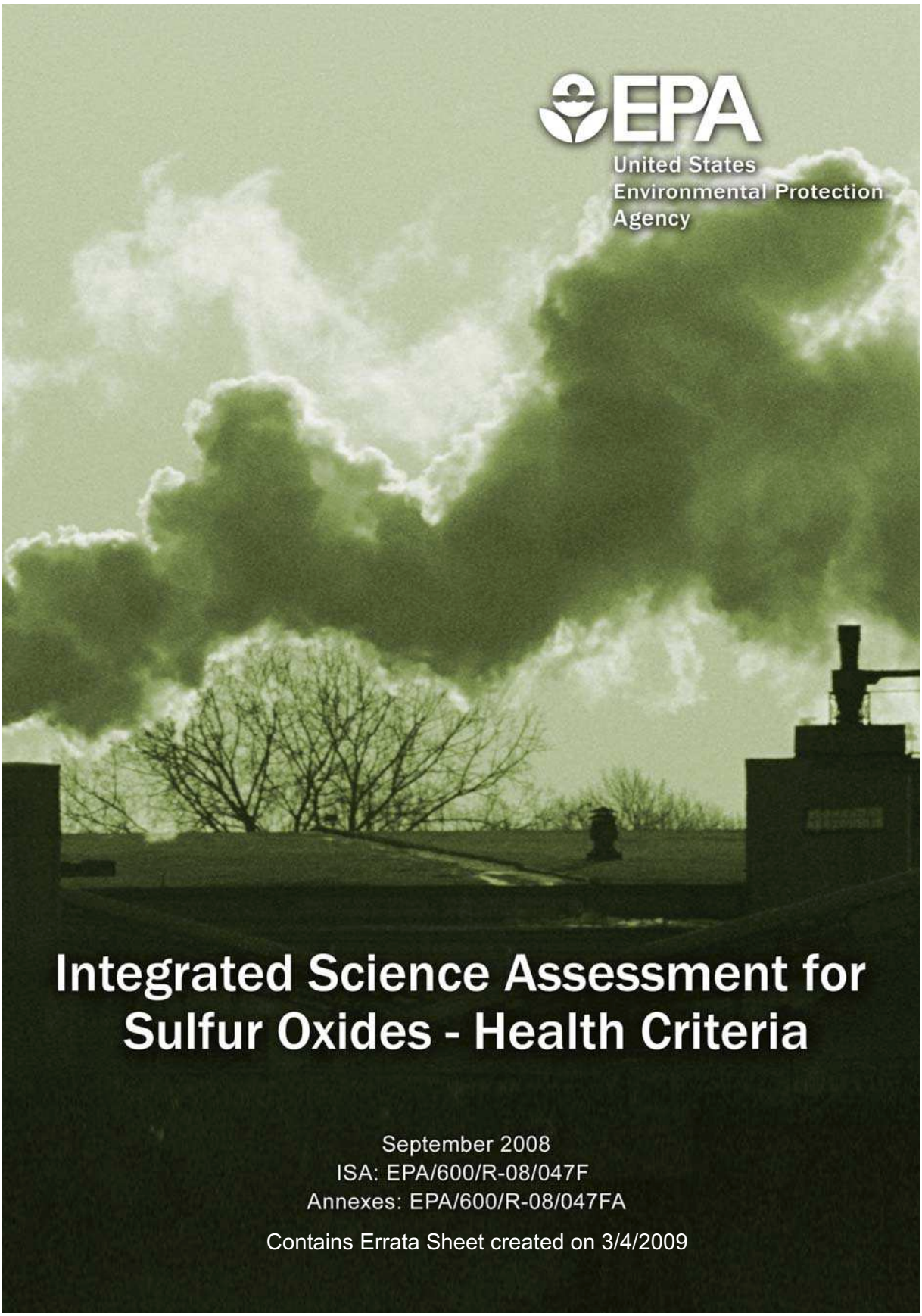

Integrated Science Assessment for Sulfur Oxides - Health Criteria

September 2008
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National Center for Environmental Assessment - RTP
Office of Research and Development
U.S. Environmental Protection Agency
Research Triangle Park, NC

Table of Contents

List of Tables

List of Figures

Acronyms and Abbreviations

α	alpha
β	beta; the calculated health effect parameter
γN_2O_5	reaction potential coefficient (gamma) for N_2O_5
Δ	delta, difference; change
τ	tau; atmospheric lifetime
µeq	microequivalent
8-OHdG	8-hydroxy-2N-deoxyguanosine
ACCENT	Atmospheric Composition Change: the European NeTwork of excellence (European Union Project)
ACS	American Cancer Society
ADS	annular denuder system
AERMOD	AMS/EPA Regulatory Model (steady-state plume model)
AHH	aryl hydrocarbon hydroxylase
AHR	airways hyper responsiveness
AIRMoN	Atmospheric Integrated Research Monitoring Network
AirPEx	Air Pollution Exposure (model)
AirQUIS	Air Quality Information System (model)
AIRS	Atmospheric Infrared Sounder (instrument)
ALSC	Adirondack Lake Survey Corporation
ALT	alanine-amino-transferase
AM	alveolar macrophages
AMMN	N-nitroso-acetoxymethylmethylamine
AMS	American Meteorological Society
AP	alkaline phosphatase
APEX	Air Pollution Exposure (model)
APHEA	Air Pollution on Health: a European Approach (study)
APIMS	atmospheric pressure ionization mass spectrometer
AQCD	Air Quality Criteria Document
AQS	Air Quality System (database)
ARIC	Atherosclerosis Risk in Communities (study)
ARP	Acid Rain Program
ASG	Atmospheric Studies Group of TRC
ASI	Acid Stress Index
asl	above sea level
AST	aspartate-amino-transferase
atm	atmosphere
ATMOS	Atmospheric Trace Molecule Spectroscopy
ATTILA	type of Lagrangian model
B[a]P	benzo[a]pyrene
Ba	barium
BAL	bronchoalveolar lavage
BC	black carbon
BCS	base-cation surplus
BHPN	N-bis(2-hydroxypropyl) nitrosamine
BHR	bronchial hyperresponsiveness

BME	Bayesian Maximum Entropy (framework)
Br	bromine
Br^-	bromine ion
Br_2	molecular bromine
BrCl	bromine chloride
BrO	bromine oxide
BS	black smoke
bw	body weight
C	carbon or carbon black particles
C_2H_6	ethane
C_5H_8	isoprene
C_a	ambient air concentration
Ca	calcium
CA	chromosome aberrations
$Ca(NO_3)_2$	calcium nitrate
$Ca(OH)_2$	calcium hydroxide
Ca^{2+}	calcium ion
$CaCl_2$	calcium chloride
$CaCO_3$	calcium carbonate
CALPUFF	Advanced non-steady-state meteorological and air quality modeling system developed by ASG scientists and distributed by TRC. Used by the EPA for assessing long range transport of pollutants.
CAMP	Childhood Asthma Management Program
CAM_X	urban multi-scale grid based model
CARB	California Air Resources Board
CASAC	Clean Air Scientific Advisory Committee (CASAC) of EPA's Science Advisory Board
CASTNet	Clean Air Status and Trends Network
CAT	catalase
CB4	Carbon Bond 4 chemical mechanism model
CDC	Centers for Disease Control and Prevention
CFD	computational fluid dynamics (modeling)
CFR	Code of Federal Regulations
CH_2I_2	diiodomethane
CH_2O	formaldehyde
$(CH_3)_2SO$	dimethyl sulfoxide, DMSO
$CH_3C(O)$	acetyl radical
$CH_3C(O)OO$	acetyl peroxy radical
CH_3CHO	acetaldehyde
CH_3Hg	methylmercury, MeHg
CH_3OOH	methyl hydroperoxide
CH_3-S-CH_3	dimethylsulfide, DMS
CH_3-S-H	methyl mercaptan
CH_3SO_3H	methanesulfonic acid
CH_3-S-S-CH_3	dimethyl disulfide, DMDS
CH_4	methane
CHAD	Consolidated Human Activities Database
CHF	congestive heart failure
chl *a*	chlorophyll *a*
Chol	cholesterol

CHS	Children's Health Study
CI	confidence interval
C_i	interstitial air concentration
CIMS	chemical ionization mass spectroscopy
Cl	chlorine
CL	critical load
Cl^-	chlorine ion
Cl_2	molecular chlorine
CLaMS	type of Lagrangian model
CMAQ	Community Multiscale Air Quality (modeling system)
CMD	count median diameter
CMSA	consolidated metropolitan statistical area
CO	carbon monoxide
CO_2	carbon dioxide
CO_3^-	carbonate ion
CoH	coefficient of haze
CONUS	contiguous United States
COPD	chronic obstructive pulmonary disease
CS_2	carbon disulfide
CTM	chemical transport model
Cu	copper
CVD	cardiovascular disease
CYP	cytochrome P450
Dae	aerodynamic diameter
DEcCBP	DEP extract coated carbon black particles
DEN	diethylnitrosamine
DEP	diesel exhaust particles
DEP+C	diesel exhaust particle extract adsorbed to C
dG	2N-deoxyguanosine
DMBA	7,12-dimethylbenzanthracene
DMDS	dimethyl disulfide, CH_3-S-S-CH_3
DMS	dimethyl sulfide, CH_3-S-CH_3
DMSO	dimethylsulfoxide
DNS	direct numerical simulation (approach)
DOAS	differential optical absorption spectroscopy
DON	dissolved organic nitrogen
EC	elemental carbon
ECG	electrocardiography; electrocardiogram
ED	emergency department
EDXRF	energy dispersive X-ray fluorescence
EE	energy expenditure (average EE rate)
EIB	exercise-induced bronchial reactivity
ELF	epithelial lining fluid
EMAP	Environmental Monitoring and Assessment Program
EMECAM	Spanish Multicentre Study on Air Pollution and Mortality
EMEP	Co-operative Programme for Monitoring and Evaluation of the Long-range Transmission of Air Pollutants in Europe
EOS	Earth Observation System
EPA	U.S. Environmental Protection Agency

ESA	European Space Agency
ET	extrathoracic
Fe	iron
FEM(s)	Federal Equivalent Method(s)
$FePO_4$	iron phosphate
FeS	iron sulfide
$FEV_{0.75}$	forced expiratory volume in 0.75 second
FEV_1	forced expiratory volume in 1 second
F-factor	fraction of the change in mineral acid anions that is neutralized by base cation release
FHLC	fetal hamster lung cells
FLEXPART	type of Lagrangian model
FPD	flame photometric detector
FR	Federal Register
FRM	Federal Reference Method
FTIR	Fourier Transform Infrared Spectroscopy
FVC	forced vital capacity
G6PD	glucose-6-phosphate dehydrogenase
GAM	Generalized Additive Model(s)
GAW	Global Atmospheric Watch (program)
GCE	Goddard Cumulus Ensemble (model)
GCS	γ-glutamylcysteine synthetase
GEOS	Goddard Earth Observing System
GEOS-1DAS	Goddard Earth Observing System Data Assimilation System
GEOS-Chem	Goddard Earth Observing System (with global chemical transport model)
GFED	Global Fire Emissions Database
GHG	greenhouse gas
GIS	Geographic Information System
GLM	Generalized Linear Model(s)
GOES	Geostationary Operational Environmental Satellites
GOME	Global Ozone Monitoring Experiment
GPx	glutathione peroxidase
GRed	glutathione reductase
GSD	geometric standard deviation
GSH	glutathione; reduced glutathione
GSSG	glutathione disulfide
$GSSO_3H$	glutathione S-sulfonate
GST	glutathione-S-transferase
GT	γ-glutamyl transpeptidase
h	hour
H	hydrogen; hydrogen atom
H^+	hydrogen ion
H_2O	water
H_2O_2	hydrogen peroxide
H_2S	hydrogen sulfide
H_2SO_3	sulfurous acid
H_2SO_4	sulfuric acid
HAP(s)	hazardous air pollutant(s)
HAPEM	Hazardous Air Pollutant Exposure Model

HAPEM6	HAPEM, version 6
HC	hydrocarbon
HCHO	formaldehyde
HCl	hydrochloric acid
HEADS	Harvard-EPA Annular Denuder System
HEI	Health Effects Institute
HF	high frequency
Hg	mercury
HNO_2, HONO	nitrous acid
HNO_3, HOONO	nitric acid
HNO_4	pernitric acid
HO_2	hydroperoxyl; hydroperoxyl radical
HO_2NO_2	peroxynitric acid
HOBr	hypobromous acid
HOCl	hypochlorous acid
HOX	hypohalous acid
HP	hydrolyzed protein
HR	heart rate
HRV	heart rate variability
HSO_3^-	hydrogen sulfite, bisulfite
HSO_4^-	bisulfate ion
HSO_4^-	sulfuric acid ion
hv	solar ultraviolet photon with energy at wavelength v
HVA-ICa	high-voltage activated calcium currents
i	microenvironment
I	iodine
IA	Integrated Assessment
IARC	International Agency for Research on Cancer (WHO)
IBEM	individual based exposure model(s)
IC	ion chromatography
ICARTT	International Consortium for Atmospheric Research on Transport and Transformation
ICD9	International Classification of Diseases, Ninth Revision
ICDs	implanted cardioverter defibrillators
Ig	immunoglobulin (e.g., IgA, IgE, IgG)
IgG	immunoglobulin
IHD	ischemic heart disease
IIASA	International Institute for Applied Systems Analysis (an international research organization)
IL	interleukin (e.g., IL-4, IL-6, IL-8)
IMPROVE	Interagency Monitoring of Protected Visual Environments (network)
IO	iodine oxide
IOM	Institute of Medicine
IPC	International Cooperative Programme
IPCC	Intergovernmental Panel on Climate Change
IPCC-AR4	IPCC 4th Assessment Report
IQR	interquartile range
IR	infrared
ISA	Integrated Science Assessment
ISAAC	International Study of Asthma and Allergies in Children

ISC3	steady-state Gaussian plume dispersion model used to assess pollutant concentrations from industrial sources
IUGR	intrauterine growth retardation
i.v.	intravenous (injection route)
JPL	Jet Propulsion Laboratory
K	potassium
K^+	potassium ion
K_a , K_b	dissociation constant(s)
K_H	Henry's Law constant in M/atm
KNO_3	potassium nitrate
K_w	ion product of water
$LC_{0.01}$	lethal concentration at which 0.01% of exposed animals die
LD_{33}	lethal dose at which 33% of exposed animals die
LDH	lactate dehydrogenase, lactic acid dehydrogenase
LES	Large Eddy Simulation (approach)
LF	low frequency
LIDAR	Light Detection and Ranging (remote sensing system)
LIF	laser-induced fluorescence
LIMS	Limb Infrared Monitor of the Stratosphere
LOD	limit of detection
LOEL	lowest-observed-effect level
LRD	lower respiratory disease
LRS	lower respiratory symptoms
LRTAP	Long Range Transport of Air Pollution
LTM	Long-Term Monitoring (project)
M	molar
MAD	median aerodynamic diameter
MAQSIP	Multiscale Air Quality Simulation Platform (model)
MAX-DOAS	multiple axis differential optical absorption spectroscopy
MBL	marine boundary layer
MCh	methacholine
ME	microenvironmental (factors)
$MEF_{50\%}$	maximal midexpiratory flow at 50% of forced vital capacity
MeHg	methylmercury, CH_3Hg
MEM	model ensemble mean
MENTOR	Modeling Environment for Total Risk
MENTOR-1A	MENTOR for One-Atmosphere (model)
MET	metabolic equivalent of tasks
Mfg	manufacturing
Mg	magnesium
Mg^{2+}	magnesium ion
MgO	magnesium oxide
MI	myocardial infarction
MIMS	membrane inlet mass spectrometry
min	minute
MM5	Penn State/NCAR (National Center for Atmospheric Research) Mesoscale Model, version 5
MMAD	mass median aerodynamic density
MMD	mass median diameter

MMEF	maximal midexpiratory flow
Mn	manganese
MN	micronuclei
MNPCE	micronucleated PCE
Mo	molybdenum
MOBILE6	Highway Vehicle Emission Factor Model
MODIS	Moderate Resolution Imaging Spectroradiometer
MONICA	Monitoring Trend and Determinants in Cardiovascular Disease (registry)
MOPITT	Measurement of Pollution in the Troposphere
MOZART	Model for Ozone and Related Chemical Tracers
MOZART-2	Model for Ozone and Related Chemical Tracers, version 2
MPAN	peroxymethacrylic nitrate
MSA	metropolitan statistical area
Mt	million tons
N	nitrogen
N, n	number of observations
N_2	molecular nitrogen; nonreactive nitrogen
N_2O	nitrous oxide
N_2O_5	dinitrogen pentoxide
NA	not available; insufficient data
Na	sodium
Na^+	sodium ion
Na_2MoO_4	sodium molybdate
Na_2SO_4	sodium sulfate
NAAQS	National Ambient Air Quality Standards
NaCl	sodium chloride
$NaCO_3$	sodium carbonate
NADP	National Atmospheric Deposition Program
NAMS	National Air Monitoring Stations
NAPAP	National Acid Precipitation Assessment Program
NARSTO	North American Regional Strategy for Atmospheric Ozone
NAS	National Academy of Sciences
NASA	National Aeronautics and Space Administration
NATTS	National Air Toxics Trends (network)
NCAR	National Center for Atmospheric Research
NCICAS	National Cooperative Inner-City Asthma Study
NCore	National Core Monitoring Network
NDMA	N-nitroso-dimethylamine
NEI	National Emissions Inventory
NEM	National Exposure Model
NEM / pNEM	NEM and pNEM
NERL	National Exposure Research Laboratory
NH_2	amino (chemical group)
NH_3	ammonia
NH_4^+	ammonium ion
$(NH_4)_2SO_4$	ammonium sulfate
NH_4Cl	ammonium chloride
NH_4NO_3	ammonium nitrate

