on characterizing: (a) how ambient PM (in particular ambient fine PM) impairs visibility, and (b) how the public perceives and values improvements in visibility, especially in urban areas.

9.3.1.1 Relationships Between Ambient PM and Visibility

The role of ambient PM in impairing visibility has long been well understood, as was recognized in the 1996 PM AQCD as follows:

> "The relationships between air quality and visibility are well understood. Ambient fine particles are the major cause of visibility impairment. Significant scientific evidence exists showing that reducing fine particle concentrations will improve visibility." (U.S. EPA, 1996, p. 1-18).

Airborne particles degrade visibility by scattering and absorbing light. These optical properties can be well characterized in terms of a light extinction coefficient, which is the fractional attenuation of light per unit distance. The extinction coefficient produced by a given distribution of particle sizes and compositions is strictly proportional to the particle mass concentration. The efficiency with which different particles attenuate light is a function of particle size, with fine particles in the accumulation mode being much more important in causing visibility impairment than coarse-mode particles. Thus, it is fine-particle mass concentrations that tend to drive extinction coefficients in polluted air.

The spatial and temporal variability in the observed extinction coefficient per measured mass of $PM_{2.5}$ is mainly due to the effects of particle-bound water, which varies with relative

humidity and is removed by drying when ambient $PM_{2.5}$ mass concentrations are measured using the Federal reference method. In arid regions such as the Southwest, where this effect is minimized, observed ratios of extinction coefficients to $PM_{2.5}$ mass concentrations are generally low and exhibit little variability (approximately in the range of 2 to somewhat greater than 3 m^2/g). In more humid areas such as the East, observed efficiencies are generally higher and more variable (ranging from about 4 to 5 m^2/g under moderate humidity conditions up to 7 m^2/g or more high under humidity conditions).

The overall effect of increasing humidity on light scattering by particles was quantified nearly 20 years ago, but current research is greatly increasing the detailed understanding of the response of aerosol particles to changing humidities and the relationship of this response to the chemical composition of the particles. Humidity effects generally become important at relative humidities between 60 and 70%, and increase particle-related light scattering by a factor of 2 at ~85% relative humidity. Light scattering by particles increases rapidly with relative humidity when the humidity exceeds 90%.

As discussed in Chapter 4, a number of studies available since the last review have resulted in refinements both (a) in the algorithms and related parameters used to calculate light extinction based on particle properties and (b) in related measurement methods and monitoring instrumentation. For example, a few studies have focused on better characterizing the hygroscopic properties of particles, with a particular focus on organic compounds and mixtures associated with different sources (e.g., Cocker et al., 2001; Chughtai et al., 1999; Hemming and Seinfeld, 2001). More broadly, Malm (2000) used data from a special study at the Great Smoky Mountain National Park to compare the performance of a number of models for calculating light extinction and found that significant model improvement could be obtained by including the degree of sulfate ammoniation in the model, so as to better estimate the ambient aerosol water content. These studies have served primarily to reinforce and refine our understanding of how airborne particles affect visibility.

Effects to address visibility impairment have historically been focused on rural areas, particularly in national parks and wilderness areas (i.e., Federal Class I areas). Visibility in such areas varies substantially between eastern and western sites in the U.S., with the haziest days in

the rural West typically being roughly equivalent to the clearest days in the East. The largest monitoring network that measures both visibility and aerosol conditions is the Interagency Monitoring of Protected Visual Environments (IMPROVE) network, formed in 1987 as a collaborative effort between Federal, regional, and state entities responsible for visibility protection in such areas. This network has been used in visibility-related research, including the advancement of visibility monitoring instrumentation and analysis techniques and source attribution field studies. This network and related research have provided substantial support to regulatory programs established to protect Federal Class I areas from local and regional sources of visibility impairment.

More recent attention has been given to addressing visibility impairment in urban areas, as well. Such efforts can now draw upon data available from the new national monitoring networks designed to assess $PM_{2.5}$ concentrations and composition in urban areas across the country that have been deployed in conjunction with establishment in 1997 of the $PM_{2.5}$ NAAQS.
In addition, higher resolution visibility data are now becoming available from the Automated Surface Observing System (ASOS) monitoring network in operation at airports across the U.S. These and other sources of visibility and ambient fine particle data provide important information that helps to facilitate the characterization of relationships between ambient PM and visibility especially in urban areas.

In addition to empirically derived relationships between ambient PM and visibility measurements, photographic modeling techniques that have been refined in recent years are useful in portraying changes in visibility specifically due to changes in ambient PM levels.
For example, the WinHaze system developed by Molenar et al. (1994) has been used to simulate changes in visibility as a function of changes in air quality for both rural and urban areas. This modeling system can produce a simulated photograph that accurately depicts a cloud-free scene as it would appear to a human observer. Such photographic representations have facilitated the evaluation of how the public perceives and values improvements in visibility in a number of urban areas, as discussed below.

9.3.1.2 Public Perception and Valuation of Visibility Improvements

The Clean Air Act (Section 169A) establishes a national visibility goal to "remedy existing impairment" and prevent future impairment in national parks and wilderness areas across the United States, and requires that long-term strategies be put in place to make reasonable progress toward this national goal. The 1990 Amendments to the Act (Section 169B) place additional emphasis on improving visibility, leading to EPA's promulgation of a Regional Haze Rule in 1999 that establishes specific goals for improving visibility in such areas. These national goals and regulations provide clear evidence of the value society places on visibility improvements that add to enjoyment of scenic vistas.

More specific information about how the public perceives and values improvements in visibility in rural and urban areas comes from both economic studies and from local and/or state initiatives in a number of areas to adopt local visibility goals and standards. As summarized in Chapter 4, there is an extensive scientific literature on the theory and application of economic valuation methods. Such studies have estimated the value of visibility improvements in the range of billions of dollars annually, for example, in analyses of visibility improvements in national parks in the Southwest (e.g., Chestnut and Rowe, 1990) and in an analysis of benefits to residents in the eastern U.S. due to visibility improvements associated with the Federal acid rain program (Chestnut and Dennis, 1997). Results vary across studies and uncertainties remain about specific dollar values estimated. Local initiatives over the past few years, for example in the Denver, CO and Phoenix, AZ areas, also provide important information about public perceptions and attitudes about visibility impairments, including what is adverse, although uncertainty would be involved in extending the public value judgments implied by these examples to other areas.

More specifically, the initiative in Denver began with a series of visibility-related studies in the 1970's through the 1980's, leading to the adoption of a visibility standard for the city of Denver in 1990. This standard is based on a light extinction level of 0.076 km^{-1}, averaged over four daylight hours, reflecting the short-term nature of the perception of changes in visibility conditions. This standard is equivalent to a visual range of approximately 50 km and reflects citizen judgments about acceptable and unacceptable levels of visual air quality. In Phoenix,

a study conducted between 1988 and 1990 led to establishment of a Blue Sky Index, which focuses on days in which the visual range, averaged over six daylight hours, is 40 km or more. This target is based on a method very similar to that used in Denver for obtaining citizen's judgments as to acceptable levels of visual air quality. While in practice these standard target values are exceeded many times per year in these areas, they reflect a reasonable degree of consistency in the outcome of the approach used to characterize the value that citizens in these two urban areas place on visual air quality. In addition, similar "acceptable" and "not acceptable" threshold determinations, convergent on a minimal visual range of 40 to 60 km, have also been identified in visibility standards in the Lake Tahoe area, the lower Fraser Valley in British Columbia, CN, and the State of Vermont. In areas across the United States, visual ranges of 40 to 60 km are approximately associated with $PM_{2.5}$ concentrations ranging from < 10 $\mu g/m^3$ up to about 20 $\mu g/m^3$.

9.3.1.3 Summary and Conclusions

Impairment of visibility in rural and urban areas is directly related to ambient concentrations of fine particles, as modulated by particle composition, size, and hygroscopic characteristics, and by relative humidity. Refinements in algorithms that relate these factors to light extinction, and thus, to visual range, as well as the availability of much expanded databases of $PM_{2.5}$ concentrations and related compositional information and higher resolution visibility data all contribute to the ability to develop improved characterizations of relationships between ambient fine particle concentrations and visibility impairment.

Various local initiatives to address visibility impairment have demonstrated the usefulness of approaches now being used to evaluate public perceptions and attitudes about visibility impairment and public judgments as to the importance of standards to improve visibility relative to current conditions. Various such initiatives, conducted in areas with notable scenic vistas (e.g., Denver, CO, Phoenix, AZ, Lake Tahoe, CA, and State of Vermont), have resulted in local standards that reflect what might be referred to as "adverse thresholds" associated with a minimum visual range of approximately 40 to 60 km. These various local standards take into account that visibility impairment is an instantaneous effect of ambient $PM_{2.5}$ concentrations and

that the public primarily values enhanced visibility during daylight hours. These considerations are reflected in local standards that are based on sub-daily averaging times (e.g., 4 to 6 hours), typically averaged across midday hours. This general convergence of visual range values and averaging times that have been determined to be acceptable to the public in a number of such locations suggests that these values and averaging times are relevant for consideration in assessing the need for a national secondary standard to protect visibility in such areas.