NHANES	National Health and Nutrition Examination Survey
NHAPS	National Human Activity Pattern Survey
NH_X	nitrogen category label for NH_3 (ammonia) plus NH_4^+(ammonium)
NH_Y	total reduced nitrogen (from ammonia and ammonium)
Ni	nickel
NILU	Norwegian Institute for Air Research
nitro-PAH	nitro-polycyclic aromatic hydrocarbon
NMBzA	N-nitrosomethylbenzylamine
NMMAPS	National Morbidity, Mortality, and Air Pollution Study
NO	nitric oxide
NO_2	nitrogen dioxide
NO_2^-	nitrite ion
NO_3	nitrate, nitrate radical
NO_3^-	nitrate, nitrate ion
NOAA	U.S. National Oceanic and Atmospheric Administration
NOAA-ARL	U.S. National Oceanic and Atmospheric Administration Air Resources Laboratory
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
NO_X	oxides of nitrogen; sum of NO and NO_2
NO_Y	sum of NO_X and NO_Z; odd nitrogen species; total oxidized nitrogen
NO_Z	sum of all inorganic and organic reaction products of NO_X (HONO, HNO_3, HNO_4, organic nitrates, particulate nitrate, nitro-PAHs, etc.)
NPS	National Park Service
NR	not reported
Nr	reactive nitrogen
NRC	National Research Council
NS	nonsignificant
NSF	National Science Foundation
nss	non-sea salt
NSTC	National Science and Technology Council
NTN	National Trends Network
NTP	National Toxicology Program
$^{16}O_2$	isotope of oxygen
O_2	molecular oxygen
O_3	ozone
OAQPS	Office of Air Quality Planning and Standards (U.S. EPA)
OC	organic carbon
OCS	carbonyl sulfide
OH	hydroxyl radical
OR	odds ratio
P	phosphorus
P, p	probability value
P_1	1st percentile
P_5	5th percentile
P_{95}	95th percentile
P_{99}	99th percentile
PAARC	Air Pollution and Chronic Respiratory Diseases (study)
PAH(s)	polycyclic aromatic hydrocarbon(s)
PAMS	Photochemical Assessment Monitoring Stations

PAN(s)	peroxyacyl nitrate(s) (e.g. most common PAN: *peroxyacetyl nitrate)*
Pb	lead
PBEM	population based exposure model(s)
PBL	planetary boundary layer
$PC(SO_2)$	provocative concentration of SO_2 that produces a 100% increase in specific airway resistance
PCB(s)	polychlorinated biphenyl compound(s)
PCE	polychromatic erythrocytes
PD_{100}	provocative dose that produces a 100% increase in sRAW
PD_{20}	provocative dose that produces a 20% decrease in FEV_1
$PD_{20}FEV_1$	20% decrease in forced expiratory volume in 1 second
pdf	bi-Gaussian (probability density function)
PEACE	Pollution Effects on Asthmatic Children in Europe (study)
PEC	pulmonary endocrine cells
PEF	peak expiratory flow
PEMs	personal exposure monitors
PF	pulsed fluorescence
pH	relative acidity
PIXE	proton induced X-ray emission
PKA	cyclic AMP-dependent protein kinase A
pK_a	dissociation constant
PKI	synthetic peptide inhibitor of PKA
PL	phospholipids
PM	particulate matter
PM_{10}	particulate matter with a 50% upper cut point at 10 µm aerodynamic diameter and a collection efficiency curve as defined in the Code of Federal Regulations
$PM_{2.5}$	particulate matter with a 50% upper cut point at 2.5 µm aerodynamic diameter and a collection efficiency curve as defined in the Code of Federal Regulations; surrogate for fine PM
$PM_{10\text{-}2.5}$	particulate matter with a 50% upper cut point at 10 µm aerodynamic diameter, a 50% lower cut point at 2.5 µm aerodynamic diameter, and collection efficiency curves identical to those for PM_{10} and $PM_{2.5}$; surrogate for thoracic coarse PM (does not include fine PM)
PM_{13}	particulate matter with a 50% upper cut point at 13 µm aerodynamic diameter
$PM\text{-}CAM_X$	Comprehensive Air Quality Model with extensions and with particulate matter chemistry
PMT	photomultiplier tube
PNC	particle number concentration
pNEM	probabilistic National Exposure Model
PnET	Photosynthesis and EvapoTranspiration (model)
PnET-BGC	Photosynthesis and EvapoTranspiration-BioGeoChemical (model)
PnET-CN	Photosynthesis and EvapoTranspiration model of C, water, and N balances
PnET-N-DNDC	Photosynthesis and EvapoTranspiration-Denitrification-Decomposition (model)
pNO_3^-	particulate nitrate
PO_4^-, PO_4^{3-}	phosphate
POPs	persistent organic pollutants
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
PPN	peroxypropionyl nitrate
ppt	parts per trillion

pptv	parts per trillion by volume
PRB	policy relevant background
pSO_4^{2-}	particulate sulfate
PTFE	Polytetrafluoroethylene Filters (Teflon filter for air sampling)
Q	flow rate; discharge
Q_{10}	temperature coefficient
QAPP	Quality Assurance Project Plan
QT interval	measure of the time interval between the start of the Q wave and the end of the T wave in the heart's electrical cycle
R-	generic organic group attached to a molecule
R, r	correlation coefficient
R^2, r^2	coefficient of determination
Ra	aerodynamic resistance
RACM	Regional Atmospheric Chemistry Mechanism
RADM	Regional Acid Deposition Model
RAMS	Regional Atmospheric Modeling System
RANS	Reynolds Averaged Numerical Simulation (approach)
RAPS	Regional Air Pollution Study
RAR	rapidly activating receptor
Raw	airway resistance
Rb	boundary layer resistance
RBC	red blood cell or erythrocyte
Rc	internal resistance
R-C(O)OO	organic peroxy radical
R-COO(s)	strongly acidic organic anion(s)
RDBMS	relational database management system
RDT	Recovery Delay Time
REMAP	Regional Environmental Monitoring and Assessment Program
RH	relative humidity
RMR	resting metabolic rate
RMSE	root mean squared error
r-MSSD	root mean square of successive differences in R-R intervals.
$R\text{-}O_2$	organic peroxyl; organic peroxy
$R\text{-}O_2NO_2$	peroxynitrate
$R\text{-}ONO_2$	organic nitrate
RR	risk ratio; relative risk
RR_X	lognormal-transformed response ratio
RuBisCO	ribulose-1,5-bisphosphate carboxylase/oxygenase
^{32}S	sulfur-32, stable isotope of sulfur
^{34}S	sulfur-34, stable isotope of sulfur
^{35}S	sulfur-35, radioactive isotope of sulfur
^{86}Sr	strontium-86, stable isotope of strontium
^{87}Sr	strontium-87, stable isotope of strontium
S	sulfur
S^{2-}	sulfur radical
S_2*	electronically excited sulfur molecule
S_2O	disulfur monoxide
SAB	Science Advisory Board
SAPALDIA	Study of Air Pollution and Lung Diseases in Adults

SAPRAC	Statewide Air Pollution Research Center
SAPRC	Stratospheric Processes and their Role in Climate
SAVIAH	Small-Area Variation in Air Pollution and Health (study)
SBL	Stable Boundary Layer
SBUV	Solar Backscatter Ultraviolet Spectrometer
s.c.	subcutaneous (route of injection)
SC	safe concentration
SCAQS	Southern California Air Quality Study
SCE	sister chromatid exchanges
SCIAMACHY	Scanning Imaging Absorption Spectrometer for Atmospheric Cartography
SD	standard deviation
SDNN	standard deviation of normal R-R intervals
Se	selenium;
SE, se; SEM, sem	standard error; standard error of mean
SEARCH	Southeastern Aerosol Research and Characterization Study (monitoring program)
SEPs	somatosensory-evoked potentials
SES	socioeconomic status
SGV	sub grid variability
SHEDS	Simulation of Human Exposure and Dose System
Si	silicon
SIDS	sudden infant death syndrome
SIP	State Implementation Plan
SLAMS	State and Local Air Monitoring Stations
SMOKE	Spare-Matrix Operator Kernel Emissions
SNP	single nucleotide polymorphism
SO	sulfur monoxide
SO_2	sulfur dioxide
SO_3	sulfur trioxide
SO_3^{2-}	sulfite ion
SO_4^{2-}	sulfate ion
SOB	shortness of breath
SOD	superoxide dismutase
SO_X	sulfur oxides
SPARROW	SPAtially Referenced Regressions on Watershed Attributes (model)
SPF	specific pathogen free
SPM	suspended particulate matter
SQCA	squamous cell carcinoma
Sr	strontium
sRaw	specific airway resistance
SRB	sulfate-reducing bacteria
SRP	soluble reactive phosphorus
SSO	seabuckthorn seed oil
SSWC	Steady State Water Chemistry (model)
STE	stratospheric-tropospheric exchange
STN	Speciation Trends Network
STRF	Spatio-Temporal Random Field (theory)
SUM06	seasonal sum of all hourly average concentrations ≥ 0.06 ppm
SV40	simian virus 40

SVOC	semivolatile organic compound
T, t	time; duration of exposure
TAF	Tracking and Analysis Framework (model)
T_{air}	air temperature
TAR	Third Assessment Report
TBARS	thiobarbituric acid reactive substances
TC	total carbon
TDLAS	Tunable Diode Laser Absorption Spectrometer
TEA	triethanolamine
Tg	teragram
TIME	Temporally Integrated Monitoring of Ecosystems (program)
TNF	tumor necrosis factor (e.g., TNF-α)
TOC	potassium channel transient outward currents
TOR	thermal-optical reflectance (method)
TRACE-P	Transport and Chemical Evolution over the Pacific
TSP	total suspended particles
TSS	total suspended solids
TTX	tetrodotoxin
TTX-R	tetrodotoxin-resistant
TTX-S	tetrodotoxin-sensitive
T_{water}	water temperature
U.S.	United States of America
UMD-CTM	University of Maryland Chemical Transport Model
UNECE	United Nations Economic Commission for Europe
URI	upper respiratory infections
URS	upper respiratory symptoms
USDA	U.S. Department of Agriculture
USFS	U.S. Forest Service
USGS	U.S. Geological Survey
UV	ultraviolet
UV-A	ultraviolet radiation of wavelengths from 320 to 400 nm
UV-B	ultraviolet radiation of wavelengths from 280 to 320 nm
$\dot{V}_E$	minute ventilation
V_d	deposition rate
VEPs	visual-evoked potentials
VOC	volatile organic compound
W	tungsten
WHO	World Health Organization
WMO	World Meteorological Organization
WRF	Weather Research and Forecasting (model)
wt %	percent by weight
XNO_3	nitrate halogen-X salt
XO	halogen-X oxide
XRF	X-ray fluorescence
yr	year
Zn	zinc
ZnO	zinc oxide

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Preface

Legislative Requirements

Section 109, Title 42 (U.S. Code, 2003) directs the U.S. Environmental Protection Agency (EPA) Administrator to propose and promulgate "primary" and "secondary" National Ambient Air Quality Standards (NAAQS) for pollutants listed under section 108. Section 109(b)(1) defines a primary standard as one "the attainment and maintenance of which in the judgment of the Administrator, based on such criteria and allowing an adequate margin of safety, are requisite to protect the public health."[1] A secondary standard, as defined in section 109(b)(2), must "specify a level of air quality the attainment and maintenance of which, in the judgment of the EPA Administrator, based on such criteria, is required to protect the public welfare from any known or anticipated adverse effects associated with the presence of [the] pollutant in the ambient air."[2] The requirement that primary standards include an adequate margin of safety was intended to address uncertainties associated with inconclusive scientific and technical information available at the time of standard setting. It was also intended to provide a reasonable degree of protection against hazards that research has not yet identified. See *Lead Industries Association v. EPA*, 647 F.2d 1130, 1154 (D.C. Cir, 1980), cert. denied, 449 U.S. 1042 (1980); *American Petroleum Institute v. Costle*, 665 F.2d 1176, 1186 (D.C. Cir, 1981) cert. denied, 455 U.S. 1034 (1982). The aforementioned uncertainties are components of the risk associated with pollution at levels below those at which human health effects can be said to occur with reasonable scientific certainty. Thus, in selecting primary standards that include an adequate margin of safety, the Administrator is seeking not only to prevent pollution levels that have been demonstrated to be harmful but also to prevent lower pollutant levels that may pose an unacceptable risk of harm, even if the risk is not precisely identified as to nature or degree.

In selecting a margin of safety, the EPA considers such factors as the nature and severity of the health effects involved, the size of sensitive or vulnerable population(s) at risk, and the kind and degree of the uncertainties that must be addressed. The selection of any particular approach to providing an adequate margin of safety is a policy choice left specifically to the Administrator's judgment. See *Lead Industries Association v. EPA*, supra, 647 F.2d at 1161-62.

In setting standards that are "requisite" to protect public health and welfare, as provided in section 109(b), EPA's task is to establish standards that are neither more nor less stringent than necessary for these purposes. In so doing, EPA may not consider the costs of implementing the standards. See *Whitman v. American Trucking Associations*, 531 U.S. 457, 465472, 475-76 (U.S. Supreme Court 2001).

Section 109(d)(1) requires that "not later than December 31, 1980, and at 5-year intervals thereafter, the Administrator shall complete a thorough review of the criteria published under section 108 and the national ambient air quality standards…and shall make such revisions in such criteria and standards and promulgate such new standards as may be appropriate…" Section 109(d)(2) requires that an independent scientific review committee "shall complete a review of the criteria…and the national primary and secondary ambient air quality standards…and shall recommend to the Administrator any new…standards and revisions of existing criteria and standards as may be appropriate…" Since the early 1980s, this independent review function has been performed by the Clean Air Scientific Advisory Committee (CASAC) of EPA's Science Advisory Board (SAB).

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[1] The legislative history of section 109 indicates that a primary standard is to be set at "the maximum permissible ambient air level . . which will protect the health of any [sensitive] group of the population," and that for this purpose "reference should be made to a representative sample of persons comprising the sensitive group rather than to a single person in such a group" [S. Rep. No. 91-1196, 91st Cong., 2d Sess. 10 (1970)]. (Tsai et al., 2006)

[2] Welfare effects as defined in section 302(h) [42 U.S.C. 7602(h)] include, but are not limited to, "effects on soils, water, crops, vegetation, man-made materials, animals, wildlife, weather, visibility and climate, damage to and deterioration of property, and hazards to transportation, as well as effects on economic values and on personal comfort and well-being."

History of Reviews of the Primary NAAQS for Sulfur Oxides

On April 30, 1971, the EPA promulgated primary NAAQS for sulfur oxides (SO_X). These primary standards, which were based on the findings outlined in the original 1969 Air Quality Criteria for Sulfur Oxides, were set at 0.14 parts per million (ppm) averaged (avg) over a 24-hour (h) period, not to be exceeded more than once per year, and 0.030 ppm annual arithmetic mean with sulfur dioxide (SO_2) as the indicator. In 1982, EPA published the *Air Quality Criteria for Particulate Matter and Sulfur Oxides* (U.S. EPA, 1982) along with an addendum of newly published controlled human exposure studies, which updated the scientific criteria upon which the initial standards were based. In 1986, a second addendum was published presenting newly available evidence from epidemiologic and controlled human exposure studies (U.S. EPA, 1986a). In 1988, EPA published a proposed decision not to revise the existing standards (53 FR 14926). However, EPA specifically requested public comment on the alternative of revising the current standards and adding a new 1-h primary standard of 0.4 ppm.

As a result of public comments on the 1988 proposal and other post-proposal developments, EPA published a second proposal in the Federal Register (FR) on November 15, 1994 (59 FR 58958). The 1994 re-proposal was based in part on a supplement to the second addendum of the criteria document, which evaluated new findings on short-term SO_2 exposures in asthmatics (U.S. EPA, 1994c). As in the 1988 proposal, EPA proposed to retain the existing 24-h and annual standards. The EPA also solicited comment on three regulatory alternatives to further reduce the health risk posed by exposure to high 5-minute (min) peaks of SO_2 if additional protection were judged to be necessary. The three alternatives were: 1) revising the existing primary SO_2 NAAQS by adding a new 5-min standard of 0.60 ppm SO_2; 2) establishing a new regulatory program under section 303 of the Act to supplement protection provided by the existing NAAQS, with a trigger level of 0.60 ppm SO_2, one expected exceedance; and 3) augmenting implementation of existing standards by focusing on those sources or source types likely to produce high 5-min peak concentrations of SO_2. On May 22, 1996, EPA's final decision, that revisions of the NAAQS for SO_X were not appropriate at that time, was announced in the Federal Register (61 FR 25566).

Chapter 1. Introduction

The Integrated Science Assessment (ISA) is a concise review, synthesis, and evaluation of the most policy-relevant science, and communicates critical science judgments relevant to the NAAQS review. As such, the ISA forms the scientific foundation for the review of the primary (health-based) NAAQS for SO_X.[1] The primary NAAQS for SO_X, with SO_2 serving as the indicator, is set at 0.14 ppm, averaged over a 24-h period, not to be exceeded more than once per year, and 0.030 ppm annual arithmetic mean. The ISA accurately reflects "the latest scientific knowledge useful in indicating the kind and extent of identifiable effects on public health which may be expected from the presence of [a] pollutant in ambient air" (Clean Air Act, Section 108, 2003). Key information and judgments formerly contained in the Air Quality Criteria Document (AQCD) for SO_X are incorporated in this assessment. Additional details of the pertinent scientific literature published since the last review, as well as selected older studies of particular interest, are included in a series of annexes. This ISA thus serves to update and revise the information available at the time of the previous review of the NAAQS for SO_X in 1996.

SO_2 is the most important of the gas-phase sulfur oxides (SO_X) for both atmospheric chemistry and health effects. SO_X is usually defined to include sulfur trioxide (SO_3) and gas-phase sulfuric acid (H_2SO_4) as well, but neither is present in the atmosphere in concentrations significant for human exposures. Descriptions of the atmospheric chemistry of SO_X include both gaseous and particulate species; a meaningful analysis would not be possible otherwise. Most studies on the health effects of gaseous SO_X focus on SO_2; effects of other gaseous species are considered as information is available. The health effects of particulate SO_X are included in the review of the NAAQS for particulate matter (PM). In evaluating the health evidence, this ISA considers possible influences of other atmospheric pollutants, including interactions of SO_2 with other co-occurring pollutants such as PM, nitrogen oxides (NO_X), carbon monoxide (CO), and ozone (O_3).

The Integrated Plan for Review of the Primary NAAQS for SO_X (U.S. EPA, 2007) identifies key policy-relevant questions that provide a framework for this review of the scientific evidence. These questions frame the entire review of the NAAQS, and thus are informed by both science and policy considerations. The ISA organizes and presents the scientific evidence such that, when considered along with findings from risk analyses and policy considerations, will help the EPA address these questions during the NAAQS review.

- How has new information altered/substantiated the scientific support for the occurrence of health effects following short- and/or long-term exposure to levels of SO_X found in the ambient air?
- How does new information influence conclusions from the previous review regarding the effects of SO_X on susceptible populations?
- At what levels of SO_X exposure do health effects of concern occur?
- How has new information altered conclusions from previous reviews regarding the plausibility of adverse health effects caused by SO_X exposure?
- To what extent have important uncertainties identified in the last review been reduced? Have new uncertainties emerged?
- What are the air quality relationships between short-term and long-term exposures to SO_X?

[1] A review of the secondary SO_2 NAAQS, in conjunction with a review of the secondary NAAQS for NO_X, is underway independently, as is a review of the primary NAAQS for NO_X and a review of the primary and secondary NAAQS for PM.

1.1. Document Development

EPA initiated the current formal review of the NAAQS for SO_X on May 15, 2006 with a call for information from the public (FR, 2006). In addition to the call for information, publications are identified through an ongoing literature search process that includes extensive computer database mining on specific topics. Additional publications were identified by EPA scientists in a variety of disciplines by combing through relevant, peer-reviewed scientific literature obtained through these ongoing literature searches, reviewing previous EPA reports, and a review of reference lists from important publications. All relevant epidemiologic, human clinical, and animal toxicological studies, including those related to exposure-response relationships, mechanism(s) of action, or susceptible subpopulations published since the last review were considered. Added to the body of research were EPA's analyses of air quality and emissions data, studies on atmospheric chemistry, transport, and fate of these emissions, as well as issues related to exposure to SO_X. Further information was acquired from consultation with content and area experts and the public. Annex A has more discussion of search strategies and criteria for study selection.

1.2. Document Organization

The ISA is composed of five chapters. This introductory chapter presents background information, and provides an overview of EPA's framework for making causal judgments. Chapter 2 highlights key concepts or issues relevant to understanding the atmospheric chemistry, sources, exposure, and dosimetry of SO_X, following a "source-to-dose" paradigm. Chapter 3 evaluates and integrates epidemiologic, human clinical, and animal toxicological information relevant to the review of the primary NAAQS for SO_X. Chapter 4 has information related to the public health impact of ambient SO_X exposure, with emphasis on potentially susceptible and vulnerable population groups. Finally, Chapter 5 presents key findings and conclusions from the atmospheric sciences, ambient air data analyses, exposure assessment, dosimetry, and health effects for consideration in the review of the NAAQS for SO_X.

A series of annexes supplement this ISA. The annexes provide additional details of the pertinent literature published since the last review, as well as selected older studies of particular interest. These annexes contain information on:

- atmospheric chemistry of SO_X as well as the sampling and analytic methods for measurement of SO_X;
- environmental concentrations and human exposure to SO_X;
- toxicological studies of health effects in laboratory animals;
- human clinical studies of health effects related to peak (5-10 min) and short-term (1-h or longer) exposure to SO_X; and
- epidemiologic studies of health effects from short- and long-term exposure to SO_X.

Detailed information about methods and results of health studies is summarized in tabular format, and generally includes information about: concentrations of SO_X and averaging times; study methods employed; results and comments; and quantitative results for relationships between effects and exposure to SO_X.

1.3. EPA Framework for Causal Determination

It is important to have a consistent and transparent basis to evaluate the causal nature of air pollution-induced health effects. The framework described below establishes uniform language

concerning causality and brings more specificity to the findings. It draws standardized language from across the federal government and wider scientific community, especially from the recent National Academy of Sciences (NAS) Institute of Medicine (IOM) document, *Improving the Presumptive Disability Decision-Making Process for Veterans* (IOM, 2007), the most recent comprehensive work on evaluating the causality of health effects. This section:

- describes the kinds of scientific evidence used in establishing a general causal relationship between exposure and health effects;
- defines cause, in contrast to statistical association;
- discusses the sources of evidence necessary to reach a conclusion about the existence of a causal relationship;
- highlights the issue of multifactorial causation;
- identifies issues and approaches related to uncertainty; and
- provides a framework for classifying and characterizing the weight of evidence in support of a general causal relationship.

Approaches to assessing the separate and combined lines of evidence (e.g., epidemiologic, human clinical, and animal toxicological studies) have been formulated by a number of regulatory and science agencies, including the IOM of the National Academies of Science (IOM, 2008), International Agency for Research on Cancer (IARC, 2006), EPA Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005), Centers for Disease Control and Prevention (CDC, 2004), and National Acid Precipitation Assessment Program (NAPAP, 1991). Highlights or excerpts from the various decision framework documents are included in Annex A.

These formalized approaches offer guidance for assessing causality. The frameworks are similar in nature, although adapted to different purposes, and have proven effective in providing a uniform structure and language for causal determinations. Moreover, these frameworks must support decision-making under conditions of uncertainty.

1.3.1. Scientific Evidence Used in Establishing Causality

Causality determinations are based on the evaluation and synthesis of evidence from across scientific disciplines; the type of evidence that is most important for such determinations will vary by pollutant or assessment. The most compelling evidence of a causal relationship between pollutant exposures and human health effects comes from human clinical studies. This type of study experimentally evaluates the health effects of administered exposures in humans under highly-controlled laboratory conditions.

In epidemiologic or observational studies of humans, the investigator does not control exposures or intervene with the study population. Broadly, observational studies can describe associations between exposures and effects. These studies fall into several categories: cross-sectional, prospective cohort, and time-series studies. “Natural experiments” offer the opportunity to investigate changes in health with a change in exposure; these include comparisons of health effects before and after a change in population exposures, such as closure of a pollution source.

Experimental animal data complement the clinical and observational data; these studies can help characterize effects of concern, exposure-response relationships, sensitive subpopulations and modes of action. In the absence of clinical or epidemiologic data, animal data alone may be sufficient to support a likely causal determination, assuming that humans respond similarly to the experimental species.

1.3.2. Association and Causation

"Cause" is a significant, effectual relationship between an agent and an associated disorder or disease. "Association" is the statistical dependence among events, characteristics, or other variables. An association is prima facie evidence for causation; alone, however, it is insufficient proof of a causal relationship between exposure and disease. Unlike an association, a causal claim supports the creation of counterfactual claims; that is, a claim about what the world would have been like under different or changed circumstances (IOM, 2007). Much of the newly available health information evaluated in this ISA comes from epidemiologic studies that report a statistical association between ambient exposure and health outcome.

Many of the health outcomes reported in these studies have complex etiologies. The diseases, such as asthma, coronary heart disease or cancer are typically initiated by a web of multiple agents. Outcomes depend on a variety of factors, such as age, genetic susceptibility, nutritional status, immune competence, and social factors (Gee and Payne-Sturges, 2004; IOM, 2007). Further, exposure to a combination of agents could cause synergistic or antagonistic effects. Thus, the observed risk represents the net effect of many actions and counteractions.

1.3.3. Evidence for Going beyond Association to Causation

Moving from association to causation involves elimination of alternative explanations for the association. Human clinical studies are experiments conducted in a controlled laboratory setting using fixed concentrations of air pollutants under carefully regulated environmental conditions and subject activity levels. Results of human clinical studies may provide evidence of potential mechanisms for observed effects and a direct quantitative assessment of the exposure-health response relationship among individuals. In a randomized crossover study design, subjects in a population are exposed to a pollutant and a sham at different time points, and the responses to the two types of exposures are compared. This study design is effective at controlling for potential confounders, since the subject is serving as his/her own control. The results are assessed by rigorous comparison of changes in appropriate outcomes between the pollutant and sham exposures. By assigning exposure randomly, the study design attempts to remove the effect of any factor that might influence exposure. Done properly, and setting aside the role of chance, only a causal relationship between exposure and health outcome should produce observed associations in randomized clinical trials.

A lack of observation of effects from human clinical studies does not necessarily mean that a causal relationship does not exist. Human clinical studies are often limited because the study population is generally small, which restricts the ability to discern statistically significant findings in the health outcomes of interest between exposure to varying concentrations of air pollutant and clean air and to precisely characterize the exposure-response relationship. In addition, the most susceptible individuals may be explicitly excluded (for ethical reasons), and other susceptible individuals or groups, such as those with preexisting health conditions, may not be included. Study subjects must either be healthy, or have a level of illness which does not preclude them from participating in the study. Asthmatics who are unable to withhold the use of bronchodilators for at least 6 hours prior to exposure and subjects with a recent history of upper respiratory tract infections are typically excluded from clinical studies of air pollution exposure. While human clinical studies provide important information on the biological plausibility of associations observed between SO_2 exposure and health outcomes in epidemiologic studies, observed effects in these studies may underestimate the response in certain subpopulations for these reasons.

Epidemiologic studies provide important information on the associations between health effects and exposure of human populations to ambient air pollution. These studies also help to identify susceptible or vulnerable subgroups and associated risk factors. However, associations observed between specific air pollutants and health outcomes in epidemiologic studies may be confounded by copollutants

or meteorological conditions. Extensive discussion of these issues is provided in the 2004 AQCD for PM (U.S. EPA, 2004) and the 2006 AQCD for Ozone and Related Photochemical Oxidants (U.S. EPA, 2006b), and therefore presented only briefly below.

Inferring causation requires consideration of potential confounders. In confounding, 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). When associations are found in epidemiologic studies, one approach to remove spurious associations from possible confounders is to control for characteristics that may differ between exposed and unexposed persons; this is frequently termed "adjustment." Multivariable regression models constitute one tool for estimating the association between exposure and outcome after adjusting for characteristics of participants that might confound the results. The use of multipollutant regression models has been the prevailing approach for controlling potential confounding by copollutants in air pollution health effects studies. Finding the likely causal pollutant from multipollutant regression models is made difficult by the possibility that one or more air pollutants may be acting as a surrogate for an unmeasured or poorly-measured pollutant or for a particular mixture of pollutants. Further, the correlation between the air pollutant of interest and various copollutants may show temporal and spatial discongruities that can influence exposures and health effects. Thus, results of models that attempt to distinguish gaseous and particle effects must be interpreted with caution. Despite these limitations, the use of multipollutant models is still the prevailing approach employed in most air pollution epidemiologic studies, and may provide some insight into the potential for confounding or interaction among pollutants.

Another way to adjust for potential confounding is through stratified analysis, i.e., examining the association within homogeneous groups with respect to the confounding variable. Stratified analysis can also be used to examine potential effect modification. The use of stratified analyses has an additional benefit: it allows examination of effect modification through comparison of the effect estimates across different groups. If investigators successfully measured characteristics that distort the results, adjustment of these factors help separate a spurious from a true causal association. Appropriate statistical adjustment for confounders requires identifying and measuring all reasonably expected confounders. Deciding which variables to control for in a statistical analysis of the association between exposure and disease depends on knowledge about possible mechanisms and the distributions of these factors in the population under study. Identifying these mechanisms makes it possible to control for potential sources that may result in a spurious association.

Measurement error is another problem encountered when adjusting for spurious associations. Controlling for confounders, whether by adjustment or stratification, is only successful when the confounder is well-measured. Considered together, the effects of a well-measured covariate may be overestimated in contrast to a covariate measured with greater error. There are several components that contribute to exposure measurement error in these studies, including the difference between true and measured ambient concentrations, the difference between avg personal exposure to ambient pollutants and ambient concentrations at central monitoring sites, and the use of average population exposure rather than individual exposure estimates.

Confidence that unmeasured confounders are not producing the findings is increased when multiple studies are conducted in various settings using different subjects or exposures; each of which might eliminate another source of confounding from consideration. Thus, multi-city studies which use a consistent method to analyze data from across locations with different levels of covariates can provide insight on potential confounding in associations. The number and degree of diversity of covariates, as well as their relevance to the potential confounders, remain matters of scientific judgment. Intervention studies, because of their experimental nature, can be particularly useful in characterizing causation.

In addition to clinical and epidemiologic studies, the tools of experimental biology have been valuable for developing insights into human physiology and pathology. Laboratory tools have been extended to explore the effects of putative toxicants on human health, especially through the study of model systems in other species. Background knowledge of the biological mechanisms by which an exposure might or might not cause disease can prove crucial in establishing, or negating, a causal claim.

At the same time, species can differ from each other in fundamental aspects of physiology and anatomy (e.g., metabolism, airway branching, hormonal regulation) that may limit extrapolation. Testable hypotheses about the causal nature of proposed mechanisms or modes of action are central to utilizing experimental data in causal determinations.

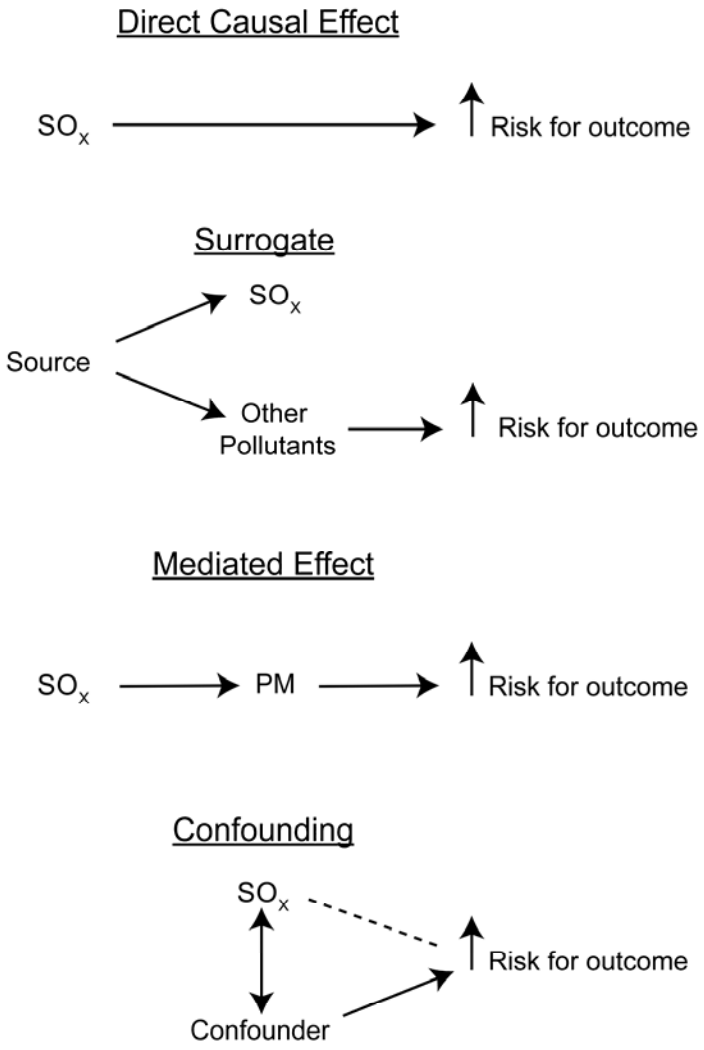

Figure 1-1. Potential relationships of SO_X with adverse health effects.

1.3.4. Multifactorial Causation

Scientific judgment is needed regarding likely sources and magnitude of confounding, together with judgment about how well the existing constellation of study designs, results, and analyses address this potential threat to inferential validity. One key consideration in this review is evaluation of the potential contribution of SO_X to health effects, when it is a component of a complex air pollutant mixture.