9.3.2 Effects of Ambient PM on Vegetation and Ecosystems

9.3.2.1 Direct and Indirect Effects of Ambient PM

The direct and indirect effects of deposited ambient PM can span the full range, scale and properties of biological organization listed under Biotic condition (Chapter 4) and can vary widely depending on the (1) sensitivity of each ecosystem and/or its component biota (biotic receptors) to a given concentration and chemical composition (acid/base, trace metal or nutrients, e.g., nitrates or sulfates) of PM components; (2) the pre-existing buffering capacity of the soils and/or waters (streams, rivers, ponds, and lakes, estuaries and ocean); (3) the magnitude (ambient concentration and deposition velocity), mode, and meteorology of the deposition; and (4) other site-specific features (e.g., terrain, hydrology, climate, land use, etc.). The ability of an ecosystem to maintain integrity in the presence of the different chemical constituents in deposited aerosols is a direct function of the sensitivity level of the ecosystem to the different PM constituents and to the ability of the ecosystem components to ameliorate the effects that can result. Changes in structural patterns and the functioning of ecological processes must be scaled in both time and space and propagated to the more complex levels of community interaction to produce observable ecosystem changes.

Direct effects result when PM is deposited onto sensitive receptors. Such effects can be either chemical and/or physical; and they have been observed largely downwind of point sources. These effects were the usually the result of dust from limestone quarries and cement kilns or heavy metals from iron and lead smelting factories (Chapter 4). Because these effects tend to be very limited in scope, they do not warrant the level of attention given the more widespread indirect, ecosystem-level, effects discussed below.

Indirect effects of major concern (such as nitrogen saturation, acidification, and eutrophication) are mediated via the soil or aquatic environment and have the potential of degrading ecosystem functioning by altering species diversity, structure, and sustainability of ecosystems to the detriment of animals and plant life, so that ecosystems provide fewer benefits and services for humans (Moomaw, 2002).

Ecosystem effects within the U.S. span the range from remote to urban. Most of the ecosystem impacts of PM that have been reported occurred at nonurban sites and, as such, nonurban ecosystems are the primary focus of the discussion that follows in subsequent subsections. In briefly considering urban ecosystems here, it is recognized that despite a large body of knowledge on concentrations and chemical reactions of air pollutants in cities, there has been little work on the rates of atmospheric deposition to urban ecosystems. However, urban ecosystems are likely to be subjected to large rates of deposition of anthropogenic pollutants (Lovett et al., 2000). Decades of research on urban air quality indicate that cities are often sources of nitrogen oxides, sulfur oxides, and dust, among many other pollutants. Some of these air pollutants are major plant nutrients (e.g., nitrogen, sulfur, and phosphorus) and may be affecting nutrient cycles in plant-dominated areas in and around cities. Though the effects of urban PM, as such, appear not to have been sufficiently measured at this time, the deployment of new $PM_{2.5}$ speciated urban monitors and concern about urban visibility impairment could lead to additional information relevant to assessing PM effects on urban ecosystems.

9.3.2.2 Major Ecosystem Stressors

In order for any specific chemical constituent of ambient PM to impact ecosystems, it must first be removed from the atmosphere through deposition. Deposition can occur in three modes: wet, dry, or occult. The factors that influence the magnitude and mode of particle deposition are numerous and complex and depend in part on particle size, shape, chemistry, atmospheric conditions (e.g., relative humidity, wind speed) and ecosystem surface features (e.g., elevation, complexity of terrain, land over type, etc.). National deposition monitoring networks routinely measure total wet or dry deposition of certain compounds. Data from these networks demonstrate that nitrogen and sulfur compounds are being deposited onto soils and aquatic

ecosystems in sufficient amounts to impact ecosystems at local, regional and national scales. Though the ambient PM contribution to total wet or dry deposition has rarely been characterized and the percentages of nitrogen and sulfur containing compounds in PM vary spatially and temporally, nitrates and sulfates make up a substantial portion of the chemical composition of PM. Therefore, the components of PM that are considered of greatest environmental significance are nitrates, sulfates and the associated hydrogen (H^+) ion (Chapter 4).

9.3.2.2.1 Nitrogen

Nitrogen is required by all organisms as it is a major constituent of the nucleic acids that determine the genetic character of all living things and the enzyme proteins that drive the metabolic machinery of every living cell (Galloway, 1998; Galloway and Cowling, 2002). It has long been recognized as the nutrient most important for plant metabolism and, to a large extent it governs the utilization of phosphorus, potassium, and other nutrients. Typically, the availability of biologically active nitrogen controls net primary productivity and, possibly, the decomposition rate of plant litter. Plants usually obtain nitrogen directly from the soil by absorbing NH_4^+ or NO_3^- through their roots and by foliar absorption through the leaves, or it is formed in their roots by symbiotic organisms (e.g., bacteria and free-living blue-green algae). The wide-ranging pathways by which nitrogen cycles through various environmental reservoirs are illustrated in Figure 9-6.

Nitrogen in nature can be divided into two groups: nonreactive (N_2) and reactive (Nr). Molecular nitrogen (N_2), though the most abundant element in the Earth's atmosphere, is not available to more than 99% of living organisms unless converted into reactive forms (Galloway et al., 2003). Reactive Nr includes the inorganic reduced forms of nitrogen (e.g., ammonia [NH_3] and ammonium [NH_4^+]), inorganic oxidized forms (e.g., nitrogen oxide [NO_x], nitric acid [HNO_3], nitrous oxide [N_2O], and nitrate [NO_3^-]) , and the organic compounds (e.g., urea, amine, proteins, and nucleic acids)]) (Galloway and Cowling, 2002).

Due mainly to three anthropogenically-driven activities, anthropogenic Nr creation now exceeds the rate of natural terrestrial Nr creation and its conversion back to N_2 by denitrification (Galloway and Cowling, 2002). Thus, increase in global Nr is the result of three main causes:

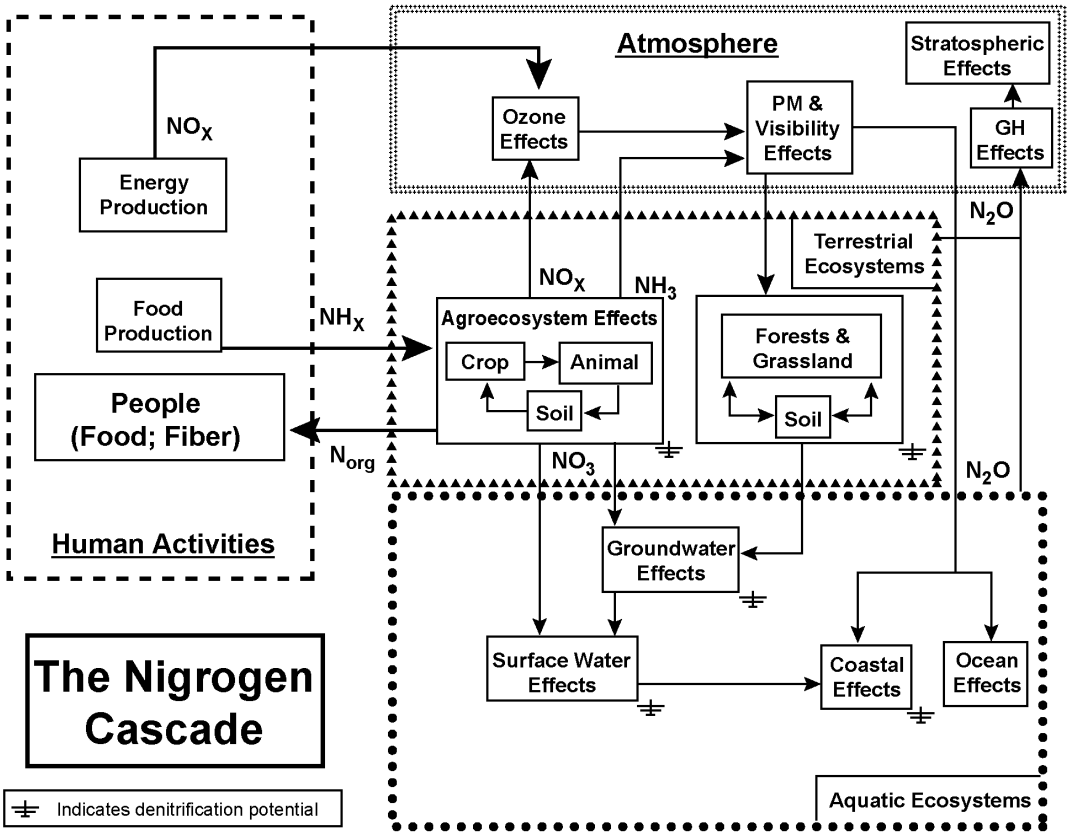

Figure 9-6. Illustration of the nitrogen cascade showing the movement of the human-produced reactive nitrogen (Nr) as it cycles through the various environment reservoirs in the atmosphere, terrestrial ecosystems, and aquatic ecosystems.

Source: Galloway et al. (2003).

(1) widespread cultivation of legumes, rice and other crops that promote conversion of N_2 to organic nitrogen through biological nitrogen fixation (BNF); (2) combustion of fossil fuels which converts both atmospheric N_2 and fossil N to reactive NO_x ; and (3) the Haber-Bosch process, developed in 1913, which converts nonreactive N_2 to reactive NH_3 mainly for use as fertilizers to sustain food production and some industrial activities (Galloway and Cowling, 2002; Galloway et al., 2003). As a result, Nr is now accumulating in the atmosphere and terrestrial and aquatic ecosystems on all spatial scales – local, regional and global (Galloway and Cowling, 2002; Galloway et al., 2003).