There are multiple ways by which SO_X might cause or be associated with adverse health effects, as illustrated in Figure 1-1. First, the reported SO_X effect estimates in epidemiologic studies may reflect independent SO_X effects on respiratory health. Second, ambient SO_X may be serving as an indicator of complex ambient air pollution mixtures that share the same source as SO_X (i.e., combustion of sulfur-containing fuels or metal smelting). Finally, copollutants may mediate the effects of SO_X or SO_X may influence the toxicity of copollutants. Epidemiologists use the term "interaction" or "effect modification" to denote the departure of the observed joint risk from what might be expected based on the separate effects of the factors. These possibilities are not necessarily exclusive. In addition, confounding can result in the production of an association between adverse health effects and SO_X that is actually attributable to another factor that is associated with SO_X in a particular study. Multivariate models are the most widely used strategy to address confounding in epidemiologic studies, but such models are not always easily interpreted when assessing effects of covarying pollutants such as PM, O_3, and nitrogen dioxide (NO_2).

1.3.5. Uncertainty[1]

In estimating the causal influence of an exposure on health outcomes, it is recognized that scientific findings incorporate uncertainty. Uncertainty can be defined as a state of having limited knowledge where it is impossible to exactly describe an existing state or future outcome – the lack of knowledge about the correct value for a specific measure or estimate.[2] Uncertainty characterization and uncertainty assessment are two activities that lead to different degrees of sophistication in describing uncertainty. Uncertainty characterization generally involves a qualitative discussion of the thought processes that lead to the selection and rejection of specific data, estimates, scenarios, etc. The uncertainty assessment is more quantitative. The process begins with simpler measures (i.e., ranges) and simpler analytical techniques and progresses, to the extent needed to support the decision for which the assessment is conducted, to more complex measures and techniques. Data will not be available for all aspects of an assessment and those data that are available may be of questionable or unknown quality. In these situations, evaluation of uncertainty can include professional judgment or inferences based on analogy with similar situation. The net result is that the assessments will be based on a number of assumptions with varying degrees of uncertainty. Additionally, uncertain information from different sources of different quality must be combined. It is important that uncertainty be qualitatively and, to the extent possible, quantitatively described.

1.3.5.1. Types of Uncertainty

Uncertainty in assessment can be classified into three broad categories: uncertainty regarding missing or incomplete information needed to fully define the exposure and dose (scenario uncertainty); uncertainty regarding some parameters (parameter uncertainty); and uncertainty regarding gaps in scientific theory required to make predictions on the basis of causal inferences (model uncertainty). Identification of the sources of uncertainty is the first step toward eventually determining the type of action necessary to reduce that uncertainty. The following sections will discuss sources of uncertainty and approaches for analyzing uncertainty.

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[1] This discussion on uncertainty was adapted from EPA's Guidelines for Exposure Assessment, May 29, 1992, Federal Register 57(104):22888-22938, EPA/600/Z-92/001.

[2] Variability is distinguished from uncertainty in that the former is an actual difference in some property of exposure or response; an intrinsic property that can be better understood with additional information but not reduced or eliminated. In contrast, uncertainty can be reduced or eliminated with additional information.

Scenario Uncertainty

The sources of scenario uncertainty include descriptive errors, aggregation errors, errors in professional judgment, and incomplete analysis. Descriptive errors include errors in information, such as misclassification of disease or pollutant exposure. Aggregation errors arise as a result of lumping approximations. Included among these are assumptions of homogeneous populations, and spatial and temporal approximations such as assumptions of steady-state conditions. Errors in professional judgment also are a source of uncertainty. A potentially serious source of uncertainty arises from incomplete analysis. For example, the lack of experimental data from clinical studies on severe asthmatics to pollutant exposures limits the qualitative and quantitative analyses of health effects.

Parameter Uncertainty

Sources of parameter uncertainty include measurement errors, sampling errors, variability, and use of generic or surrogate data. Measurement errors can be random or systematic. Random error results from imprecision in the measurement process. Systematic error is a bias or tendency away from the true value. Sampling errors concern sample representativeness. The purpose of sampling is to make an inference about the nature of the whole from a measurement of a subset of the total population. The inability to characterize the inherent variability in various parameters is a major source of uncertainty. The use of generic or surrogate data is common when site-specific data are not available, for example generalized descriptions of environmental settings. The approach to characterizing uncertainty in parameter values will vary. It can involve an order-of-magnitude bounding of the parameter range when uncertainty is high, or a description of the range for each of the parameters including the lower- and upper-bound and the best estimate values and justification for these based on available data or professional judgment. In some circumstances, characterization can take the form of a probabilistic description of the parameter range. The appropriate characterization will depend on several factors, including whether a sensitivity analysis indicates that the results are significantly affected by variations within the range. When the results are significantly affected by a particular parameter an attempt should be made to reduce the uncertainty by developing a description of the likely occurrence of particular values within the range. If enough data are available, standard statistical methods can be used to obtain a meaningful representation.

Model Uncertainty

Model uncertainty can be defined as gaps in scientific theory required to make predictions on the basis of causal inferences. Modeling errors are due to models being simplified representations of reality; hence, rationales for model selection should be discussed. Even after the most appropriate model has been selected for the purpose at hand, one is still faced with the question of how well the model represents the real situation. This question is compounded by the overlap between modeling uncertainties and other uncertainties, e.g., natural variability in inputs, representativeness of the modeling scenario, and aggregation errors. A dilemma is that many existing models (particularly the very complex ones) and the hypotheses contained within them cannot be fully tested, although certain components of the model may be tested. Even when a model has been validated under a particular set of conditions, uncertainty will exist in its application to situations beyond the test system.

1.3.5.2. Approaches to Characterizing Uncertainty

Various approaches to characterizing uncertainty can be described, such as classical statistical methods, sensitivity analysis, or probabilistic uncertainty analysis, in order of increasing complexity and data requirements.

Classical statistical methods are used to analyze uncertainty in measured values (Robinson, 1989). Given a data set of measured exposure values for a series of individuals, the population distribution may be estimated directly, provided that the sample design was developed properly to capture a representative sample. The measured exposure values also may be used to directly compute confidence interval estimates for percentiles of the distribution. When the distribution is estimated from measured exposures for a probability sample of population members, confidence interval estimates for percentiles of the exposure distribution are the primary uncertainty characterization.

Sensitivity analysis is the process of changing one variable while leaving the others constant and determining the effect on the output. The procedure involves fixing each uncertain quantity, one at a time, at its credible lower-bound and then its upper-bound (holding all others at their medians), and then computing the outcomes for each combination of values. These results are useful to identify the variables that have the greatest effect on exposure and to help focus further information gathering. The results do not provide any information about the probability of a quantity's value being at any level within the range; therefore, this approach is most useful at the screening level when deciding about the need and direction of further analyses.

Probabilistic uncertainty analysis is generally considered the next level of complexity (Eggleston, 1993). The most common example is the Monte Carlo technique where probability density functions are assigned to each parameter, then values from these distributions are randomly selected and inserted into the equation. After this process is completed many times, a distribution of predicted values results that reflects the overall uncertainty in the inputs to the calculation. By averaging over many different competing models, Bayesian Model Averaging incorporates model uncertainty into conclusions about parameters and prediction.

1.3.6. Application of Framework for Causal Determination

EPA uses a two-step approach to evaluate the scientific evidence on health effects of criteria pollutants. The first step determines the weight of evidence in support of causation and characterizes the strength of any resulting causal classification. The second step includes further evaluation of the quantitative evidence regarding the concentration-response relationships and the levels, duration and pattern of exposures at which effects are observed.

To aid judgment, various "aspects"[1] of causality have been discussed by many philosophers and scientists. The most widely cited aspects of causality in epidemiology, and public health in general, were articulated by Sir Austin Bradford Hill in 1965 and have been widely used (CDC, 2004; U.S. EPA, 2005; IARC, 2006; IOM, 2007). These nine aspects (Hill, 1965) have been modified (below) for use in causal determinations specific to health and environmental effects and pollutant exposures.[2]

Table 1-1. Aspects to aid in judging causality.

1. ***Consistency of the observed association.*** An inference of causality is strengthened when a pattern of elevated risks is observed across several independent studies. The reproducibility of findings constitutes one of the strongest arguments for causality. If there are discordant

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[1]The "aspects" described by Hill (1965) have become, in the subsequent literature, more commonly described as "criteria." The original term "aspects" is used here to avoid confusion with "criteria" as it is used, with different meaning, in the Clean Air Act.

[2] The Hill apects were developed for use with epidemiology data. They have been modified here for use with a broader array of data, i.e., epidemiologic, controlled human exposure, and animal toxicological studies, as well as *in vitro* data, and to be more consistent with EPA's Guidelines for Carcinogen Risk Assessment.

results among investigations, possible reasons such as differences in exposure, confounding factors, and the power of the study are considered.

2. ***Strength of the observed association.*** The finding of large, precise risks increases confidence that the association is not likely due to chance, bias, or other factors. A modest risk, however, does not preclude a causal association and may reflect a lower level of exposure, an agent of lower potency, or a common disease with a high background level.

3. ***Specificity of the observed association.*** As originally intended, this refers to increased inference of causality if one cause is associated with a single effect or disease (Hill, 1965). Based on current understanding this is now considered one of the weaker guidelines for causality; for example, many agents cause respiratory disease and respiratory disease has multiple causes. The ability to demonstrate specificity under certain conditions remains, however, a powerful attribute of experimental studies. Thus, although the presence of specificity may support causality, its absence does not exclude it.

4. ***Temporal relationship of the observed association.*** A causal interpretation is strengthened when exposure is known to precede development of the disease.

5. ***Biological gradient (exposure-response relationship).*** A clear exposure-response relationship (e.g., increasing effects associated with greater exposure) strongly suggests cause and effect, especially when such relationships are also observed for duration of exposure (e.g., increasing effects observed following longer exposure times). There are, however, many possible reasons that a study may fail to detect an exposure-response relationship. Thus, although the presence of a biologic gradient may support causality, the absence of an exposure-response relationship does not exclude a causal relationship.

6. ***Biological plausibility***. An inference of causality tends to be strengthened by consistency with data from experimental studies or other sources demonstrating plausible biological mechanisms. A lack of biologic understanding, however, is not a reason to reject causality.

7. ***Coherence.*** An inference of causality may be strengthened by other lines of evidence (e.g., clinical and animal studies) that support a cause-and-effect interpretation of the association. The absence of other lines of evidence, however, is not a reason to reject causality.

8. ***Experimental evidence (from human populations).*** The strongest evidence for causality can be provided when a change in exposure brings about a change in adverse health effect or disease frequency in either clinical or observational studies.

9. ***Analogy.*** Structure-activity relationships and information on the agent's structural analogs can provide insight into whether an association is causal. Similarly, information on mode of action for a chemical, as one of many structural analogs, can inform decisions regarding likely causality.

While these aspects provide a framework for assessing the evidence, they do not lend themselves to being considered in terms of simple formulas or fixed rules of evidence leading to conclusions about causality (Hill, 1965). For example, one cannot simply count the number of studies reporting statistically significant results or statistically nonsignificant results for health effects and reach credible conclusions about the relative weight of the evidence and the likelihood of causality. Rather, these important considerations are taken into account with the goal of producing an objective appraisal of the evidence, informed by peer and public comment and advice, which includes weighing alternative views on controversial issues. Additionally, it is important to note that the principles in Table 1-1 cannot be used as a strict checklist, but rather to determine the weight of the evidence for inferring causality. In particular, not meeting one or more of the principles does not automatically exclude a study from consideration (e.g., see discussion in U.S. Surgeon General's Report, CDC, 2004).

1.3.7. First Step—Determination of Causality

In the ISA, EPA assesses results of recent relevant publications, in light of evidence available during the previous NAAQS review, to draw conclusions on the causal relationships between relevant pollutant exposures and health outcomes. This ISA uses a five-level hierarchy that classifies the weight of evidence for causation, not just association[1]; that is, whether the weight of scientific evidence makes causation at least as likely as not, in the judgment of the reviewing group. In developing this hierarchy, EPA has drawn on the work of previous evaluations, most prominently the IOM's Improving the Presumptive Disability Decision-Making Process for Veterans (IOM, 2007), EPA's Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005), and the U.S. Surgeon General's smoking reports (CDC, 2004). Excerpts from these reports are presented in Annex A. In the ISA, EPA uses a series of five descriptors to characterize the weight of evidence for causality. This weight of evidence evaluation is based on various lines of evidence from epidemiologic, controlled human exposure and animal studies, or other mechanistic, toxicological, or biological sources. These separate judgments are integrated into a qualitative statement about the overall weight of the evidence and causality. The five descriptors for causal determination are described in Table 1-2.

Table 1-2. Weight of evidence for causal determination.

Relationship	Description
Causal relationship	Evidence is sufficient to conclude that there is a causal relationship between relevant pollutant exposures and the health outcome. That is, a positive association has been observed between the pollutant and the outcome in studies in which chance, bias, and confounding could be ruled out with reasonable confidence. Evidence includes, for example, controlled human exposure studies; or observational studies that cannot be explain by plausible alternatives or are supported by other lines of evidence (e.g. animal studies or mechanism of action information). Evidence includes replicated and consistent high-quality studies by multiple investigators.
Likely to be a causal relationship	Evidence is sufficient to conclude that a causal relationship is likely to exist between relevant pollutant exposures and the health outcome but important uncertainties remain. That is, a positive association has been observed between the pollutant and the outcome in studies in which chance and bias can be ruled out with reasonable confidence but potential issues remain. For example: a) observational studies show positive associations but copollutant exposures are difficult to address and/or other lines of evidence (controlled human exposure, animal, or mechanism of action information) are limited or inconsistent; or b) animal evidence from multiple studies, sex, or species is positive but limited or no human data are available. Evidence generally includes replicated and high-quality studies by multiple investigators.
Suggestive of a causal relationship	Evidence is suggestive of a causal relationship between relevant pollutant exposures and the health outcome, but is limited because chance, bias and confounding cannot be ruled out. For example, at least one high-quality study shows a positive association but the results of other studies are inconsistent.
Inadequate to infer a causal relationship	Evidence is inadequate to determine that a causal relationship exists between relevant pollutant exposures and the health outcome. The available studies are of insufficient quantity, quality, consistency or statistical power to permit a conclusion regarding the presence or absence of an association between relevant pollutant exposure and the outcome.
Suggestive of no causal relationship	Evidence is suggestive of no causal relationship between relevant pollutant exposures and the health outcome Several adequate studies, covering the full range of levels of exposure that human beings are known to encounter and considering sensitive subpopulations, are mutually consistent in not showing a positive association between exposure and the outcome at any level of exposure. The possibility of a very small elevation in risk at the levels of exposure studied can never be excluded.

[1] It should be noted that the CDC and IOM frameworks use a four-category hierarchy for the strength of the evidence. A five-level hierarchy is used here to be consistent with the EPA Guidelines for Carcinogen Risk Assessment and to provide a more nuanced set of categories.

1.3.8. Second Step—Evaluation of Population Response

Beyond judgments regarding causality are questions relevant to quantifying risks to populations. The fundamental issue is to understand the relationships between pollutant exposures and health effects in the human population. In addressing this issue several important questions must be considered:

- What is the concentration-response or dose-response relationship in the human population?
- What is the interrelationship between incidence and severity of effect?
- What exposure conditions (dose or exposure, duration and pattern) are important?
- What subpopulations appear to be differentially affected i.e., more susceptible to effects?

To address these questions the second step of the framework evaluates the entirety of policy-relevant quantitative evidence regarding the concentration-response relationships including levels of pollutant and exposure durations at which effects are observed, and subpopulations that differ from the general population. This integration of evidence results in identification of a study or set of studies that best approximates the concentration-response relationship for the U.S. population, given the current state of knowledge and the uncertainties that surround these estimates.

To accomplish this integration, evidence from multiple and diverse types of studies is considered. Response is evaluated over a range of observations which is determined by the type of study and methods of exposure or dose and response measurements. Results from different protocols are compared and contrasted. Extensive human concentration-response data exist for all criteria pollutants, unlike most other environmental pollutants. Animal data also inform evaluation of concentration-response, particularly relative to dosimetry, mechanisms of action, and characteristics of susceptible subpopulations. For some health outcomes, the probability and severity of health effects and associated uncertainties can be characterized. Chapter 5 presents the integrated findings informative for evaluation of population risks.

An important consideration in characterizing the public health impacts associated with exposure to a pollutant is whether the concentration-response relationship is linear across the full concentration range encountered, or if nonlinear relationships exist along any part of this range. Of particular interest is the shape of the concentration-response curve at and below the level of the current standards. The shape of the concentration-response curve varies, depending on the type of health outcome, underlying biological mechanisms and dose. At the human population level, however, various sources of variability and uncertainty tend to smooth and "linearize" the concentration-response function (such as the low data density in the lower concentration range, possible influence of measurement error, and individual differences in susceptibility to air pollution health effects). Additionally, many chemicals and agents may act by perturbing naturally occurring background processes that lead to disease, which also linearizes population concentration-response relationships (Clewell and Crump, 2005; Crump et al., 1976; Hoel, 1980). These attributes of population dose-response may explain why the available human data at ambient concentrations for some environmental pollutants (e.g., O_3, lead [Pb], PM, secondhand tobacco smoke, radiation) do not exhibit evident thresholds for cancer or noncancer health effects, even though likely mechanisms of action include nonlinear processes for some key events. These attributes of human population dose-response relationships have been extensively discussed in the broader epidemiologic literature (e.g., Rothman and Greenland, 1998).