Nitrogen oxides (a compound of Nr) is the only ambient air criteria pollutant that has not decreased since the passage of the Clean Air Act. Despite decreases in emissions from fossil fuel burning industries, emissions from automobiles have increased approximately 10% since 1970 due to greater total miles driven (Howarth et al., 2002). Nitrogen oxides emissions from fuel burning increased exponentially from 1940 until the 1970s, leveled off after the passage in of the Clean Air Act in 1970, and stabilized at approximately 7 Tg NO_x /yr in the late 1990s. Contemporary emissions of NO_x in the U.S. from fossil fuel burning are nearly two-thirds the rate of Nr releases from the use of inorganic fertilizers and comprise 30% of the global emissions of NO_x from fossil fuel combustion. Some NO_x emissions are converted/transformed into a portion of ambient air PM (particulate nitrate) and are deposited onto sensitive ecosystems.

Environmental Effects of Nr

The term "nitrogen cascade" refers to the sequential transfers and transformations of Nr molecules as they move from one environmental system or reservoir (atmosphere, biosphere, hydrosphere) to another and the multiple linkages that develop among the different ecological components. Because of these linkages, the addition of anthropogenic Nr alters a wide range of biogeochemical processes and exchanges as it moves among the different environmental reservoirs, with the consequences becoming magnified through time (Figure 4-15; Galloway and Cowling, 2002; Galloway et al., 2003). These changes in the nitrogen cycle are contributing to both beneficial and detrimental effects to the health and welfare of humans and ecosystems (Rabalais, 2002; van Egmond et al., 2002; Galloway, 1998).

Some of the detrimental effects resulting from increased inputs of atmospheric Nr (e.g., particulate nitrates) include: (1) increases in productivity of Nr-limited forests and grasslands followed by decreases wherever increase in atmospheric deposition of Nr significantly exceeds critical thresholds; Nr additions have also been shown to decrease biodiversity in many natural habitats (Aber et al., 1995); (2) formation of O_3 and ozone-induced injury to crops, forests, and natural ecosystems and the resulting predisposition to attack by pathogens and insects; (3) nitrogen saturation of soils in forests and other natural ecosystems, leading to shifts in community composition and leaching of Nr into streams, lakes and rivers; (4) eutrophication,

hypoxia, loss of biodiversity, and habitat degradation in coastal ecosystems, now considered the biggest pollution problem in coastal waters (Rabalais, 2002); (5) acidification and loss of biodiversity in lakes and streams in many regions of the world when associated with sulfur (Vitousek et al., 1997); and (6) alteration of ecosystem processes through changes in the functioning and species composition of beneficial soil organisms (Galloway and Cowling 2002).

Indirect effects of Nr on societal values include: (1) increases in fine PM resulting in regional hazes that decrease visibility at scenic rural and urban vistas and airports; (2) depletion of stratospheric ozone by N_2O emissions which can in turn affect ecosystems and human health; (3) global climate change induced by emissions of N_2O; and (4) formation of acidic deposition when in association with sulfate (Galloway et al., 2003).

Large uncertainties, however, still exist concerning the rates of Nr accumulation in the various environmental reservoirs which limits our ability to determine the temporal and spatial distribution of environmental effects for a given input of Nr. These uncertainties are of great significance because of the sequential nature of Nr effects on environmental processes. Reactive nitrogen does not cascade at the same rate through all environmental systems. The only way to eliminate Nr accumulation and stop the cascade is to convert Nr back to nonreactive N_2 (Galloway et al., 2003).

Nitrogen Saturation and Ecosystem Response

A major environmental concern is nitrogen saturation of soils. Nitrogen saturation occurs when chronic additions of Nr (including nitrate deposition from ambient PM) to soil (nitrogen loading) exceeds the capacity of plants and soil microorganisms to utilize and retain nitrogen (Aber et al., 1989, 1998; Garner 1994; U.S. Environmental Protection Agency, 1993). Nitrogen saturation implies that some resource other than nitrogen is now limiting biotic functions. The appearance of nitrate in soil solution (leaching) is an early symptom of excess Nr accumulation.

Nitrogen saturation does not occur at a specific point in time, but is a set of gradually developing critical changes in ecosystem processes which represent the integrated response of a system to increased nitrogen availability over time (Aber, 1992).

Not all vegetation or ecosystems react in the same manner to Nr deposition. Responses vary depending on numerous factors, including soil composition and the length of time Nr

deposition has been occurring. For example, ecosystems comprised of older, mature forests with high stores of soil Nr and low carbon/nitrogen (C:N) ratios receiving high Nr deposition are prone to Nr saturation (Fenn et al., 1998).

Variations in the response of different forest types ecosystems across the eastern and the western United States to differing amounts of nitrate deposition illustrate this point (Chapter 4, Table 4-14). Although soils of most North American forest ecosystems are nitrogen limited, some exhibit severe symptoms of nitrogen saturation (See Figure 4-17; Chapter 4 (Aber et al., 1989). In the east, these include the Great Smoky Mountains National Park (3.1 to 26.6 kg N ha^{-1} yr) (Johnson and Lindberg, 1992); the Fernow Experimental Forest, WV (15 to 20 kg N ha^{-1} yr) (Gilliam et al., 1996); Whitetop Mountain, VA (32 kg N ha^{-1} yr); the Catskill Mountains in southeastern NY (10.2 kg N ha^{-1} yr); and the Adirondack Mountains of northeastern NY (9.3 kg N ha^{-1} yr) (see Table 4-14).

In the west, wildland ecosystems within the South Coast Air Basin of California receive the highest Nr deposition in the United States (Fenn et al., 1998; 2003). The areas receiving the greatest deposition are the south-facing slopes of the San Gabriel Mountains and the western and southern edges of the San Bernardino Mountains where deposition ranges from 23.3 to 30 kg N ha^{-1} per yr. Deposition in the low- and mid-elevation chaparral and mixed conifer forests ranges from 20 to 45 kg Nr ha^{-1} per yr in the most exposed areas. However, when fog occurs in late summer with unusually high NO_3^- and NH_4^+ concentrations, deposition values can be higher than 90 kg Nr ha^{-1} yr (Fenn et al., 2003). The forests in the southwestern Sierra Nevada of Central California receive 6-11 kg N ha^{-1} yr as throughfall (Fenn et al; 1998). Nr deposition since the 1980s has resulted in saturation in the high-elevation Front Range in northern Colorado where deposition values currently range from 8 to 10 kg Nr ha^{-1} yr (Bowman and Steltzer, 1998; Bowman, 2000; Baron et al., 2000) (Chapter 4, Table 4-14.)

On the other hand, the Harvard Forest hardwood stand in Massachusetts has absorbed over 900 kg Nr ha^{-1} without significant nitrate leaching during a nitrogen amendment study of 8 years. However, leaching losses were high in Harvard pine sites suggesting that deciduous forests may have a greater capacity for Nr retention (Fenn et al., 1998). Magill et al. (2000) suggest that the sharp contrasts that exist between hardwood and pine forests indicate that the mosaic of

community types across the landscape must be considered when determining regional scale response to Nr deposition.

Increases in soil Nr can also play a selective role in ecosystems, by affecting competition among species that result in changes in biodiversity, i.e., community composition. In general, plants adapted to living in an environment of low nitrogen availability will be replaced by nitrophilic plants which are capable of using increased amounts of Nr, because they have a competitive advantage when nitrogen becomes more readily available (Fenn et al., 1998). Several long-term fertilization studies have observed these effects. For example, fertilization and nitrogen gradient experiments at Mount Ascutney, VT suggest that nitrogen saturation may lead to the slow-growing, slow nitrogen-cycling spruce-fir forest stands being replaced by fast-growing deciduous forests that cycle nitrogen rapidly. Similarly, experimental studies of the effects of Nr deposition over a 12-year period on Minnesota grasslands dominated by native warm-season grasses observed the shift to low-diversity mixtures dominated by cool-season grasses at all but the lowest rates of Nr addition (Wedin and Tilman, 1996). The shift to low-diversity mixtures was associated with the decrease in biomass carbon to Nr (C:N) ratios, increased Nr mineralization, increased soil nitrate, high nitrogen losses, and low carbon storage (Wedin and Tilman, 1996).

The mutualistic relationship between plant roots, fungi, and microbes is critical for the growth of the organisms involved. The rhizosphere, the soil that surrounds and is influenced by plant roots is an important region of nutrient dynamics. Bacteria are essential components of the nitrogen and sulfur cycles while fungi in association with plant roots form mycorrhizae that are essential in the uptake of mineral nutrients. The action of bacteria make N, S, Ca, P, Mg, K available for plant growth while mycorrhizae are of special importance in the uptake of N and P (Section 4.3.3; Wall and Moore, 1999; Rovira and Davy, 1974). Changes in soil Nr influence the mycorrhizal-plant relationship. Mycorrhizal fungal diversity is associated with above-ground plant biodiversity, ecosystem variability, and productivity (Wall and Moore, 1999). During nitrogen saturation, soil microbial communities change from being fungal, and dominated by mycorrhizae, to being dominated by bacteria. The decline in the coastal sage scrub species can be directly linked to the decline of the arbuscular mycorrhizal community (Edgerton-Warburton and Allen, 2000; Allen et al., 1998; Padgett et al., 1999).