1.3.9. Concepts in Evaluating Adversity of Health Effects

In evaluating the health evidence, a number of factors can be considered in determining the extent to which health effects are "adverse" for health outcomes such as changes in lung function. What constitutes an adverse health effect may vary between populations. Some changes in healthy individuals may not be considered adverse while those of a similar type and magnitude are potentially adverse in more susceptible individuals.

The American Thoracic Society (ATS) published an official statement titled "What Constitutes an Adverse Health Effect of Air Pollution?" (ATS, 2000). This statement updated the guidance for defining adverse respiratory health effects that had been published 15 years earlier (ATS, 1985), taking into account new investigative approaches used to identify the effects of air pollution and reflecting concern for impacts of air pollution on specific susceptible groups. In the 2000 update, there was an increased focus on quality of life measures as indicators of adversity and a more specific consideration of population risk. Exposure to air pollution that increases the risk of an adverse effect to the entire population is viewed as adverse, even though it may not increase the risk of any identifiable individual to an unacceptable level. For example, a population of asthmatics could have a distribution of lung function such that no identifiable single individual has a level associated with significant impairment. Exposure to air pollution could shift the distribution such that no one individual experiences clinically relevant effects; however, this shift toward decreased lung function would be considered adverse because individuals within the population would have diminished reserve function and, therefore, would be at increased risk if affected by another agent.

1.4. Conclusions

The ISA is a concise review, synthesis, and evaluation of the most policy-relevant science, and communicates critical science judgments relevant to the NAAQS review. It reviews the most policy relevant evidence from epidemiologic, human clinical, and animal toxicological studies, including mechanistic evidence from basic biological science. Annexes to the ISA provide additional details of the literature published since the last review. A framework for making critical judgments concerning causality is presented in this chapter. It relies on a widely accepted set of principles and standardized language to express evaluation of the evidence. This approach can bring rigor and clarity to the current and future assessments. This ISA should assist EPA and others, now and in the future, to represent accurately what is presently known—and what remains unknown—concerning the effects of SO_X on human health.

Chapter 2. Source to Dose

This chapter contains basic information about concepts and findings in atmospheric sciences, human exposure assessment, and human dosimetry. It is meant to serve as a prologue for the detailed discussions of health effects data in Chapters 3 and 4. Section 2.1 gives an overview of the sources of SO_2. Atmospheric chemistry processes involved in the oxidation of SO_2 and those involved in the production of SO_2 from reduced sulfur gases in the atmosphere are discussed in Section 2.2. A description of SO_2 measurement methods and monitor siting are presented in Sections 2.3 and 2.4. Data for ambient SO_2 concentrations are characterized in Section 2.5. Policy relevant background (PRB) concentrations of SO_2, i.e., those concentrations defined to result from uncontrollable emissions, are also presented in Section 2.5. Factors related to personal exposure to SO_2 are discussed in Section 2.6. Finally, Section 2.7 covers the dosimetry of SO_2 in the respiratory tract. This organization generally follows that given in the National Research Council (NRC) paradigm for integrating air pollutant research (NRC, 1998).

2.1. Sources of Sulfur Oxides

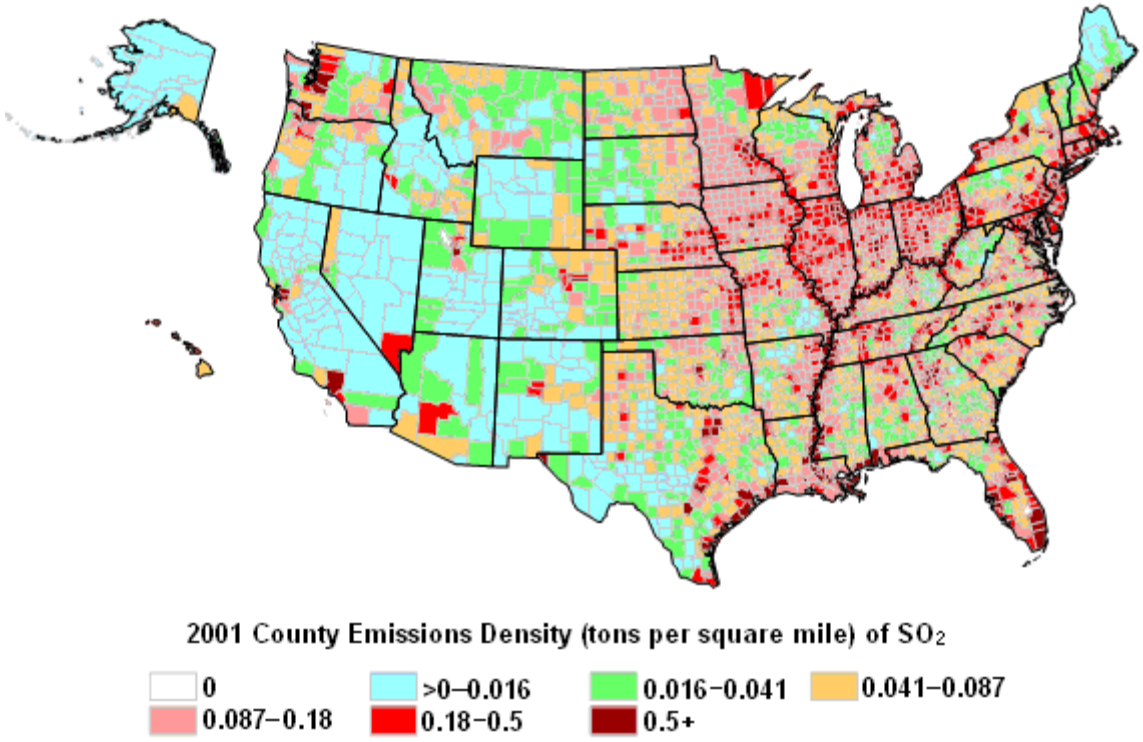
Anthropogenic emissions of SO_2 in the U.S. are mainly due to combustion of fossil fuels by electrical utilities (~66 %) and industry (~29%). Transportation-related sources contribute only ~5% based on 2002 statistics (U.S. EPA, 2006c). Thus, most SO_2 emissions originate from point sources. Annex B has a detailed breakdown of emissions by source category. Almost all of the S in fuel is released as volatile components (SO_2 or SO_3) during combustion. Hence, based on S content in fuel stocks, sulfur emissions can be calculated to a higher degree of accuracy than other pollutants such as NO_X or primary PM. However, these estimates are national averages and may not accurately reflect the contribution of specific local sources for determining individual exposure to SO_2 at a particular location and time.

An additional source of SO_2 emissions of concern in particular locations not immediately obvious from national-scale averages and totals are transit and in-port activities in areas with substantial shipping traffic (Wang et al., 2007). Because of the importance of these SO_2 emissions, the ports of Long Beach and Los Angeles, CA, for example, are part of a Sulfur Emissions Control Area in which S contents of fuels are not to exceed 1.5%. Figure 2-1 shows SO_2 emissions densities combined for all non- or off-road transportation-related emitters in which coastal areas with ports, and shipping routes, such as the Mississippi River, are easily discerned. In Los Angeles County, CA, for example, off-road transportation including shipping and port traffic contributed 1.4 of the total 4.1 tons of SO_2 per square mile in 2001; in King County (including the city of Seattle), WA, the off-road transportation fraction was 42% of the total SO_2 emissions density, or 1.2 of the total 2.8 tons per square mile. Emissions data more specific to the ports are not available in the routine emissions inventories. Increased uncertainty accompanies estimates of the actual SO_2 loads from these sources. Modeling studies by Vutukuru and Dabdub (2008) for southern California ports, for example, have shown that ships contribute >1 ppb to the 24-h avg SO_2 concentration at the coast, in Long Beach, CA, with < 10% of that (<0.1 ppb) farther inland.

The largest natural sources of SO_2 are volcanoes and wildfires. Although SO_2 constitutes a relatively minor fraction (0.005% by volume) of total volcanic emissions (Holland, 1978), concentrations in volcanic plumes can be in the range of several to tens of ppm. Volcanic sources of SO_2 in the U.S. are limited to the Pacific Northwest, Alaska, and Hawaii. Sulfur is a component of amino acids in vegetation and is released during combustion. Gaseous S emissions from this source are mainly in the form of SO_2.

In addition to its role as an emitted primary pollutant, SO_2 is also produced by the photochemical oxidation of reduced S compounds such as dimethyl sulfide (CH_3-S-CH_3, or DMS), hydrogen sulfide (H_2S), carbon disulfide (CS_2), carbonyl sulfide (OCS), methyl mercaptan (CH_3-S-H), and dimethyl disulfide (CH_3-S-S-CH_3). The sources for these compounds are mainly biogenic (see Annex Table B-3).

Emissions of reduced S species are associated typically with marine organisms living either in pelagic or coastal zones, and with anaerobic bacteria in marshes and estuaries. Emissions of DMS from marine plankton represent the largest single atmospheric source of reduced sulfur species (Berresheim et al., 1995). OCS is lost mainly by photolysis (e-folding lifetime[1], [τ] ~6 months). Other reduced S species are lost mainly by reaction with hydroxyl radical (OH) and NO_3 radicals, and are relatively short-lived; lifetimes range from a few hours to a few days (see Annex Table B-1). Reaction with NO_3 radicals at night most likely represents the major loss process for DMS and CH_3-S-H. Although the mechanisms for the oxidation of DMS are not completely understood, excess sulfate in marine aerosol appears related mainly to the production of SO_2 from the oxidation of DMS. Emissions of S from natural sources are small compared to industrial emissions within the U.S. However, important exceptions occur locally as the result of volcanic activity, wildfires and in certain coastal zones as described above.



Source: EPA, 2006

Figure 2-1. 2001 County-level SO_2 emissions densities (tons per square mile) from off-road mobile and other transportation sources.

Because OCS is relatively long-lived, it can survive oxidation in the troposphere and be transported upward into the stratosphere. Crutzen (1976) proposed that its oxidation to sulfate in the stratosphere serves as the major source of the stratospheric aerosol layer. However, Myhre et al. (2004) proposed that SO_2 transported upward from the troposphere by deep convection is the most likely source, since the flux of OCS is too small. In addition, in situ measurements of the isotopic composition of S in stratospheric

[1] The e-folding lifetime is the time needed to reduce the concentration to i/e of its initial value.

sulfate do not match those of OCS (Leung et al., 2002). Thus, anthropogenic SO_2 emissions could be important precursors to the formation of the stratospheric aerosol layer.

2.2. Atmospheric Chemistry

The only gaseous forms of SO_X of interest in tropospheric chemistry are SO_2 and SO_3. SO_3 can be emitted from the stacks of power plants and factories; however, it reacts extremely rapidly with water (H_2O) in the stacks or immediately after release into the atmosphere to form H_2SO_4, which mainly condenses onto existing particles when particle loadings are high; it can nucleate to form new particles under lower concentration conditions. Thus, only SO_2 is present in the tropospheric boundary layer at concentrations of concern for human exposures. The gas phase oxidation of SO_2 is initiated by the reaction

$$SO_2 + OH + M \rightarrow HSO_3 + M$$

Reaction 2-1

where M is an atmospheric constituent such as N_2 and O_2 that helps stabilize the reaction product. Reaction 2-1 is followed by

$$HSO_3 + O_2 \rightarrow SO_3 + HO_2$$

Reaction 2-2

$$SO_3 + H_2O \rightarrow H_2SO_4$$

Reaction 2-3

Because the saturation vapor pressure of H_2SO_4 is extremely low, it will be removed rapidly from the gas phase by transfer to aerosol particles and cloud drops. Depending on atmospheric conditions and concentrations of ambient particles and gaseous species that can participate in new particle formation, it can also nucleate to form new particles. Rate coefficients for the reactions of SO_2 with either the hydroperoxyl radical (HO_2) or NO_3 are too low to be significant (Jet Propulsion Laboratory, 2003). Note: for the subsequent discussion that sulfates such as H_2SO_4 are referenced using the S(VI) notation and intermediate sulfites such as SO_3^{2-} are denoted by S(IV).

S(VI) species, including the bisulfate ion (HSO_4^-) and sulfate (SO_4^{2-}) are the dominant S species in clouds. Intermediate S(IV) products, such as hydrogen sulfite (HSO_3^-) and sulfite (SO_3^{2-}) are also present in clouds following dissolution of SO_2 in water but preceding transformation to S(VI) products. The chief species capable of oxidizing S(IV) to S(VI) in cloud water are O_3, peroxides (either hydrogen peroxide (H_2O_2) or organic peroxides), hydroxyl (OH) radicals, and ions of transition metals such as iron (Fe), manganese (Mn) and copper (Cu) that can catalyze the oxidation of S(IV) to S(VI) by O_2. The basic mechanism of the aqueous phase oxidation of SO_2 has long been studied and can be found in numerous texts on atmospheric chemistry, e.g., Seinfeld and Pandis (1998), Finlayson-Pitts and Pitts (1999), Jacob (1999), and Jacobson (2002). Following Jacobson (2002), the steps involved in the aqueous phase oxidation of SO_2 can be summarized as:

Dissolution of SO_2

$$SO_2(g) \Leftrightarrow SO_2(aq)$$

Reaction 2-4

The formation and dissociation of H_2SO_3

$$SO_2(aq) + H_2O(aq) \Leftrightarrow H_2SO_3 \Leftrightarrow H^+ + HSO_3^- \Leftrightarrow 2H^+ + SO_3^{2-}$$

Reaction 2-5

In the pH range commonly found in rainwater (pH 2 to 6), the most important reaction converting S(IV) to S(VI) is

$$HSO_3^- + H_2O_2 + H^+ \Leftrightarrow SO_4^{2-} + H_2O + 2H^+$$

Reaction 2-6

because SO_3^{2-} is much less abundant than HSO_3^-.

For pH up to about 5.3, H_2O_2 is the dominant oxidant. At pH > 5.3, O_3 becomes dominant, followed by Fe(III), according to Seinfeld and Pandis (1998). However, differences in concentrations of oxidants result in differences in the pH at which this transition occurs. It should also be noted that the oxidation of SO_2 by O_3 and O_2 tends to be self-limiting: as sulfate is formed, the pH decreases and the rates of these reactions decrease. Higher pH levels are expected to be found mainly in marine aerosols. However, in marine aerosols, the chloride-catalyzed oxidation of S(IV) may be more important (Hoppel and Caffrey, 2005; Zhang and Millero, 1991). Because the ammonium ion (NH_4^+) is so effective in neutralizing acidity, it affects the rate of oxidation of S(IV) to S(VI) and the rate of dissolution of SO_2 in particles and cloud drops.

A comparison of the relative rates of oxidation by gas and aqueous phase reactions by Warneck (1999) indicates that on average only about 20% of SO_2 is oxidized by gas phase reactions; the remainder is oxidized by aqueous phase reactions. In areas away from strong pollution sources, the SO_2 τ is ~7 days with respect to gas phase oxidation, based on measurements of the rate constant for Reaction 2-1 (Jet Propulsion Laboratory, 2003) and a nominal concentration for the OH radical of $10^6/cm^3$. However, the mechanism of SO_2 oxidation at a particular location depends on local environmental conditions. For example, oxidants such as OH radicals are depleted near stacks. Under this condition, almost no SO_2 is oxidized in the gas phase. Further downwind, as the plume is diluted with background air, the gas phase oxidation of SO_2 increases in importance. Conditions in the plume can become more oxidizing than in background air as distance from the stack increases. This can cause the SO_2 oxidation rate to exceed that in background air. SO_2 in the planetary boundary layer is also removed from the atmosphere by dry deposition to moist surfaces, resulting in an atmospheric τ with respect to dry deposition of approximately 1 day to 1 week. Wet deposition of S naturally depends on the variable nature of rainfall, but in general results in τ ~7 days for SO_2. Oxidation and deposition together lead to an overall lifetime of SO_2 in the atmosphere of < 1 to 4 days, depending on altitude and location and meteorological conditions. Smaller values are expected near the surface.

2.3. Measurement Methods and Associated Issues

Currently, ambient SO_2 is measured using instruments based on pulsed ultraviolet (UV) fluorescence. The UV fluorescence monitoring method for atmospheric SO_2 was developed as an improvement to the flame photometric detection (FPD) method, which in turn had replaced the pararosaniline wet chemical method. This latter method is still the EPA's Federal Reference Method (FRM) for atmospheric SO_2, but it is rarely used because it is complex and has slow response even in its automated forms. Both the UV fluorescence and FPD methods are designated as Federal Equivalent Methods (FEMs) by EPA, but UV fluorescence has largely supplanted the FPD approach because the UV method is inherently linear and the FPD method needs consumable hydrogen gas.

In the UV fluorescence method, SO_2 molecules absorb UV light at one wavelength and emit UV light at longer wavelengths through excitation of the SO_2 molecule to a higher energy (singlet) electronic state. Once excited, the molecule decays nonradiatively to a lower-energy electronic state from which it then decays to the original electronic state by emitting a photon of light at a longer wavelength (i.e., a lower-energy photon) than the original, incident photon. The intensity of the emitted light is thus proportional to the number of SO_2 molecules in the sample gas.