Nitrate Effects on Aquatic Habitats

Aquatic ecosystems (streams, rivers, lakes, estuaries or oceans) receive increased nitrogen inputs either from direct atmospheric deposition (including nitrogen-containing particles), surface runoff, or leaching from saturated soils into ground or surface waters. The primary pathways of Nr loss from forest ecosystems are hydrological transport beyond the rooting zone into groundwater or stream water, or surface flows of organic nitrogen as nitrate and Nr loss associated with soil erosion (Fenn et al., 1998). Based on data from a number of hydrologic, edaphic, and plant indicators, the mixed conifer forest and chaparral watershed with high smog exposure in the Los Angeles Air Basin exhibited the highest stream water NO_3^- concentrations in wilderness areas of North America (Bytnerowicz and Fenn, 1996; Fenn et al., 1998). High nitrate concentrations have also been observed in streams draining watersheds in the Great Smoky Mountains National Park in Tennessee and North Carolina (Fenn et al., 1998).

Estuaries are among the most intensely fertilized systems on Earth (Fenn et al., 1998). They receive far greater nutrient inputs than other systems. For example, atmospheric Nr deposition into soils in watershed areas feeding into estuarine sound complexes (e.g., Chesapeake Bay, the Pamlico Sound of North Carolina) contribute to excess Nr flows that also include runoff from agricultural practices or other uses (e.g., fertilization of lawns or gardens). Especially during and after heavy rainfall events such as hurricanes, massive influxes of nitrogen into watersheds and sounds can lead to dramatic decreases of oxygen in water and increases in algae blooms that can cause extensive fish kills and damage to commercial fish and sea food harvesting (Paerl et al., 2001).

9.3.2.2.2 Acidification from PM Deposition

Acidic deposition is composed of ions, gases, and particles derived from the precursor gaseous emissions of sulfur dioxide (SO_2), nitrogen oxides (NO_x), ammonia (NH_3) and particulate emissions of other acidifying compounds. It connects air pollution to diverse terrestrial and aquatic ecosystems and alters the interactions of the (H^+) and many elements (e.g., S, N, Ca, Mg, Al, and Hg) (Driscoll et al., 2001). Linked also to the nitrogen cascade (see Figure 4-15), acid precipitation is a critical environmental stress that affects forest landscapes and aquatic ecosystems in North America, Europe, and Asia (Driscoll et al., 2001).

Acid deposition and acidification of soils can lead to high Al-to-nutrient ratios that limit plant uptake of essential nutrients, such as Ca and Mg. Calcium is essential in the formation of wood and the maintenance of the primary plant tissues necessary for tree growth (Shortle and Smith, 1988), and tree species can be adversely affected if altered Ca/Al ratios impair Ca or Mg uptake. A region-wide increase in Ca above expected levels followed by decreasing changes in wood Ca suggests that Ca mobilization began possibly 30 to 40 years ago and has been followed by decreased accumulation in wood, presumably associated with decreasing Ca availability in soil (Chapter 4; Bondietti and McLaughlin, 1992).

9.3.2.3 Characterization of PM-Related Ecosystem Stressors

The critical loads concept has been used in Europe for estimating the amounts of pollutants that sensitive ecosystems can absorb on a sustained basis without experiencing measurable degradation (Lokke et al., 1996). The estimation of ecosystem critical loads requires an understanding of how an ecosystem will respond to different loading rates in the long term and can be of special value for ecosystems receiving chronic deposition of Nr and sulfur independently and as acid deposition when in combination. Time scales must be considered when selecting and evaluating ecosystems response(s) to changes in atmospheric deposition. Indicators of ecosystems at risk of nitrogen saturation should include those that can be identified when nitrogen availability exceeds biotic demand. The cardinal indicator of nitrogen saturation in all ecosystem types is increased and prolonged NO_3^- loss below the main rooting zone in stream water (Fenn and Poth, 1998). A paucity of baseline data makes it difficult to determine the time scale for critical loading of most U.S. ecosystems because nitrogen deposition began so many years ago. Though atmospheric sources of Nr, including ambient PM, are clearly contributing to the overall excess nitrogen load/burden entering ecosystems annually, insufficient data are available at this time to quantify the contribution of ambient PM to total Nr or acidic deposition as its role varies both temporally and spatially along with a number of other factors.

9.3.2.4 Summary and Conclusions

A number of ecosystem-level conditions (e.g., nitrogen saturation, terrestrial and aquatic acidification, coastal eutrophication) that can lead to negative impacts on human health and welfare have been associated with chronic, long-term exposure of ecosystems to elevated inputs of compounds containing Nr, sulfur and/or associated hydrogen ions. Some percentage of total ecosystem inputs of these chemicals is contributed by deposition of atmospheric particles, although the percentage greatly varies temporally and geographically and has not generally been well quantified. Unfortunately, our ability to relate ambient concentrations of PM to ecosystem response is hampered by a number of significant data gaps and uncertainties.

First, U.S. monitoring networks have only recently begun to measure speciated PM. Historically, measurements were focused only on a particular size fraction such as PM_{10} and, more recently, $PM_{2.5}$. An exception to this is the IMPROVE network, which collects speciated measurements. Additionally, except for the IMPROVE and some CASTNet sites, much of the PM monitoring effort has focused on urban or near urban exposures, rather than on those in sensitive ecosystems. Thus, the lack of a long-term, historic database of annual speciated PM deposition rates precludes establishing relationships between PM deposition (exposure) and ecosystem response at this time.

A second source of uncertainty lies in predicting deposition velocities based on ambient concentrations of PM. There are a multitude of factors that influence the amounts of PM that get deposited from the air onto sensitive receptors, including the mode of deposition, e.g., wet, dry, and occult (cloud and fog deposition), windspeed, surface roughness/stickiness, elevation, particle characteristics (e.g., size, shape, chemical composition, etc.) relative humidity, etc. Therefore, modeled deposition rates, used in the absence of monitored data, can be highly uncertain.

Third, each ecosystem has developed within a context framed by the topography, underlying bedrock, soils, climate, meteorology, hydrologic regime, natural and land use history, species associations that co-occur at that location (i.e., soil organisms, plants, etc.), and successional stage, making it unique from all others. Because of this variety, and insufficient baseline data on each of these features for most ecosystems, it is currently impossible to extrapolate with much confidence any effect from one ecosystem to another, or to predict an

appropriate "critical load." Thus, for example, a given PM deposition rate or load of nitrates in one ecosystem may produce entirely different responses than the same deposition rate at another location.

Finally, related in part to the complexity and unique set of characteristics belonging to each ecosystem as discussed above, there remain large uncertainties associated with the length of residence time of Nr in a particular ecosystem component or reservoir, and thus, its impact on the ecosystem as it moves through the various levels of the N cascade. As additional PM speciated air quality and deposition monitoring data become available, there is much room for fruitful research into the areas of uncertainty identified above.

9.3.3 Relationships Between Atmospheric PM and Climate Change Processes

With regard to the role of ambient PM in affecting climate change-related processes, the 1996 PM AQCD stated:

> "Particles [primarily fine particles] suspended in the atmosphere affect the earth's energy budget and thus exert an impact on climate: (a) directly by increasing the reflection of solar radiation by cloud-free portions of the atmosphere, and (b) indirectly by affecting cloud microphysical properties in ways that increase the brightness and stability of clouds." Since aerosol lifetimes are much shorter than the time required for global mixing, "aerosol radiative effects are most likely to exert their influence on a regional rather than on a global basis." (U.S. Environmental Protection Agency, 1996, p. 1-19, 1-21)

The same physical processes (i.e., light scattering and absorption) responsible for visibility degradation are also responsible for airborne particle effects on transmission of solar visible and ultraviolet radiation. Scattering of solar radiation back to space and absorption of solar radiation determine the effects of an aerosol layer on solar radiation. Atmospheric particles greatly complicate projections of future trends in global warming processes because of emissions of greenhouse gases; consequent increases in global mean temperature; resulting changes in regional and local weather patterns; and mainly deleterious (but some beneficial) location-specific human health and environmental effects. Available evidence, ranging from satellite to in situ measurements of aerosol effects on incoming solar radiation and cloud properties, is strongly indicative of an important role in climate for aerosols, but this role is still poorly

quantified. No significant advances have been made since the 1996 PM AQCD in reducing the uncertainties assigned to forcing estimates for aerosol-related forcing, especially for black carbon-containing aerosol. The IPCC characterizes the scientific understanding of greenhouse gas-related forcing as "high" in contrast to that for aerosol, which it describes as "low" to "very low."

In addition to direct climate effects through the scattering and absorption of solar radiation, particles also exert indirect effects on climate by serving as cloud condensation nuclei, thus affecting the abundance and vertical distribution of clouds. The direct and indirect effects of particles appear to have significantly offset global warming effects caused by the buildup of greenhouse gases on a globally averaged basis. However, because the lifetime of particles is much shorter than that required for complete mixing within the Northern Hemisphere, the climate effects of particles generally are felt much less homogeneously than are the effects of long-lived greenhouse gases.

Quantification of the effect of anthropogenic aerosol on hydrological cycles requires more information than is presently available regarding ecosystems responses to reduced solar radiation and other changes occurring in the climate system. However, several global-scale studies indicate that aerosol cooling alone can slow down the hydrological cycle, while cooling plus the nucleation of additional cloud droplets can dramatically reduce precipitation rates.