In commercial analyzers, light from a high-intensity UV lamp passes through a bandwidth filter to allow only photons with wavelengths around the SO_2 absorption peak (near 214 nanometers [nm]) to enter the optical chamber. The light passing through the source bandwidth filter is collimated using a UV lens and passes through the optical chamber, where it is detected on the opposite side of the chamber by the reference detector. A photomultiplier tube (PMT) is offset from and placed perpendicular to the light path to detect the SO_2 fluorescence. Since the SO_2 fluorescence at 330 nm is different from its excitation wavelength, an optical bandwidth filter is placed in front of the PMT to filter out any stray light from the UV lamp. A lens is located between the filter and the PMT to focus the fluorescence onto the active area of the detector and optimize the fluorescence signal. The limit of detection (LOD) for a non-trace level SO_2 analyzer is required to be 10 ppb (40 CFR 53.23.c). However, most commercial analyzers have detection limits of about 3 ppb; many monitors might have lower effective detection limits. The EPA, through its National Core (NCore) initiative (U.S. EPA, 2005b) is in the process of supporting state, local, tribal, and federal networks in the implementation of newer trace-level SO_2 instrumentation. These new trace-level instruments have detection limits of 0.1 ppb or lower. More information related to SO_2 sampling and analysis is in Annex Section B.6.

2.3.1. Sources of Positive Interference

The most common sources of interference to the UV fluorescence method for SO_2 are other gases that fluoresce in a similar fashion when exposed to UV radiation. The most significant of these are polycyclic aromatic hydrocarbons (PAHs), of which naphthalene is a prominent example. Xylene is another common hydrocarbon that can cause fluorescent interference. Consequently, any such aromatic hydrocarbons in the optical chamber can act as positive interference. To remove this source of interference, high-sensitivity SO_2 analyzers, such as those to be used in the NCore network (U.S. EPA, 2005b), have hydrocarbon scrubbers to remove these compounds from the sample stream before the sample air enters the optical chamber.

Luke (1997) reported positive artifacts of a modified pulsed fluorescence detector generated by the coexistence of nitric oxide (NO), CS_2, and a number of highly fluorescent aromatic hydrocarbons such as benzene, toluene, *o*-xylene, *m*-xylene, *p*-xylene, *m*-ethyltoluene, ethylbenzene, and 1,2,4-trimethylbenzene. The positive artifacts could be reduced by using a hydrocarbon "kicker" membrane. At a flow rate of 300 standard cc/min and a pressure drop of 645 torr across the membrane, the interference from ppm levels of many aromatic hydrocarbons was eliminated. NO fluoresces in a spectral region close to that of SO_2. However, in high-sensitivity SO_2 analyzers, the bandpass filter in front of the PMT is

designed to prevent NO fluorescence from being detected at the PMT. Care must be exercised when using multicomponent calibration gases containing both NO and SO_2, so that the NO rejection ratio of the SO_2 analyzer is sufficient to prevent NO interference.

The most common source of positive bias (as contrasted with positive spectral interference) in high-sensitivity SO_2 monitoring is stray light in the optical chamber. Since SO_2 can be electronically excited by a broad range of UV wavelengths, any stray light with an appropriate wavelength that enters the optical chamber can excite SO_2 in the sample and increase the fluorescence signal. Furthermore, stray light at the wavelength of the SO_2 fluorescence that enters the optical chamber may impinge on the PMT and increase the fluorescence signal. Several design features minimize stray light, including the use of light filters, dark surfaces, and opaque tubing.

Nicks and Benner (2001) reported a sensitive SO_2 chemiluminescence detector based on a differential measurement: response from ambient SO_2 is determined by the difference between air containing SO_2 and air scrubbed of SO_2 when both air samples contain other detectable sulfur species. Assuming monotonic efficiency of the sulfur scrubber, all positive artifacts should also be reduced with this technique.

2.3.2. Sources of Negative Interference

Nonradiative deactivation (quenching) of excited SO_2 molecules can occur from collisions with common molecules in air, including nitrogen, oxygen, and water. During collisional quenching, the excited SO_2 molecule transfers energy, kinetically allowing the SO_2 molecule to return to the original lower energy state without emitting a photon. Collisional quenching results in a decrease in the SO_2 fluorescence and, hence, an underestimation of SO_2 concentration in the air sample. Of particular concern is the variable water vapor content of air. Luke (1997) reported that the response of the detector could be reduced by an amount of ~7 to 15% at water vapor mixing ratios of 1 to 1.5 mole percent (relative humidity [RH] = 35 to 50% at 20 to 25°C and 1 atmosphere [atm] for a modified pulsed fluorescence detector [Thermo Environmental Instruments, Model 43s]). Condensation of water vapor in sampling lines must be avoided, as water on the inlet surfaces can absorb SO_2 from the sample air. The simplest approach to avoid condensation is to heat sampling lines to a temperature above the expected dew point and to within a few degrees of the controlled optical bench temperature. At very high SO_2 concentrations, reactions between electronically excited SO_2 and ground state SO_2 might occur, forming SO_3 and SO (Calvert et al., 1978). However, the possibility that this artifact might be affecting measurements at very high SO_2 levels has not been examined.

2.3.3. Other Techniques for Measuring SO_2

More sensitive techniques for measuring SO_2 are available, but most of these systems are too complex and expensive for routine monitoring applications. However, techniques such as those described by Luke (1997) can be used to improve the sensitivity of ambient SO_2 monitors by eliminating sources of common interference. See descriptions in Annex B.

2.4. Monitoring Site Characteristics

2.4.1. Design Criteria for the NAAQS SO_2 Monitoring Networks[1]

Trace level SO_2 monitoring is currently required at the approximately 75 proposed NCore sites, as noted in CFR 40 Part 58 Appendices C and D. Continued operation of existing State and Local Air Monitoring Sites (SLAMS) for SO_2 using Federal Reference Methods (FRM) or Federal Equivalent Methods (FEM) is required until discontinuation is approved by the EPA Regional Administrator. Where SLAMS SO_2 monitoring is required, at least one of the sites must be a maximum concentration site for that specific area. In 2007, there were ~500 SO_2 monitors reporting values to the EPA Air Quality System database (AQS). The AQS contains measurements of air pollutant concentrations in the 50 states, plus the District of Columbia, Puerto Rico, and the Virgin Islands, for the 6 criteria air pollutants and hazardous air pollutants.

The appropriate spatial scales for SO_2 SLAMS monitoring are the microscale, middle, and possibly neighborhood scales.

- ***Micro (~5 - 100 meters(m) and middle scale (~100 - 500 m)***—Some data uses associated with microscale and middle scale measurements for SO_2 include assessing the effects of control strategies to reduce concentrations (especially for the 3-h and 24-h averaging times), and monitoring air pollution episodes.
- ***Neighborhood scale (~500 m – 4 km)***—This scale applies where there is a need to collect air quality data as part of an ongoing SO_2 stationary source impact investigation. Typical locations might include suburban areas adjacent to SO_2 stationary sources, for example, or for determining background concentrations as part of studies of population responses to SO_2 exposure.

2.4.1.1. Horizontal and Vertical Placement

The probe, or at least 80 percent of the monitoring path, must be located between 2 and 15 m above ground level for all SO_2 monitoring sites. The probe, or at least 90 percent of the monitoring path, must be positioned at least 1 m vertically or horizontally from any supporting structure, walls, parapets, penthouses, etc., and away from dusty or dirty areas. If the probe, or a significant portion of the monitoring path, is located near the side of a building, it should be located on the windward side relative to the prevailing wind direction during the season of highest concentration potential for the pollutant being measured.

2.4.1.2. Spacing from Minor Sources

Local minor sources of a primary pollutant such as SO_2 can affect concentrations of that particular pollutant at a monitoring site. If the objective for that site is to investigate these local primary pollutant emissions, then the site should be located where the spatial and temporal variability in these emissions can be captured. This type of monitoring site would likely be the microscale type. If a monitoring site is to be used to determine air quality over a much larger area, such as a neighborhood or city, a monitoring

[1] This section is adapted from Code of Federal Regulations 40 CFR Parts 53 and 58 and Appendix E to Part 58, as revised: Vol. 71, No. 200 / 17 October 2006

agency should avoid placing a monitor probe, path, or inlet near local, minor sources. The plume from the local minor sources should not be allowed to inappropriately influence the air quality data collected.

To minimize these potential interferences, the probe, or at least 90 percent of the monitoring path, must be placed away from the furnace, incineration flues, or other minor sources of SO_2. The separation distance should take into account the heights of the flues, type of waste or fuel burned, and the S content of the fuel.

2.4.1.3. Spacing from Obstructions

Buildings and other obstacles may possibly scavenge SO_2 and can act to restrict airflow for any pollutant. To avoid this interference, the probe, inlet, or at least 90 percent of the monitoring path must have unrestricted airflow and be located away from obstacles. The distance from the obstacle to the probe, inlet, or monitoring path must be at least twice the height of the obstruction's protrusion. An exception can be made for measurements taken in street canyons or at source-oriented sites where buildings and other structures are unavoidable. Generally, a probe or monitoring path located near or along a vertical wall is undesirable, because air moving along the wall may be subject to possible removal mechanisms. A probe, inlet, or monitoring path must have unrestricted airflow in an arc of at least 180 degrees. This arc must include the predominant wind direction for the season of greatest pollutant concentration potential.

Special consideration must be devoted to the use of open path analyzers, due to their inherent potential sensitivity to certain types of interferences, or optical obstructions. A monitoring path must be clear of all trees, brush, buildings, plumes, dust, or other optical obstructions, including potential obstructions that may move due to wind, human activity, growth of vegetation, etc. Temporary optical obstructions, such as rain, particles, fog, or snow, should be considered when locating an open path analyzer. Any temporary obstructions that are of sufficient density to obscure the light beam will affect the ability of the open path analyzer to measure pollutant concentrations continuously. Transient, but significant obscuration of especially longer measurement paths could occur because certain meteorological conditions (e.g., heavy fog, rain, snow) and/or aerosol levels are of sufficient density to prevent the analyzer's light transmission. If certain compensating measures are not otherwise implemented at the onset of monitoring (e.g., shorter path lengths, higher light source intensity), data recovery during periods of greatest primary pollutant potential could be compromised. For instance, if heavy fog or high particulate levels are coincident with periods of projected NAAQS-threatening pollutant potential, the resulting data may not be representative for reflecting maximum pollutant concentrations, despite the fact that the site may otherwise exhibit an acceptable, even exceedingly high overall valid data capture rate.

2.4.1.4. Spacing from Trees

Trees can provide surfaces for SO_2 adsorption or reactions and surfaces for particle deposition. Trees can also act as obstructions in cases where they are located between the air pollutant sources or source areas and the monitoring site, and where the trees are of sufficient height and leaf canopy density to interfere with normal airflow around the probe, inlet, or monitoring path. To reduce possible interference, the probe, inlet, or at least 90 percent of the monitoring path must be at least 10 meters or further from the drip line of trees.

For microscale sites, no trees or shrubs should be located between the probe and the source under investigation, such as a roadway or a stationary source.

2.4.2. Locations of SO_2 Monitors in Selected Metropolitan Areas

Figures 2-2 through 2-7 display SO_2 monitor density with respect to population density for the six metropolitan regions analyzed. The locations of SO_2 monitors in selected areas where air pollution-health outcome studies have been conducted are characterized in this section. The studies are described in later chapters of the ISA. The study areas included six regions comprising eight metropolitan statistical areas (MSAs), as defined by the U.S. Census Bureau (http://www.census.gov/): Atlanta, Cincinnati, Cleveland, Los Angeles/Riverside, New York City/Philadelphia, and St. Louis. SO_2 monitor location data (i.e., latitude/longitude) for 2004 were obtained from EPA's AirData website (http://www.epa.gov/air/data/). Monitors were mapped for a particular region if they were contained by the MSA or if they were within 15 km of its boundary. The total population and populations of three sensitive subgroups (under age 5, age 5 to 17, and those over age 65) were calculated for those areas using the population data contained within the census block maps.

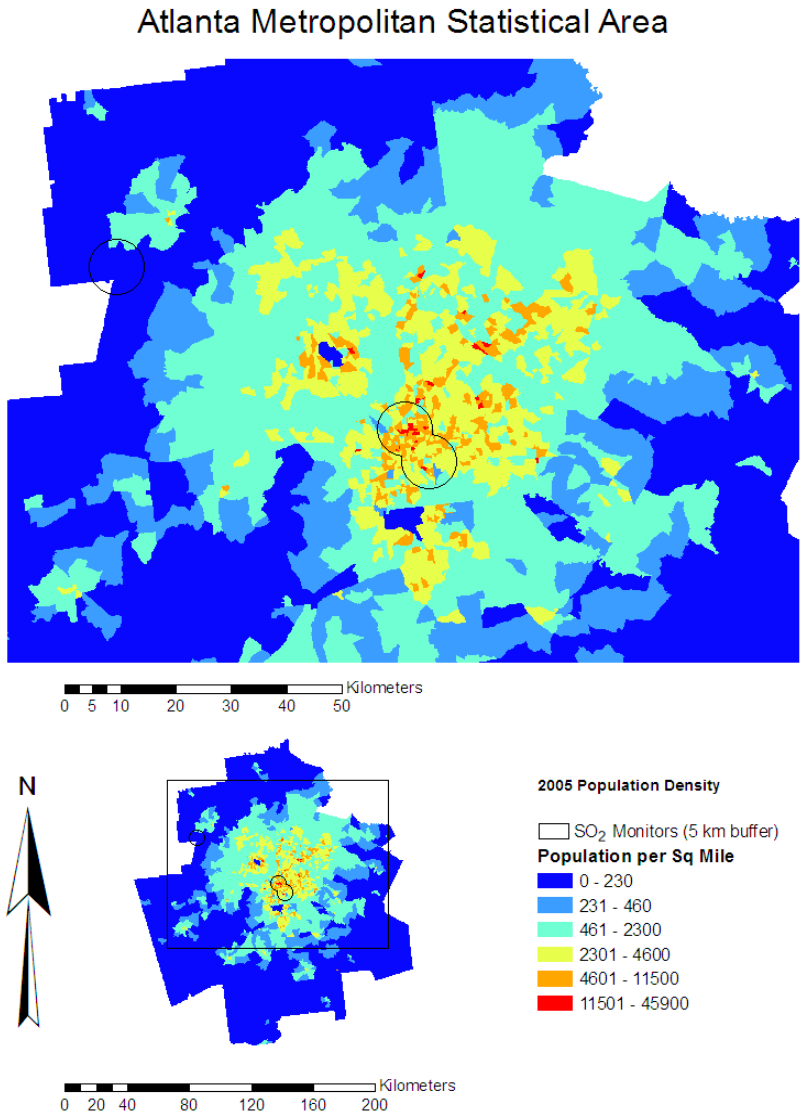


Figure 2-2. Location of SO_2 monitors with respect to population density in the Atlanta, GA MSA.

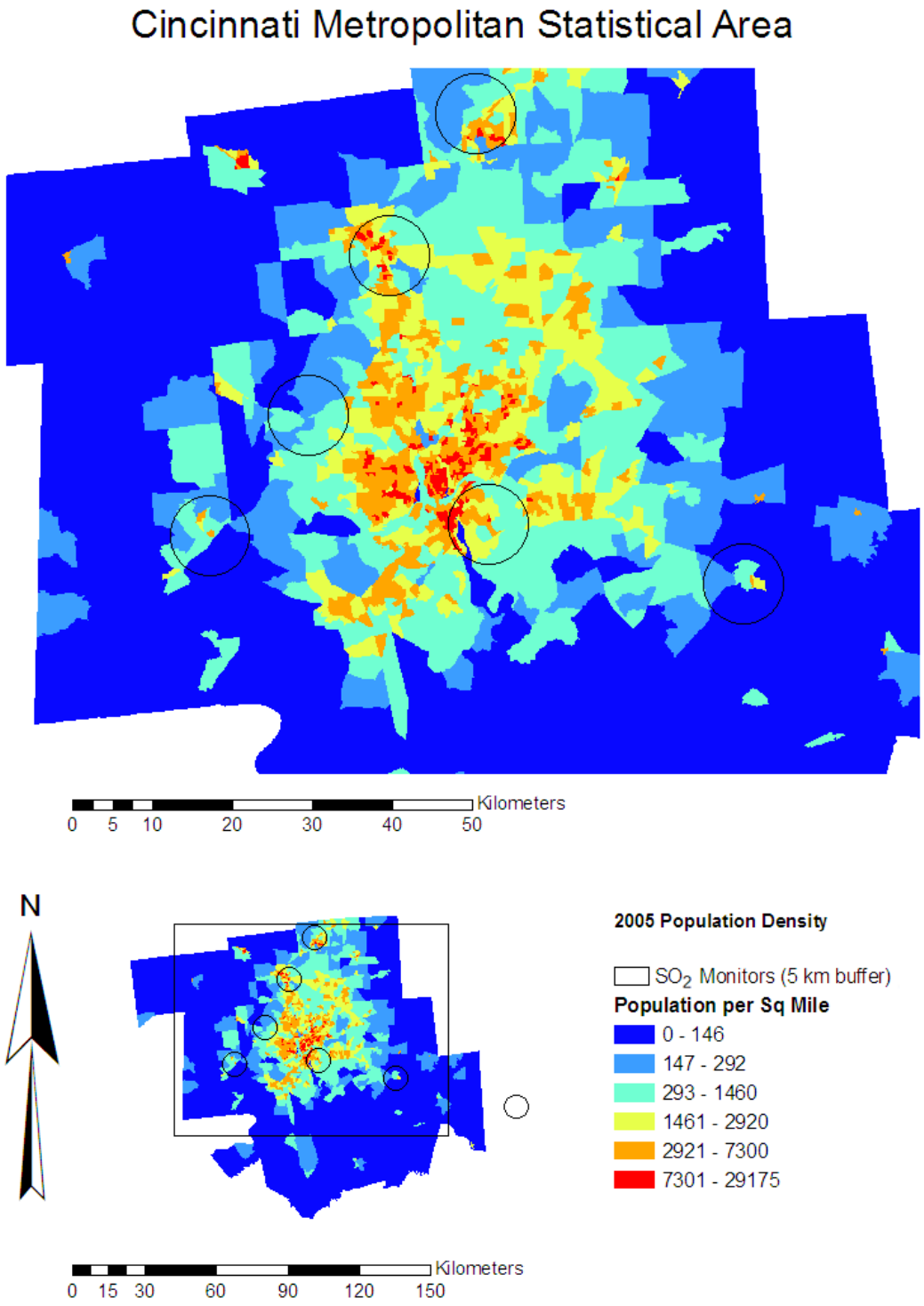


Figure 2-3. Location of SO_2 monitors with respect to population density in the Cincinnati, OH MSA.