Any effort to model the impacts of local alterations in particle concentrations on projected global climate change or consequent local and regional weather patterns would be subject to considerable uncertainty.

Atmospheric particles also complicate estimation of potential future impacts on human health and the environment projected as possible to occur because of increased transmission of solar ultraviolet-B radiation (UV-B) through the Earth's atmosphere, secondary to stratospheric ozone depletion due to anthropogenic emissions of chlorofluorocarbons (CFCs), halons, and certain other gases. The transmission of solar UV-B radiation is strongly affected by atmospheric particles. Measured attenuations of UV-B under hazy conditions range up to 37% of the incoming solar radiation. Measurements relating variations in PM mass directly to UV-B transmission are lacking. Particles also can affect the rates of photochemical reactions occurring in the atmosphere, e.g., those involved in catalyzing tropospheric ozone formation. Depending

on the amount of absorbing substances in the particles, photolysis rates either can be increased or decreased. Thus, atmospheric particle effects on UV-B radiation, which vary depending on size and composition of particles, can differ substantially over different geographic areas and from season to season over the same area. Any projection of effects of location-specific airborne PM alterations on increased atmospheric transmission of solar UV radiation (and associated potential human health or environmental effects) due to stratospheric ozone-depletion would, therefore, also be subject to considerable uncertainty.

9.3.4 Effects of Ambient PM on Man-Made Materials

The 1996 PM AQCD arrived at the following key findings and conclusions related to PM effects on man-made materials:

> "Particle exposure results in the soiling of painted surfaces and other building materials, increasing the cleaning frequency for exposed surfaces and possibly reducing their useful lifetimes." (U.S. EPA, 1996, p. 1-19) Damage to materials can result from the deposition of acid aerosols and the dissolution of acid forming gases on metal surfaces, increasing the corrosion of metals; "exposure to acid forming gases may also limit the life expectancy of paints and may damage various building stones and cement products beyond that resulting from natural weathering processes." (U.S. Environmental Protection Agency, 1996, p. 1-20).

As noted in the 1996 PM AQCD and restated in Chapter 4 (Section 4.4), building materials (metals, stones, cements, and paints) undergo natural weathering processes from exposure to environmental elements (wind, moisture, temperature fluctuations, sun light, etc.). Metals form a protective film of oxidized metal (e.g., rust) that slows environmentally induced corrosion. On the other hand, the natural process of metal corrosion from exposure to natural environmental elements is enhanced by exposure to anthropogenic pollutants, in particular SO_2 or other acidic substances, that render the protective film less effective. For example, dry deposition of SO_2 enhances the effects of environmental elements on calcereous stones (limestone, marble, and cement) by converting calcium carbonate (calcite) to calcium sulfate dihydrate (gypsum). The rate of deterioration is determined by the SO_2 concentration, the deposition rate, and the stone's permeability and moisture content; however, the extent of the damage to stones produced by the pollutant species above and beyond that from the natural weathering processes is uncertain.

Sulfur dioxide also has been found to limit the life expectancy of paints by causing discoloration and loss of gloss and thickness of the paint film layer.

As also highlighted in the 1996 PM AQCD, the soiling of painted surfaces and other building materials is a significant detrimental effect of PM pollution. Soiling changes the reflectance of a material from opaque and decreases the transmission of light through transparent materials; it is also a degradation process that requires remediation by cleaning or washing and, depending on the soiled surface, repainting. Available data indicate that airborne particles can result in increased cleaning frequency of exposed surfaces and may decrease the usefulness of soiled materials. Attempts have been made to quantify the pollutant exposures at which materials damage and soiling have been observed; but, to date, insufficient data are available to advance our knowledge regarding perception thresholds with respect to pollutant concentration, particle size, and chemical composition.

REFERENCES

Abbey, D. E.; Nishino, N.; McDonnell, W. F.; Burchette, R. J.; Knutsen, S. F.; Beeson, W. L.; Yang, J. X. (1999) Long-term inhalable particles and other air pollutants related to mortality in nonsmokers. Am. J. Respir. Crit. Care Med. 159: 373-382.

Aber, J. D. (1992) Nitrogen cycling and nitrogen saturation in temperate forest ecosystems. Trends Ecol. Evol. 7: 220-224.

Aber, J. D.; Nadelhoffer, K. J.; Steudler, P.; Melillo, J. M. (1989) Nitrogen saturation in northern forest ecosystems: excess nitrogen from fossil fuel combustion may stress the biosphere. Bioscience 39: 378-386.

Aber, J. D.; Magill, A.; McNulty, S. G.; Boone, R. D.; Nadelhoffer, K. J.; Downs, M.; Hallett, R. (1995) Forest biogeochemistry and primary production altered by nitrogen saturation. Water Air Soil Pollut. 85: 1665-1670.

Aber, J.; McDowell, W.; Nadelhoffer, K.; Magill, A.; Berntson, G.; Kamakea, M.; McNulty, S.; Currie, W.; Rustad, L.; Fernandez, I. (1998) Nitrogen saturation in temperate forest ecosystems. BioScience 48: 921-934.

Adams, P. F.; Hendershot, G. E.; Marano, M. A. (1999) Current estimates from the National Health Interview Survey, 1996. Hyattsville, MD: U.S. Department of Health and Human Services, Public Health Service, National Center for Health Statistics; DHHS publication no. (PHS) 99-1528. (Vital and health statistics: v. 10, data from the National Health Survey, no. 200). Available: http://www.cdc.gov/nchs/products/pubs/pubd/series/sr10/pre-200/pre-200.htm [12 March, 2001].

Allen, E. B.; Padgett, P. E.; Bytnerowicz, A.; Minich, R. (1998) Nitrogen deposition effects on coastal sage vegetation of southern California. USDA Forest Service Gen. Tech. Rep. PSW-GTR-166, pp. 131-139.

American Conference of Governmental Industrial Hygienists. (1994) Appendix D: particle size-selective sampling criteria for airborne particulate matter. In: 1994-1995 Threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH: American Conference of Governmental Industrial Hygienists; pp. 43-46.

Arias, E.; Anderson, R. N.; Kung, H.-S.; Murphy, S. L.; Kochanek, K. D. (2003) Deaths: final data for 2001. Hyattsville, MD: U.S. Department of Health & Human Services, National Center for Health Statistics; DHHS publication no. (PHS) 2003-1120. (National vital statistics reports: v. 52, no. 3). Available: http://www.cdc.gov/nchs/data/nvsr/nvsr52/nvsr52_03.pdf (9 June, 2004).

Baluk, P.; Nadel, J. A.; McDonald, D. M. (1992) Substance P-immunoreactive sensory axons in the rat respiratory tract: a quantitative study of their distribution and role in neurogenic inflammation. J. Compar. Neurol. 319: 586-598.

Baron, J. S.; Rueth, H. M.; Wolfe, A. M.; Nydick, K. R.; Allstott, E. J.; Minear, J. T.; Moraska, B. (2000) Ecosystem responses to nitrogen deposition in the Colorado front range. Ecosystems 3: 352-368.

Blackwell, D. L.; Vickerie, J. L.; Wondimu, E. A. (2003) Summary health statistics for U.S. children: National Health Interview Study, 2000. Hyattsville, MD: U.S. Department of Health & Human Services, National Center for Health Statistics. (Vital and health statistics, series 10, no. 213). Available: http://www.cdc.gov/nchs/data/series/sr_10/sr10_213.pdf [15 June, 2004].

Bondietti, E. A.; McLaughlin, S. B. (1992) Evidence of historical influences of acidic deposition on wood and soil chemistry. In: Johnson, D. W.; Lindberg, S. E., eds. Atmospheric deposition and forest nutrient cycling: a synthesis of the integrated forest study. New York, NY: Springer-Verlag: pp. 358-377. (Billings, W. D.; Golley, F.; Lange, O. L.; Olson, J. S.; Remmert, H., eds. Ecological studies analysis and synthesis: v. 91).

Bowman, W. D. (2000) Biotic controls over ecosystem response to environmental change in alpine tundra of the Rocky Mountains. Ambio 29: 396-400.

Bowman, W. D.; Steltzer, H. (1998) Positive feedbacks to anthropogenic nitrogen deposition in Rocky Mountain alpine tundra. Ambio 27: 514-517.

Braunwald, E. (1997) Cardiovascular medicine at the turn of the millennium: triumphs, concerns, and opportunities. N. Engl. J. Med. 337: 1360-1369.

Burnett, R. T.; Goldberg, M. S. (2003) Size-fractionated particulate mass and daily mortality in eight Canadian cities. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 85-90. Available: http://www.healtheffects.org/news.htm [16 May, 2003].

Burnett, R. T.; Cakmak, S.; Brook, J. R.; Krewski, D. (1997) The role of particulate size and chemistry in the association between summertime ambient air pollution and hospitalization for cardiorespiratory diseases. Environ. Health Perspect. 105: 614-620.

Bytnerowicz, A.; Fenn, M. E. (1996) Nitrogen deposition in California forests: a review. Environ. Pollut. 92: 127-146.

Campen, M. J.; Costa, D. L.; Watkinson, W. P. (2000) Cardiac and thermoregulatory toxicity of residual oil fly ash in cardiopulmonary-compromised rats. In: Phalen, R. F., ed. Inhalation toxicology: proceedings of the third colloquium on particulate air pollution and human health (second special issue); June, 1999; Durham, NC. Inhalation Toxicol. 12(suppl. 2): 7-22.

Centers for Disease Control and Prevention. (2004) The health consequences of smoking: a report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. Available: http://www.cdc.gov/tobacco/sgr/sgr_2004/chapters.htm (18 August, 2004).

Cherry, D. K.; Burt, C. W.; Woodwell, D. A. (2003) National ambulatory medical care survey: 2001 summary. Hyattsville, MD: U.S. Department of Health & Human Resources, National Center for Health Statistics; DHHS publication no. (PHS) 2003-1250. (Advance data from vital and health statistics: no. 337). Available: http://www.cdc.gov/nchs/data/ad/ad337.pdf (9 June, 2004).

Chestnut, L. G.; Dennis, R. L. (1997) Economic benefits of improvements in visibility: acid rain. Provisions of the 1990 Clean Air Act Amendments. J. Air Waste Manage. Assoc. 47: 395-402.

Chestnut, L. G.; Rowe, R. D. (1990) Preservation values for visibility protection at the national parks (draft final report). Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards, Economic Analysis Branch.

Chock, D. P.; Winkler, S. L.; Chen, C. (2000) A study of the association between daily mortality and ambient air pollutant concentrations in Pittsburgh, Pennsylvania. J. Air Waste Manage. Assoc. 50: 1481-1500.

Choudhury, A. H.; Gordian, M. E.; Morris, S. S. (1997) Associations between respiratory illness and PM_{10} air pollution. Arch. Environ. Health 52: 113-117.

Chughtai, A. R.; Williams, G. R.; Atteya, M. M. O.; Miller, N. J.; Smith, D. M. (1999) Carbonaceous particle hydration. Atmos. Environ. 33: 2679-2687.

Cocker, D. R., III; Whitlock, N. E.; Flagen, R. C.; Seinfield, J. H. (2001) Hygroscopic properties of Pasadena, California aerosol. Aerosol Sci. Technol. 35: 637-647.

Darlington, T. L.; Kahlbaum, D. F.; Heuss, J. M.; Wolff, G. T. (1997) Analysis of PM_{10} trends in the United States from 1988 through 1995. J. Air Waste Manage. Assoc. 47: 1070-1078.

Delfino, R. J.; Murphy-Moulton, A. M.; Burnett, R. T.; Brook, J. R.; Becklake, M. R. (1997) Effects of air pollution on emergency room visits for respiratory illnesses in Montreal, Quebec. Am. J. Respir. Crit. Care Med. 155: 568-576.

Delfino, R. J.; Murphy-Moulton, A. M.; Becklake, M. R. (1998) Emergency room visits for respiratory illnesses among the elderly in Montreal: association with low level ozone exposure. Environ. Res. 76: 67-77.

Di Minno, G.; Mancini, M. (1990) Measuring plasma fibrinogen to predict stroke and mycardial infarction. Arteriosclerosis 10: 1-7.

Dockery, D. W.; Cunningham, J.; Damokosh, A. I.; Neas, L. M.; Spengler, J. D.; Koutrakis, P.; Ware, J. H.; Raizenne, M.; Speizer, F. E. (1996) Health effects of acid aerosols on North American children: respiratory symptoms. Environ. Health Perspect. 104: 500-505.

Dominici, F.; McDermott, A.; Daniels, M.; Zeger, S. L.; Samet, J. M. (2003) Mortality among residents of 90 cities. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 9-24. Available: http://www.healtheffects.org/Pubs/TimeSeries.pdf [12 May, 2004].

Driscoll, C. T.; Lawrence, G. B.; Bulger, A. J.; Butler, T. J.; Cronan, C. S.; Eagar, C.; Lambert, K. F.; Likens, G. E.; Stoddard, J. L.; Weathers, K. C. (2001) Acidic deposition in the northeastern United States: sources and inputs, ecosystem effects, and management strategies. BioScience 51: 180-198.

Edgerton-Warburton, L. M.; Allen, E. B. (2000) Shifts in arbuscular mycorrhizal communities along an anthropogenic nitrogen deposition gradient. Ecol. Appl. 10: 484-496.

Fairley, D. (2003) Mortality and air pollution for Santa Clara County, California, 1989-1996. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 97-106. Available: http://www.healtheffects.org/news.htm [16 May, 2003].

Fanucchi, M. V.; Wong, V. J.; Hinds, D.; Tarkington, B. K.; Van Winkle, L. S.; Evans, M. J.; Plopper, C. G. (2000) Repeated episodes of exposure to ozone alters postnatal development of distal conducting airways in infant rhesus monkeys. Am. J. Respir. Crit. Care Med. 161: A615.

Fenn, M. E.; Poth, M. A. (1998) Indicators of nitrogen status in California forests. U.S.D.A. Forest Service Gen. Tech. Rep. PSW-GTR-166.

Fenn, M. E.; Poth, M. A.; Aber, J. D.; Baron, J. S.; Bormann, B. T.; Johnson, D. W.; Lemly, A. D.; McNulty, S. G.; Ryan, D. F.; Stottlemyer, R. (1998) Nitrogen excess in North American ecosystems: predisposing factors, ecosystem responses, and management strategies. Ecol. Appl. 8: 706-733.

Fenn, M. E.; Haeuber, R.; Tonnesen, G. S.; Baron, J. S.; Grossman-Clarke, S.; Hope, D.; Jaffe, D. A.; Copeland, S.; Geiser, L.; Rueth, H. M.; Sickman, J. O. (2003) Nitrogen emissions, deposition, and monitoring in the western United States. Bioscience 53: 391-403.

Friedlander, S. K.; Yeh, E. K. (1998) The submicron atmospheric aerosol as a carrier of reactive chemical species: case of peroxides. Appl. Occup. Environ. Hyg. 13: 416-420.

Galloway, J. N. (1998) The global nitrogen cycle: changes and consequences. Environ. Pollut. 102(suppl. 1): 15-24.

Galloway, J. N.; Cowling, E. B. (2002) Reactive nitrogen and the world: 200 years of change. Ambio 31: 64-71.

Galloway, J. N.; Aber, J. D.; Erisman, J. W.; Seitzinger, S. P.; Howarth, R. W.; Cowling, E. B.; Cosby, B. J. (2003) The nitrogen cascade. Bioscience 53: 341-356.

Garner, J. H. B. (1994) Nitrogen oxides, plant metabolism, and forest ecosystem response. In: Alscher, R. G.; Wellburn, A. R., eds. Plant responses to the gaseous environment: molecular, metabolic and physiological aspects, [3rd international symposium on air pollutants and plant metabolism]; June 1992; Blacksburg, VA. London, United Kingdom: Chapman & Hall; pp. 301-314.

Gilliam, F. S.; Adams, M. B.; Yurish, B. M. (1996) Ecosystem nutrient responses to chronic nitrogen inputs at Fernow Experimental Forest, West Virginia. Can. J. For. Res. 26: 196-205.

Hall, M. J.; DeFrances, C. J. (2003) 2001 national hospital discharge survey. Hyattsville, MD: U.S. Department of Health & Human Resources, National Center for Health Statistics; DHHS publication no. (PHS) 2003-1250. (Advance data from vital and health statistics: no. 332). Available: http://www.cdc.gov/nchs/data/ad/ad332.pdf (9 June, 2004).

Health Effects Institute. (2003) Revised analyses of time-series studies of air pollution and health. Boston, MA: Health Effects Institute; special report. Available: http://www.healtheffects.org/Pubs/TimeSeries.pdf [27 June 2003].

Hemming, B. L.; Seinfeld, J. H. (2001) On the hygroscopic behavior of atmospheric organic aerosols. Ind. Eng. Chem. Res. 40: 4162-4171.

Hill, A. B. (1965) The environment and disease: association or causation? Proc. R. Soc. Med. 58: 295-300.

Howarth, R. W.; Boyer, E. W.; Pabich, W. J.; Galloway, J. N. (2002) Nitrogen use in the United States from 1961-2000 and potential future trends. Ambio 31: 88-96.

Ito, K. (2003) Associations of particulate matter components with daily mortality and morbidity in Detroit, Michigan. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 143-156. Available: http://www.healtheffects.org/Pubs/TimeSeries.pdf [12 May, 2004].

Ito, K.; Thurston, G. D. (1996) Daily PM_{10}/mortality associations: an investigation of at-risk subpopulations. J. Exposure Anal. Environ. Epidemiol. 6: 79-95.

Johnson, D. W.; Lindberg, S. E. (1992) Nitrogen chemistry, deposition, and cycling in forests. In: Johnson, D. W.; Lindberg, S. E., eds. Atmospheric deposition and forest nutrient cycling: a synthesis of the integrated forest study. New York, NY: Springer-Verlag, Inc.; pp. 150-213. (Billings, W. D.; Golley, F.; Lange, O. L.; Olson, J. S.; Remmert, H., eds. Ecological studies: analysis and synthesis: v. 91).

Kao, A. S.; Friedlander, S. K. (1995) Temporal variations of particulate air pollution: a marker for free radical dosage and adverse health effects? Inhalation Toxicol. 7: 149-156.