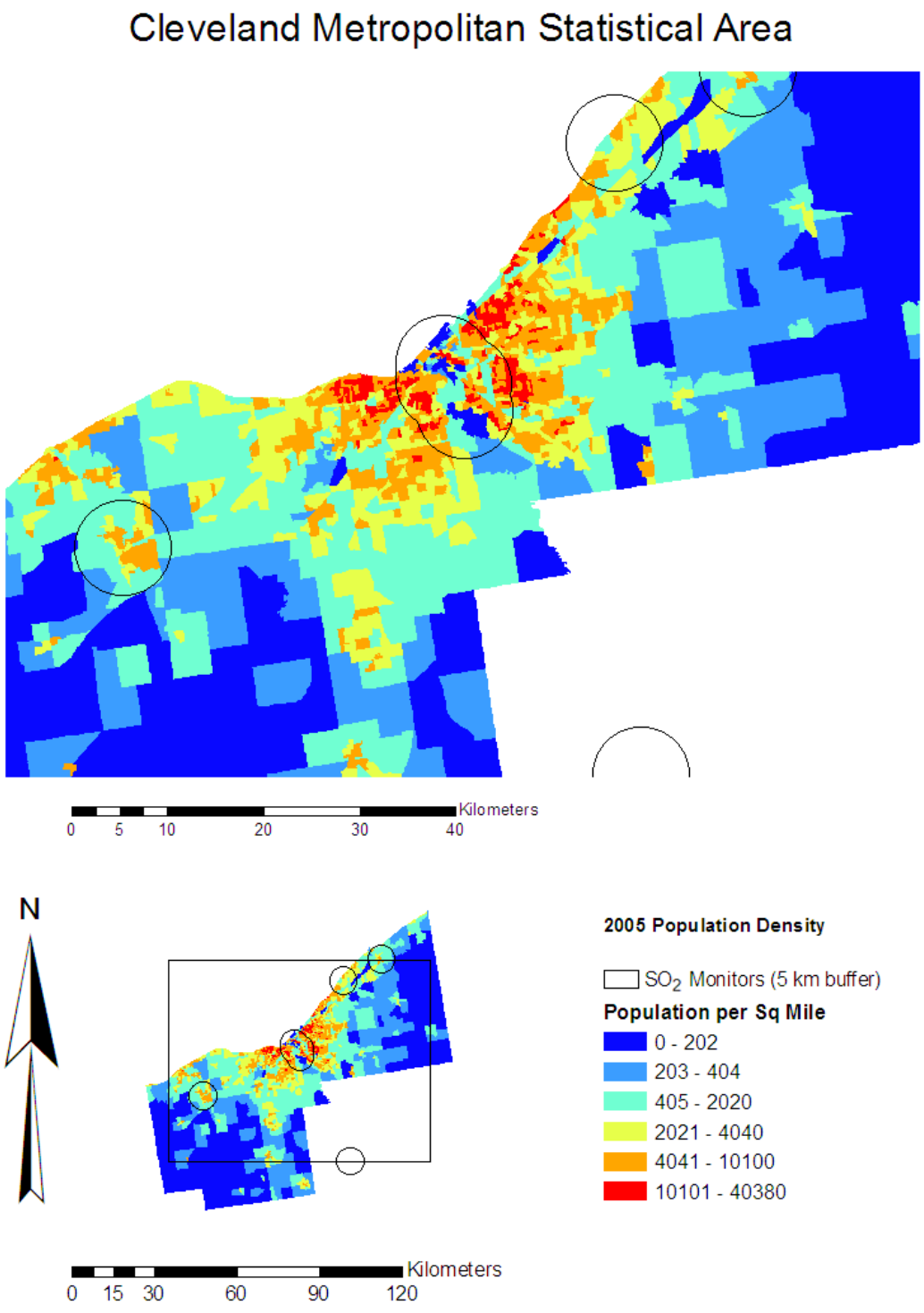


Figure 2-4. Location of SO_2 monitors with respect to population density in the Cleveland, OH MSA.

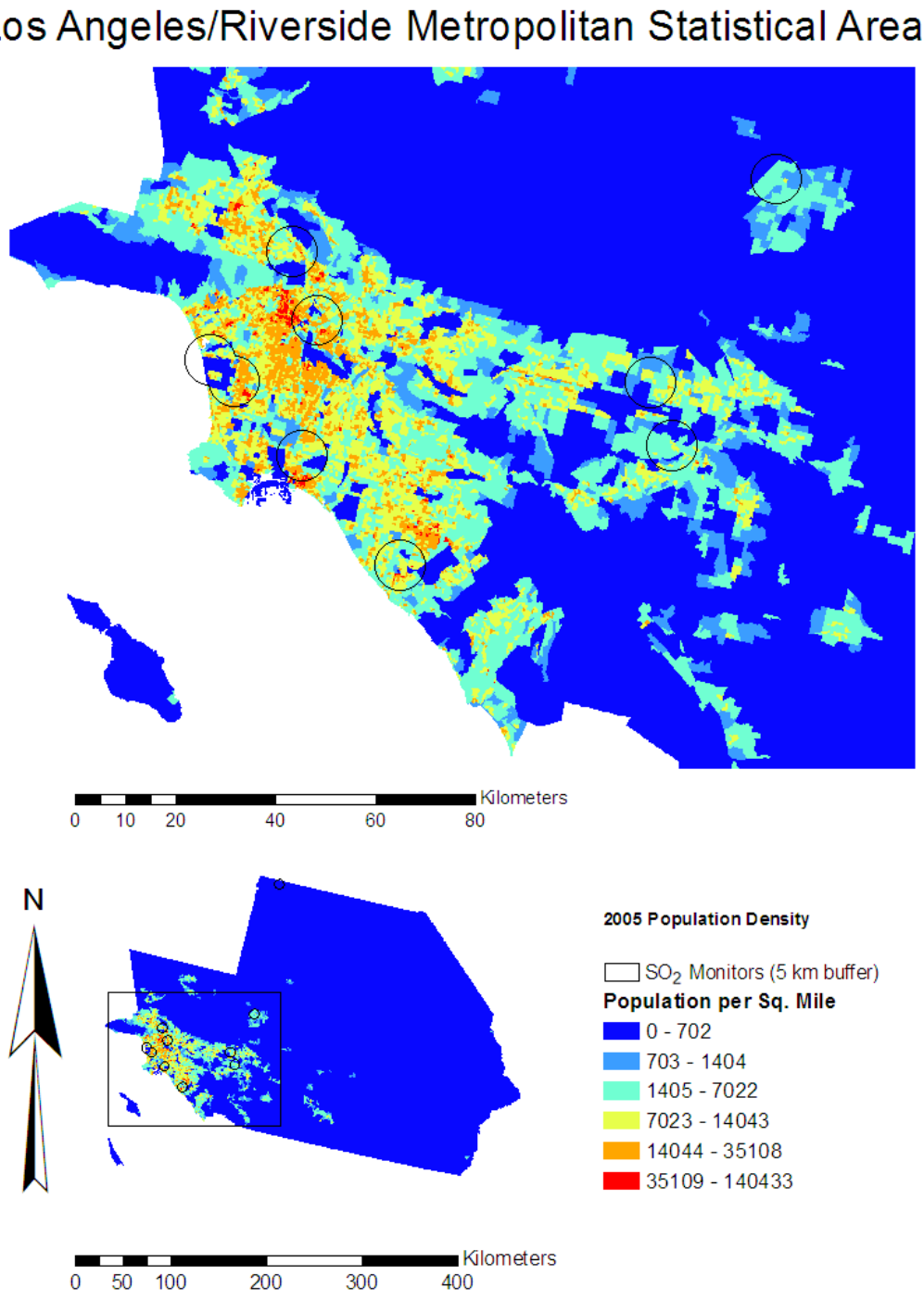


Figure 2-5. Location of SO_2 monitors with respect to population density in the Los Angeles/Riverside, CA MSA.

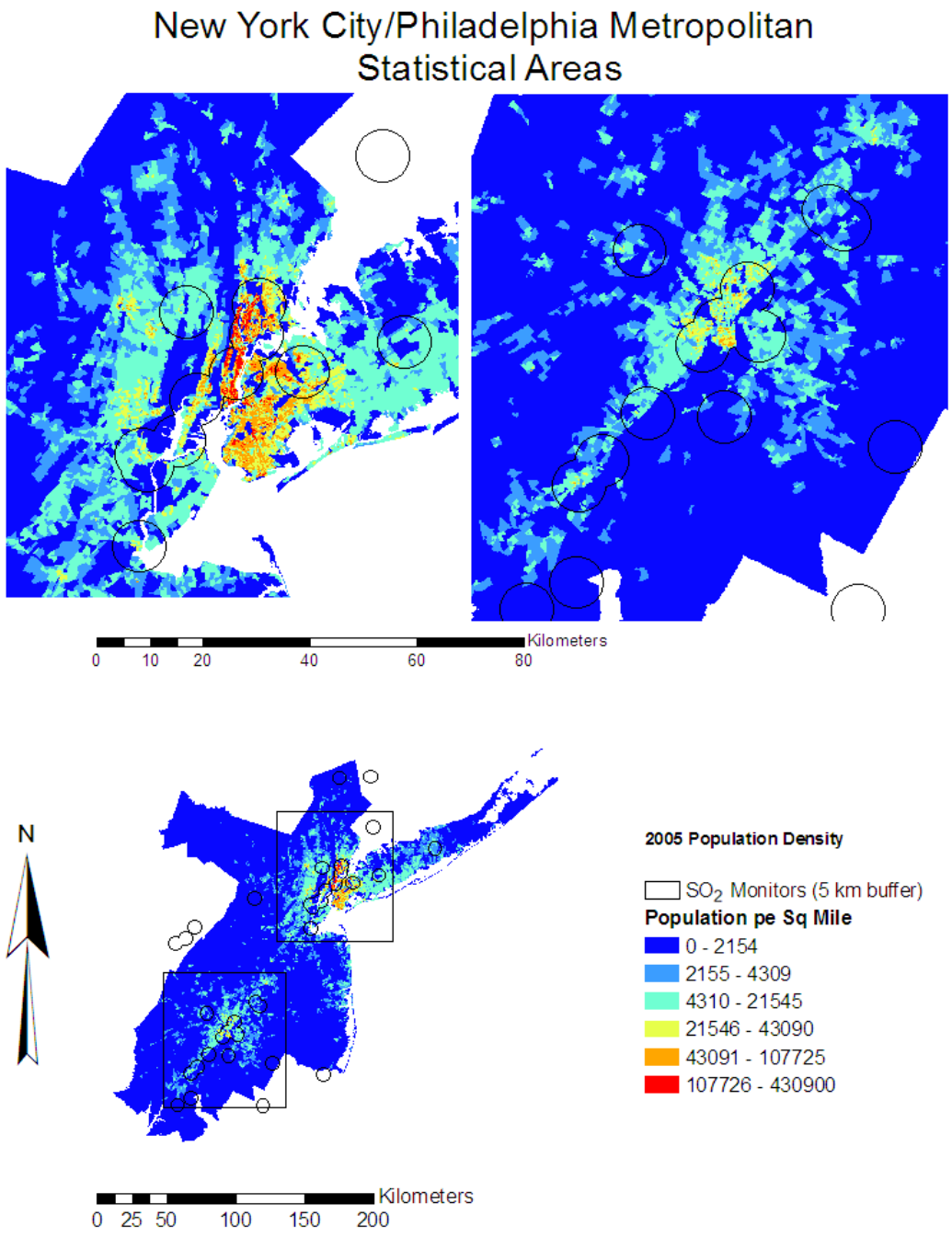


Figure 2-6. Location of SO_2 monitors with respect to population density in the New York City, NY/Philadelphia, PA MSA.

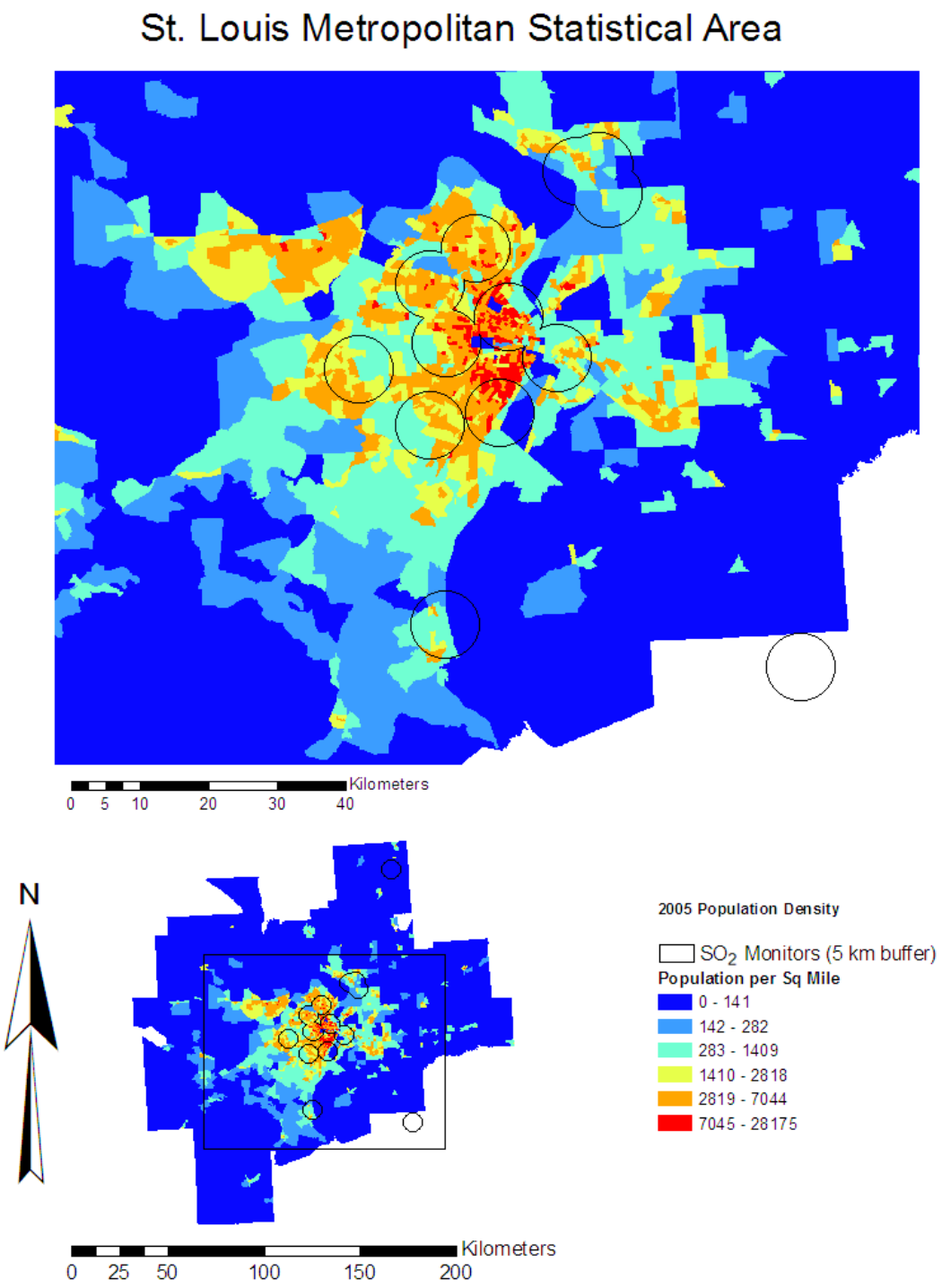


Figure 2-7. Location of SO_2 monitors with respect to population density in the St. Louis, MO MSA.

Tables 2-1 through Table 2-4 break down the population density around SO_2 monitors for the total population and for sub-populations of children aged 0-4 yr and 5-17 yr, and adults aged 65 yr and over, for each region. Variation in percentage within a certain radius of the monitor was fairly low for each city across the three age groups. However, between-city disparities in population density were larger. The New York City/Philadelphia region had the highest population density in all three age groups and overall

with the highest or near highest proportion, ~72-73%, of each population within 15 km of the monitors. The mid-western cities of Cincinnati, Cleveland, and St. Louis also had a large proportion, ~66-75%, of their population within 15 km of a monitor. This suggests that these sub-populations, as well as the total populace, are well represented by the monitoring networks in these regions. Los Angeles and Atlanta had lower proportions of their populations within 15 km of an SO_2 monitor, with Atlanta having only ~22% for the total population within 15 km, with similar proportions of children and a slightly higher (~27%) of the elder population represented. These latter figures likely reflect the lower density of local SO_2 sources in these regions.