Katsouyanni, K.; Touloumi, G.; Samoli, E.; Petasakis, Y.; Analitis, A.; Le Tertre, A.; Rossi, G.; Zmirou, D.; Ballester, F.; Boumghar, A.; Anderson, H. R.; Wojtyniak, B.; Paldy, A.; Braunstein, R.; Pekkanen, J.; Schindler, C.; Schwartz, J. (2003) Sensitivity analysis of various models of short-term effects of ambient particles on total mortality in 29 cities in APHEA2. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 157-164. Available: http://www.healtheffects.org/news.htm [16 May, 2003].

Killingsworth, C. R.; Alessandrini, F.; Krishna Murthy, G. G.; Catalano, P. J.; Paulauskis, J. D.; Godleski, J. J. (1997) Inflammation, chemokine expression, and death in monocrotaline-treated rats following fuel oil fly ash inhalation. Inhalation Toxicol. 9: 541-565.

Kinney, P. L.; Ito, K.; Thurston, G. D. (1995) A sensitivity analysis of mortality/PM_{10} associations in Los Angeles. In: Phalen, R. F.; Bates, D. V., eds. Proceedings of the colloquium on particulate air pollution and human mortality and morbidity; January 1994; Irvine, CA. Inhalation Toxicol. 7: 59-69.

Klemm, R. J.; Mason, R. M., Jr. (2000) Aerosol Research and Inhalation Epidemiological Study (ARIES): air quality and daily mortality statistical modeling–interim results. J. Air. Waste Manage. Assoc. 50: 1433-1439.

Klemm, R. J.; Mason, R. (2003) Replication of reanalysis of Harvard Six-City mortality study. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 165-172. Available: http://www.healtheffects.org/Pubs/TimeSeries.pdf [12 May, 2004].

Krewski, D.; Burnett, R. T.; Goldberg, M. S.; Hoover, K.; Siemiatycki, J.; Jerrett, M.; Abrahamowicz, M.; White, W. H. (2000) Reanalysis of the Harvard Six Cities study and the American Cancer Society study of particulate air pollution and mortality: a special report of the Institute's Particle Epidemiology Reanalysis Project. Cambridge, MA: Health Effects Institute.

Künzli, N.; Medina, S.; Kaiser, R.; Quénel, P.; Horak, F., Jr.; Studnicka, M. (2001) Assessment of deaths attributable to air pollution: should we use risk estimates based on time series or on cohort studies? Am. J. Epidemiol. 153: 1050-1055.

Laden, F.; Neas, L. M.; Dockery, D. W.; Schwartz, J. (2000) Association of fine particulate matter from different sources with daily mortality in six U.S. cities. Environ. Health Perspect. 108: 941-947.

Linn, W. S.; Szlachcic, Y.; Gong, H., Jr.; Kinney, P. L.; Berhane, K. T. (2000) Air pollution and daily hospital admissions in metropolitan Los Angeles. Environ. Health Perspect. 108: 427-434.

Lipfert, F. W. (1998) Trends in airborne particulate matter in the United States. Appl. Occup. Environ. Hyg. 13: 370-384.

Lipfert, F. W.; Morris, S. C.; Wyzga, R. E. (2000) Daily mortality in the Philadelphia metropolitan area and size-classified particulate matter. J. Air Waste Manage. Assoc. 50: 1501-1513.

Lippmann, M.; Ito, K.; Nádas, A.; Burnett, R. T. (2000) Association of particulate matter components with daily mortality and morbidity in urban populations. Cambridge, MA: Health Effects Institute; research report no. 95.

Lipsett, M.; Hurley, S.; Ostro, B. (1997) Air pollution and emergency room visits for asthma in Santa Clara County, California. Environ. Health Perspect. 105: 216-222.

Løkke, H.; Bak, J.; Falkengren-Grerup, U.; Finlay, R. D.; Ilvesniemi, H.; Nygaard, P. H.; Starr, M. (1996) Critical loads of acidic deposition for forest soils: is the current approach adequate. Ambio 25: 510-516.

Long, C. M.; Suh, H. H.; Catalano, P. J.; Koutrakis, P. (2001) Using time- and size-resolved particulate data to quantify indoor penetration and deposition behavior. Environ. Sci. Technol. 35: 2089-2099.

Lovett, G. M.; Traynor, M. M.; Pouyat, R. V.; Carreiro, M. M.; Zhu, W.-X.; Baxter, J. W. (2000) Atmospheric deposition to oak forest along an urban-rural gradient. Environ. Sci. Technol. 34: 4294-4300.

Lowe, G. D. O.; Lee, A. J.; Rumley, A.; Price, J. F.; Fowkes, F. G. R. (1997) Blood viscosity and risk of cardiovascular events: the Edinburgh Artery Study. Br. J. Haematol. 96: 168-173.

Magill, A. H.; Aber, J. D.; Berntson, G. M.; McDowell, W. H.; Nadelhoffer, K. J.; Melillo, J. M.; Steudler, P. (2000) Long-term nitrogen additions and nitrogen saturation in two temperate forests. Ecosystems 3: 238-253.

Malm, W. C. (2000) Spatial and seasonal patterns and temporal variability of haze and its constituents in the United States. Report III. Fort Collins, CO: Cooperative Institute for Research in the Atmosphere, Colorado State University. Available: http://vista.cira.colostate.edu/improve/Publications/Reports/2000/2000.htm [22 March, 2002].

Mar, T. F.; Norris, G. A.; Koenig, J. Q.; Larson, T. V. (2000) Associations between air pollution and mortality in Phoenix, 1995-1997. Environ. Health Perspect. 108: 347-353.

Mar, T. F.; Norris, G. A.; Larson, T. V.; Wilson, W. E.; Koenig, J. Q. (2003) Air pollution and cardiovascular mortality in Phoenix, 1995-1997. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 177-182. Available: http://www.healtheffects.org/news.htm [16 May, 2003].

McCaig, L. F.; Burt, C. W. (2004) National hospital ambulatory medical care survey: 2002 emergency department summary. Hyattsville, MD: U.S. Department of Health & Human Resources, Centers for Disease Control and Prevention, National Center for Health Statistics; DHHS publication no. (PHS) 2004-1250. (Advance data from vital and health statistics: no. 340). Available: http://www.cdc.gov/nchs/data/ad/ad340.pdf (9 June, 2004).

Meade, T. W.; Ruddock, V.; Stirling, Y.; Chakrabarti, R.; Miller, G. J. (1993) Fibrinolytic activity, clotting factors, and long-term incidence of ischaemic heart disease in the Northwick Park Heart Study. Lancet 342: 1076-1079.

Molenar, J. V.; Malm, W. C.; Johnson, C. E. (1994) Visual air quality simulation techniques. Atmos. Environ. 28: 1055-1063.

Moolgavkar, S. H. (2003) Air pollution and daily deaths and hospital admissions in Los Angeles and Cook counties. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 183-198. Available: http://www.healtheffects.org/news.htm [16 May, 2003].

Moomaw, W. R. (2002) Energy, industry and nitrogen: strategies for decreasing reactive nitrogen emissions. Ambio 31: 184-189.

Morris, R. D.; Naumova, E. N. (1998) Carbon monoxide and hospital admissions for congestive heart failure: evidence of an increased effect at low temperatures. Environ. Health Perspect. 106: 649-653.

National Acid Precipitation Assessment Program. (1991) National Acid Precipitation Assessment Program 1990 integrated assessment report. Washington, DC: National Acid Precipitation Assessment Program.
National Acid Precipitation Assessment Program. (1998) NAPAP biennial report to Congress. Washington, DC: National Acid Precipitation Assessment Program.
National Research Council. (1993) Protecting visibility in national parks and wilderness areas. Washington, DC: National Academy Press. 3v.
Nauenberg, E.; Basu, K. (1999) Effect of insurance coverage on the relationship between asthma hospitalizations and exposure to air pollution. Public Health Rep. 114: 135-148.
Ostro, B. D.; Lipsett, M. J.; Mann, J. K.; Braxton-Owens, H.; White, M. C. (1995) Air pollution and asthma exacerbations among African-American children in Los Angeles. In: Phalen, R. F.; Bates, D. V., eds. Proceedings of the colloquium on particulate air pollution and human mortality and morbidity, part II; January 1994; Irvine, CA. Inhalation Toxicol. 7: 711-722.
Ostro, B.; Lipsett, M.; Mann, J.; Braxton-Owens, H.; White, M. (2001) Air pollution and exacerbation of asthma in African-American children in Los Angeles. Epidemiology 12: 200-208.
Ostro, B. D.; Broadwin, R.; Lipsett, M. J. (2003) Coarse particles and daily mortality in Coachella Valley, California. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 199-204. Available: http://www.healtheffects.org/news.htm [16 May, 2003].
Padgett, P. E.; Allen, E. B.; Bytnerowicz, A.; Minich, R. A. (1999) Changes in soil inorganic nitrogen as related to atmospheric nitrogenous pollutants in southern California. Atmos. Environ. 33: 769-781.
Paerl, H. W.; Bales, J. D.; Ausley, L. W.; Buzzelli, C. P.; Crowder, L. B.; Eby, L. A.; Go, M.; Peierls, B. L.; Richardson, T. L.; Ramus, J. S. (2001) Ecosystem impacts of three sequential hurricanes (Dennis, Floyd, and Irene) on the United States' largest lagoonal estuary, Pamlico Sound, NC. Proc. Nat. Acad. Sci. U. S. A. 98: 5655-5611.
Piedimonte, G.; Hoffman, J. I. E.; Husseini, W. K.; Hiser, W. L.; Nadel, J. A. (1992) Effect of neuropeptides released from sensory nerves on blood flow in the rat airway microcirculation. J. Appl. Physiol. 72: 1563-1570.
Pleis, J. R.; Benson, V.; Schiller, J. S. (2003) Summary health statistics for U.S. adults: National Health Interview Study, 2000. Hyattsville, MD: U.S. Department of Health & Human Services, National Center for Health Statistics. (Vital and health statistics, series 10, no. 215). Available: http://www.cdc.gov/nchs/data/series/sr_10/sr10_215.pdf [15 June, 2004].
Plopper, C. G.; Fanucchi, M. V. (2000) Do urban environmental pollutants exacerbate childhood lung diseases? Environ. Health Perspect. 108: A252-A253.
Pope, C. A., III; Schwartz, J.; Ransom, M. R. (1992) Daily mortality and PM_{10} pollution in Utah valley. Arch. Environ. Health 47: 211-217.
Pope, C. A., III; Burnett, R. T.; Thun, M. J.; Calle, E. E.; Krewski, D.; Ito, K.; Thurston, G. D. (2002) Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. JAMA J. Am. Med. Assoc. 287: 1132-1141.
Rabalais, N. N. (2002) Nitrogen in aquatic ecosystems. Ambio 31: 102-112.
Raizenne, M.; Neas, L. M.; Damokosh, A. I.; Dockery, D. W.; Spengler, J. D.; Koutrakis, P.; Ware, J. H.; Speizer, F. E. (1996) Health effects of acid aerosols on North American children: pulmonary function. Environ. Health Perspect. 104: 506-514.
Rovira, A. D.; Davey, C. B. (1974) Biology of the rhizosphere. In: Carson, E. W., ed. The plant root and its environment: proceedings of an institute; July, 1971; Blacksburg, VA. Charlottesville, VA: University Press of Virginia; pp. 153-204.
Samet, J. M.; Zeger, S. L.; Dominici, F.; Curriero, F.; Coursac, I.; Dockery, D. W.; Schwartz, J.; Zanobetti, A. (2000) The national morbidity, mortality, and air pollution study. Part II: morbidity, mortality, and air pollution in the United States. Cambridge, MA: Health Effects Institute; research report no. 94, part II.
Schwartz, J. (1994) Air pollution and hospital admissions for the elderly in Detroit, Michigan. Am. J. Respir. Crit. Care Med. 150: 648-655.
Schwartz, J. (2003) Airborne particles and daily deaths in 10 US cities. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 211-218. Available: http://www.healtheffects.org/news.htm [16 May, 2003].
Schwartz, J.; Morris, R. (1995) Air pollution and hospital admissions for cardiovascular disease in Detroit, Michigan. Am. J. Epidemiol. 142: 23-35.

Schwartz, J.; Zanobetti, A.; Bateson, T. (2003) Morbidity and mortality among elderly residents of cities with daily PM measurements. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 25-58. Available: http://www.healtheffects.org/Pubs/TimeSeries.pdf [20 June, 2004].

Seaton, A.; MacNee, W.; Donaldson, K.; Godden, D. (1995) Particulate air pollution and acute health effects. Lancet (8943): 176-178.

Sheppard, L. (2003) Ambient air pollution and nonelderly asthma hospital admissions in Seattle, Washington, 1987-1994. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 227-230. Available: http://www.healtheffects.org/news.htm [16 May, 2003].

Shortle, W. C.; Smith, K. T. (1988) Aluminum-induced calcium deficiency syndrome in declining red spruce. Science (Washington, DC) 240: 1017-1018.

Sjögren, B. (1997) Occupational exposure to dust: inflammation and ischaemic heart disease. Occup. Environ. Med. 54: 466-469.

Smiley-Jewell, S. M.; Liu, F. J.; Weir, A. J.; Plopper, C. G. (2000) Acute injury to differentiating Clara cells in neonatal rabbits results in age-related failure of bronchiolar epithelial repair. Toxicol. Pathol. 28: 267-276.

Stieb, D. M.; Beveridge, R. C.; Brook, J. R.; Smith-Doiron, M.; Burnett, R. T.; Dales, R. E.; Beaulieu, S.; Judek, S.; Mamedov, A. (2000) Air pollution, aeroallergens and cardiorespiratory emergency department visits in Saint John, Canada. J. Exposure Anal. Environ. Epidemiol. 10: 461-477.

Styer, P.; McMillan, N.; Gao, F.; Davis, J.; Sacks, J. (1995) Effect of outdoor airborne particulate matter on daily death counts. Environ. Health Perspect. 103: 490-497.

Thurston, G. D.; Ito, K.; Hayes, C. G.; Bates, D. V.; Lippmann, M. (1994) Respiratory hospital admissions and summertime haze air pollution in Toronto, Ontario: consideration of the role of acid aerosols. Environ. Res. 65: 271-290.

Tolbert, P. E.; Mulholland, J. A.; Maclntosh, D. L.; Xu, F.; Daniels, D.; Devine, O. J.; Carlin, B. P.; Klein, M.; Dorley, J.; Butler, A. J.; Nordenberg, D. F.; Frumkin, H.; Ryan, P. B.; White, M. C. (2000) Air quality and pediatric emergency room visits for asthma in Atlanta, Georgia. Am. J. Epidemiol. 151: 798-810.

Tsai, F. C.; Apte, M. G.; Daisey, J. M. (2000) An exploratory analysis of the relationship between mortality and the chemical composition of airborne particulate matter. Inhalation Toxicol. 12(suppl.): 121-135.

U.S. Environmental Protection Agency. (1993) Air quality criteria for oxides of nitrogen. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; report nos. EPA/600/8-91/049aF-cF. 3v. Available from: NTIS, Springfield, VA; PB95-124533, PB95-124525, and PB95-124517.

U.S. Environmental Protection Agency. (1995) Interim findings on the status of visibility research. Research Triangle Park, NC: Office of Research and Development; report no. EPA/600/R-95/021.

U.S. Environmental Protection Agency. (1996) Air quality criteria for particulate matter. Research Triangle Park, NC: National Center for Environmental Assessment-RTP Office; report nos. EPA/600/P-95/001aF-cF. 3v.

U.S. Environmental Protection Agency. (2003) National air quality and emissions trends report. 2003 special studies edition. Research Triangle Park, NC: Office of Air Quality Standards; Emissions Monitoring and Analysis Division; report no. EPA 454/R-03-005. Available: http://www.epa.gov/air/airtrends/aqtrnd03/toc.html (27 August, 2004).

Van Egmond, K.; Bresser, T.; Bouwman, L. (2002) The European nitrogen case. Ambio 31: 72-78.

Veronesi, B.; Oortgiesen, M. (2001) Neurogenic inflammation and particulate matter (PM) air pollutants. Neurotoxicology 22: 795-810.

Vincent, R.; Kumarathasan, P.; Goegan, P.; Bjarnason, S. G.; Guénette, J.; Bérubé, D.; Adamson, I. Y.; Desjardins, S.; Burnett, R. T.; Miller, F. J.; Battistini, B. (2001) Inhalation toxicology of urban ambient particulate matter: acute cardiovascular effect in rats. Boston, MA: Health Effects Institute; research report no. 104. Available: http://www.healtheffects.org/Pubs/Vincent.pdf [29 January 02].

Vitousek, P. M.; Mooney, H. A.; Lubchenco, J.; Melillo, J. M. (1997) Human domination of Earth's ecosystems. Science (Washington, DC) 277: 494-499.

Wall, D. H.; Moore, J. C. (1999) Interactions underground: soil biodiversity, mutualism, and ecosystem processes. BioScience 49: 109-117.

Watkinson, W. P.; Campen, M. J.; Costa, D. L. (1998) Cardiac arrhythmia induction after exposure to residual oil fly ash particles in a rodent model of pulmonary hypertension. Toxicol. Sci. 41: 209-216.

Wedin, D. A.; Tilman, D. (1996) Influence of nitrogen loading and species composition on the carbon balance of grasslands. Science (Washington, DC) 274: 1720-1723.

Whitby, K. T. (1978) The physical characteristics of sulfur aerosols. Atmos. Environ. 12: 135-159.

Wilson, W. E. (1995) Aerosol exposure, physics, and chemistry. Inhalation Toxicol. 7: 769-772.

Wilson, W. E.; Suh, H. H. (1997) Fine particles and coarse particles: concentration relationships relevant to epidemiologic studies. J. Air Waste Manage. Assoc. 47: 1238-1249.

Zanobetti, A.; Schwartz, J. (2003) Airborne particles and hospital admissions for heart and lung disease. In: Revised analyses of time-series studies of air pollution and health. Special report. Boston, MA: Health Effects Institute; pp. 241-248. Available: http://www.healtheffects.org/news.htm [16 May, 2003].

United States
Environmental Protection
Agency

Please make all necessary changes in the below label, detach copy or copy, and return to the address in the upper left-hand corner.

If you do not wish to receive these reports CHECK HERE ☐; detach copy or copy, and return to the address in the upper left-hand corner.

National Center for
Environmental Assessment
Research Triangle Park, NC 27711

Official Business
Penalty for Private Use
$300

EPA/600/P-99/002bF
October 2004