Table 2-1. Proximity to SO_2 monitors for the total population by city. Percentages are given with respect to the total population in each city.

Proximity to SO_2 Monitor (km)	Region											
	Atlanta		Cincinnati		Cleveland		Los Angeles		New York/ Philadelphia		St. Louis	
	n	%	n	%	n	%	n	%	n	%	n	%
0-1	13,389	0.3	14,745	0.7	29,733	1.4	72,465	0.4	432,621	1.7	42,211	1.5
0-5	214,238	4.3	225,274	10.8	382,849	17.8	1,663,990	9.9	6,985,553	27.8	799,941	28.5
0-10	610,742	12.3	733,054	35.2	1,006,787	46.8	6,030,847	35.8	13,727,129	54.7	1,561,159	55.6
0-15	1,080,472	21.7	1,367,658	65.6	1,553,286	72.3	9,694,760	57.6	18,304,364	72.9	1,897,492	67.6
Total MSA	4,980,447	100.0	2,085,092	100.0	2,149,472	100.0	16,839,035	100.0	25,094,739	100.0	2,807,659	100.0

Note that population in proximity to the monitor is cumulative (i.e. those within 5 km includes those within 1 km) and the total MSA population includes those living in the region beyond the 15 km radius of the monitor.

Table 2-2. Proximity to SO_2 monitors for children aged 0-4 yr by city. Percentages are given with respect to the total population in the age group in each city.

Proximity to SO_2 Monitor (km)	Region											
	Atlanta		Cincinnati		Cleveland		Los Angeles		New York/ Philadelphia		St. Louis	
	n	%	n	%	n	%	n	%	n	%	n	%
0-1	425	0.1	1,057	0.8	2,409	1.7	4,548	0.4	28,421	1.7	2,485	1.4
0-5	14,216	4.5	15,606	11.0	30,903	21.9	126,764	10.4	453,267	27.7	50,937	28.5
0-10	37,440	11.8	48,942	34.6	71,852	50.8	451,417	37.1	890,406	54.4	100,856	56.4
0-15	68,231	21.5	94,851	67.0	105,809	74.8	721,458	59.2	1,198,850	73.3	121,685	68.0
Total MSA	317,949	100.0	141,537	100.0	141,425	100.0	1,218,227	100.0	1,635,831	100.0	178.868	100.0

Note that population in proximity to the monitor is cumulative (i.e. those within 5 km includes those within 1 km) and the total MSA population includes those living in the region beyond the 15 km radius of the monitor.

Table 2-3. Proximity to SO_2 monitors for children aged 5-17 yr by city. Percentages are given with respect to the total population in the age group in each city.

Proximity to SO_2 Monitor (km)	Region											
	Atlanta		Cincinnati		Cleveland		Los Angeles		New York/ Philadelphia		St. Louis	
	n	%	n	%	n	%	n	%	n	%	n	%
0-1	833	0.1	2,629	0.7	5,639	1.4	11,611	0.4	70,589	1.6	8,512	1.6
0=5	33,552	4.1	41,083	10.5	77,974	19.3	321,665	9.9	1,185,810	26.9	151,317	28.7
0-10	92,715	11.4	133,500	34.2	194,495	48.2	1,146,231	35.4	2,375,339	53.9	295,508	56.0
0-15	168,430	20.5	258,819	66.2	291,335	72.2	1,853,488	57.2	3,212,239	72.9	356,514	67.6
Total USA	813,107	100.0	390,704	100.0	403,465	100.0	3,238,473	100.0	4,406,226	100.0	527,773	100.0

Note that population in proximity to the monitor is cumulative (i.e. those within 5 km includes those within 1 km) and the total MSA population includes those living in the region beyond the 15 km radius of the monitor.

Table 2-4. Proximity to SO_2 monitors for adults aged 65 yr and over by city. Percentages are given with respect to the total population in the age group in each city.

Proximity to SO_2 Monitor (km)	Region											
	Atlanta		Cincinnati		Cleveland		Los Angeles		New York/ Philadelphia		St. Louis	
	n	%	n	%	n	%	n	%	n	%	n	%
0-1	279	0.1	1,826	0.8	3,425	1.1	7,197	0.5	52,315	1.7	6,929	2.0
0-5	17,237	5.3	29,363	12.5	46,067	14.8	138,838	7.0	805,226	25.9	123,954	35.4
0-10	53,503	16.4	90,437	38.5	144,465	46.4	511,431	33.0	1,668,273	53.6	219,972	62.9
0-15	88,867	27.2	164,229	69.9	233,210	74.9	852,535	55.0	2,243,853	72.1	257,891	73.7
Total MSA	326,858	100.0	235,116	100.0	311,579	100.0	1,549,138	100.0	3,113,768	100.0	349,881	100.0

Note that population in proximity to the monitor is cumulative (i.e. those within 5 km includes those within 1 km) and the total MSA population includes those living in the region beyond the 15 km radius of the monitor.

Figures 2-8 through 2-13 illustrate the 2005 geospatial locations of monitors for SO_2, NO_2, CO, particulate matter $\leq$ 10 μm (PM_{10}), particulate matter $\leq$ 2.5 μm ($PM_{2.5}$), and O_3. These locations, sited in several cities in six states, were selected as relevant for SO_2 health effects studies presented in Chapter 3; see the discussion of intracity SO_2 correlations that follows. For each state, Map A shows locations of each monitor for all six pollutants; and Map B shows only the SO_2 monitor locations. Totals for each monitor type are included. These figures demonstrate the important point that not all SO_2 monitors in any Consolidated Metropolitan Statistical Area (CMSA) are co-located with monitors for other pollutants.

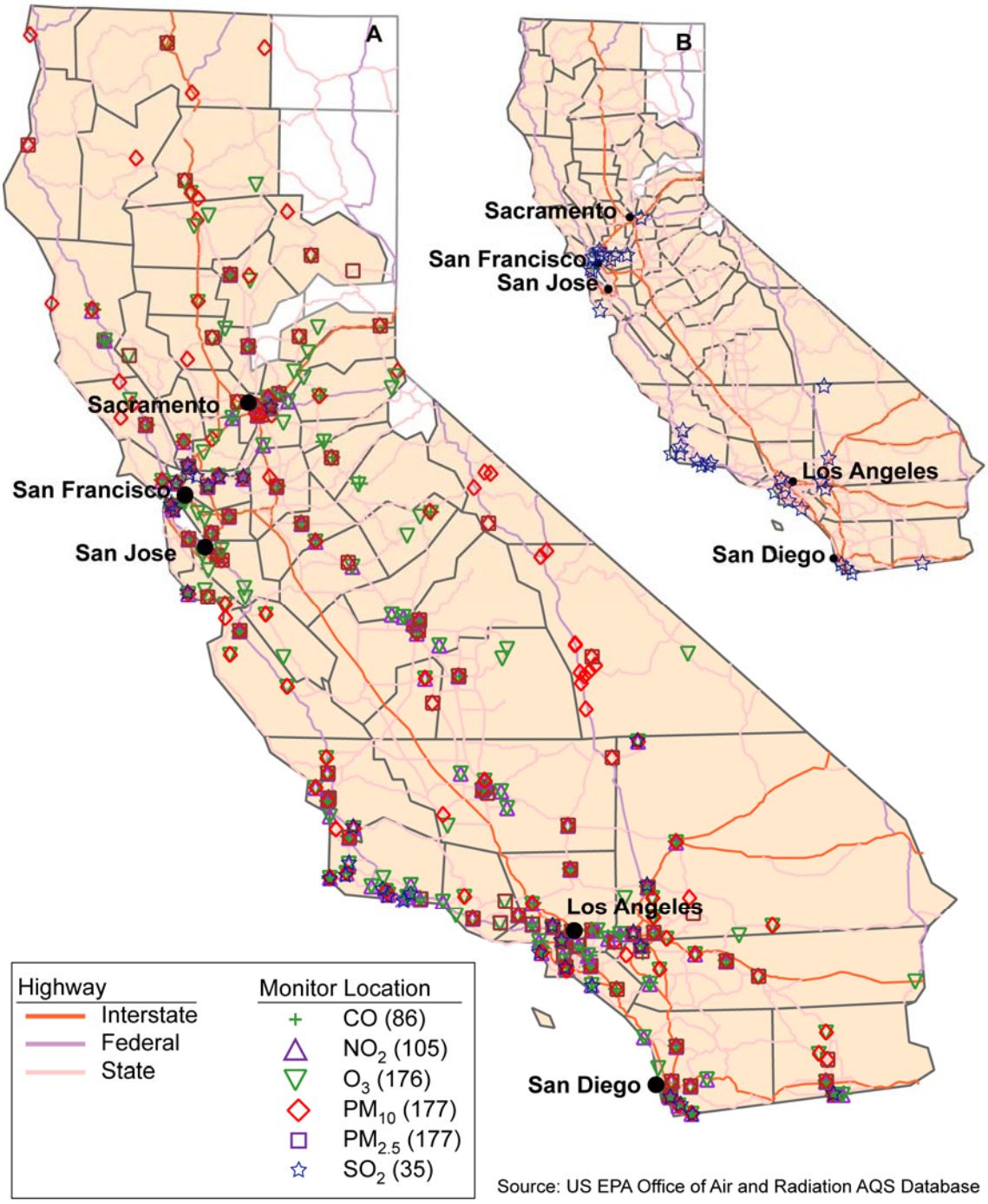


Figure 2-8. Criteria pollutant monitor locations (A) and SO_2 monitor locations (B), California, 2005. Shaded counties have at least one monitor.

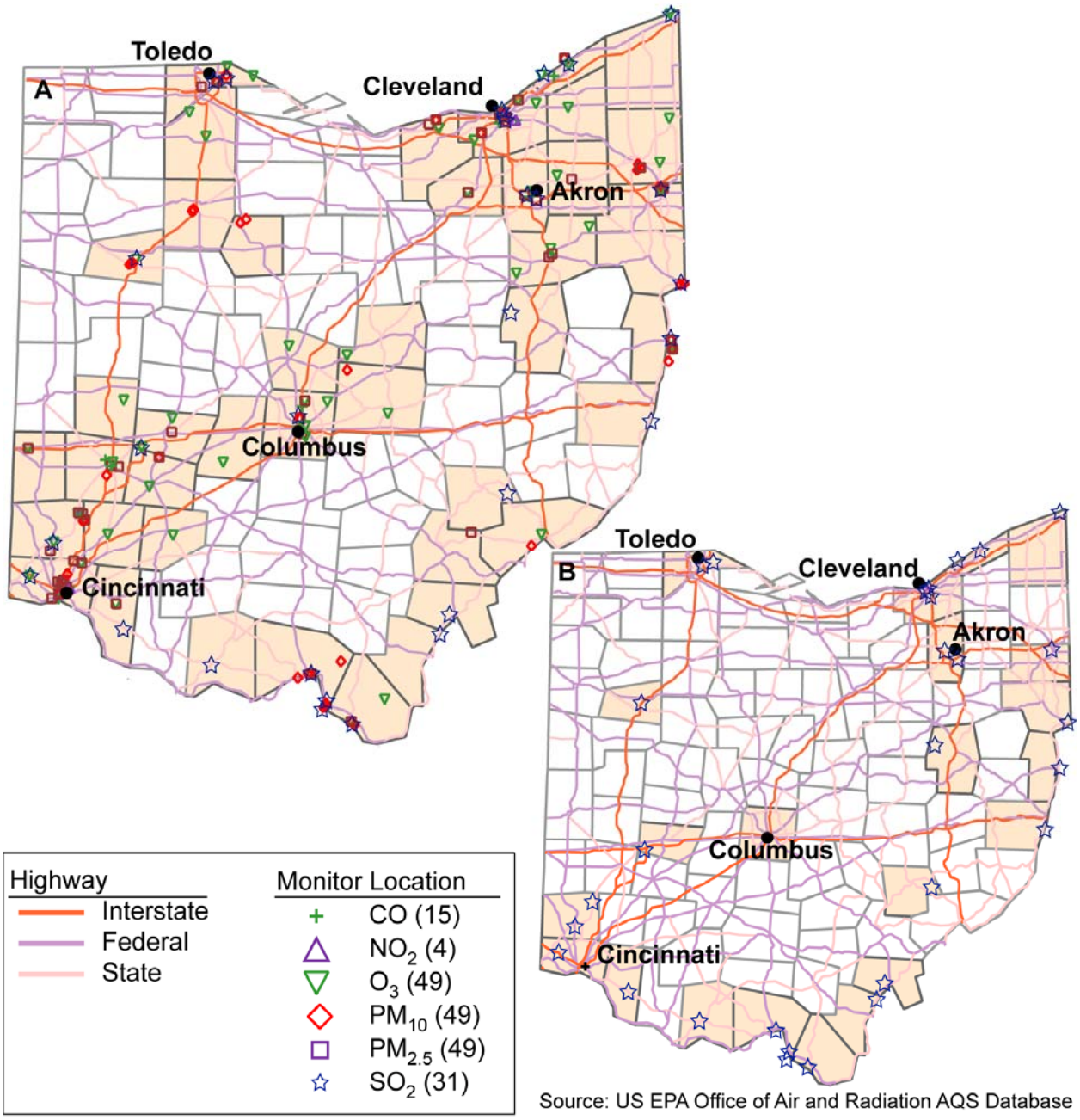


Figure 2-9. Criteria pollutant monitor locations (A) and SO_2 monitor locations (B), Ohio, 2005. Shaded counties have at least one monitor.

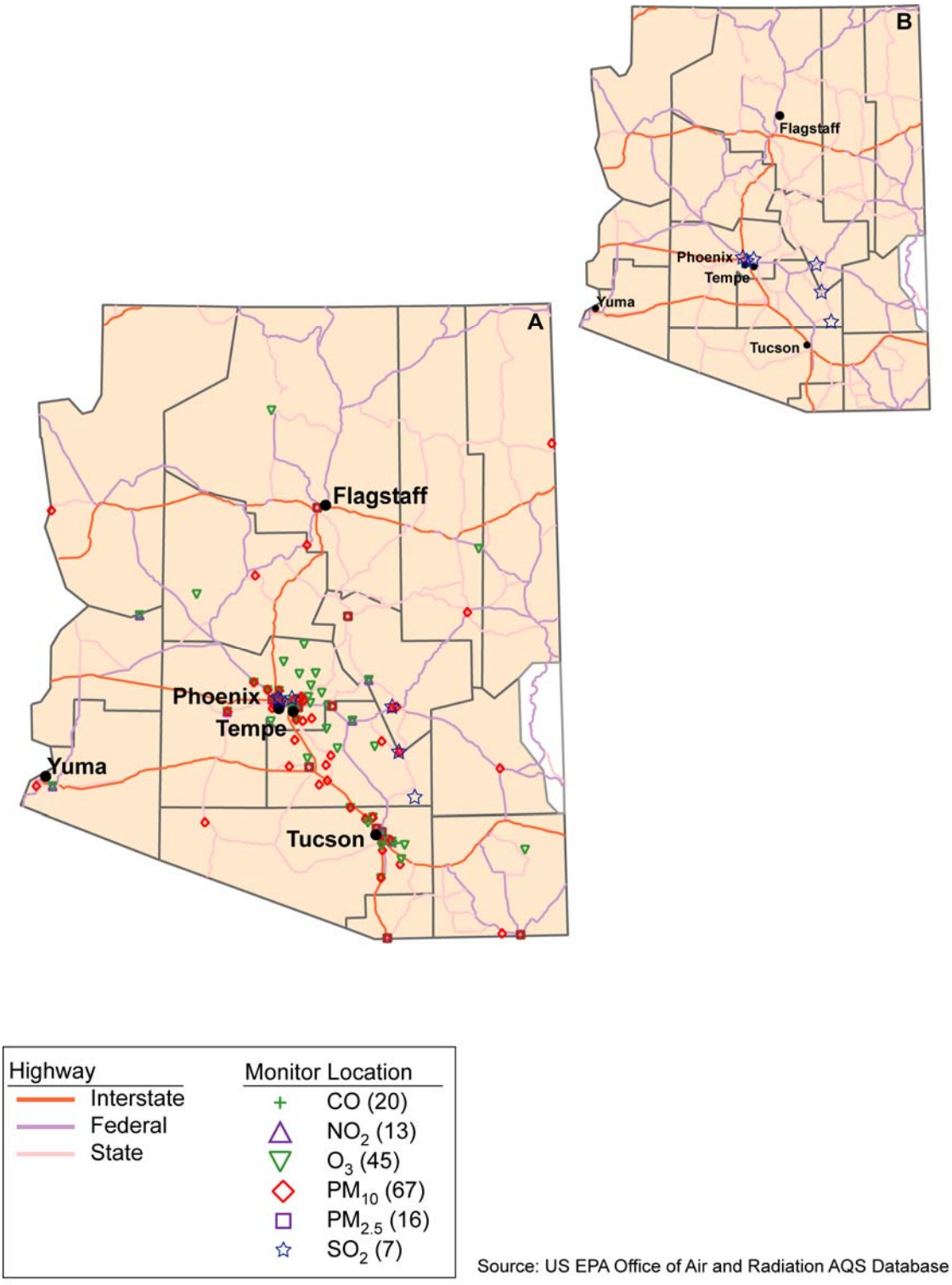
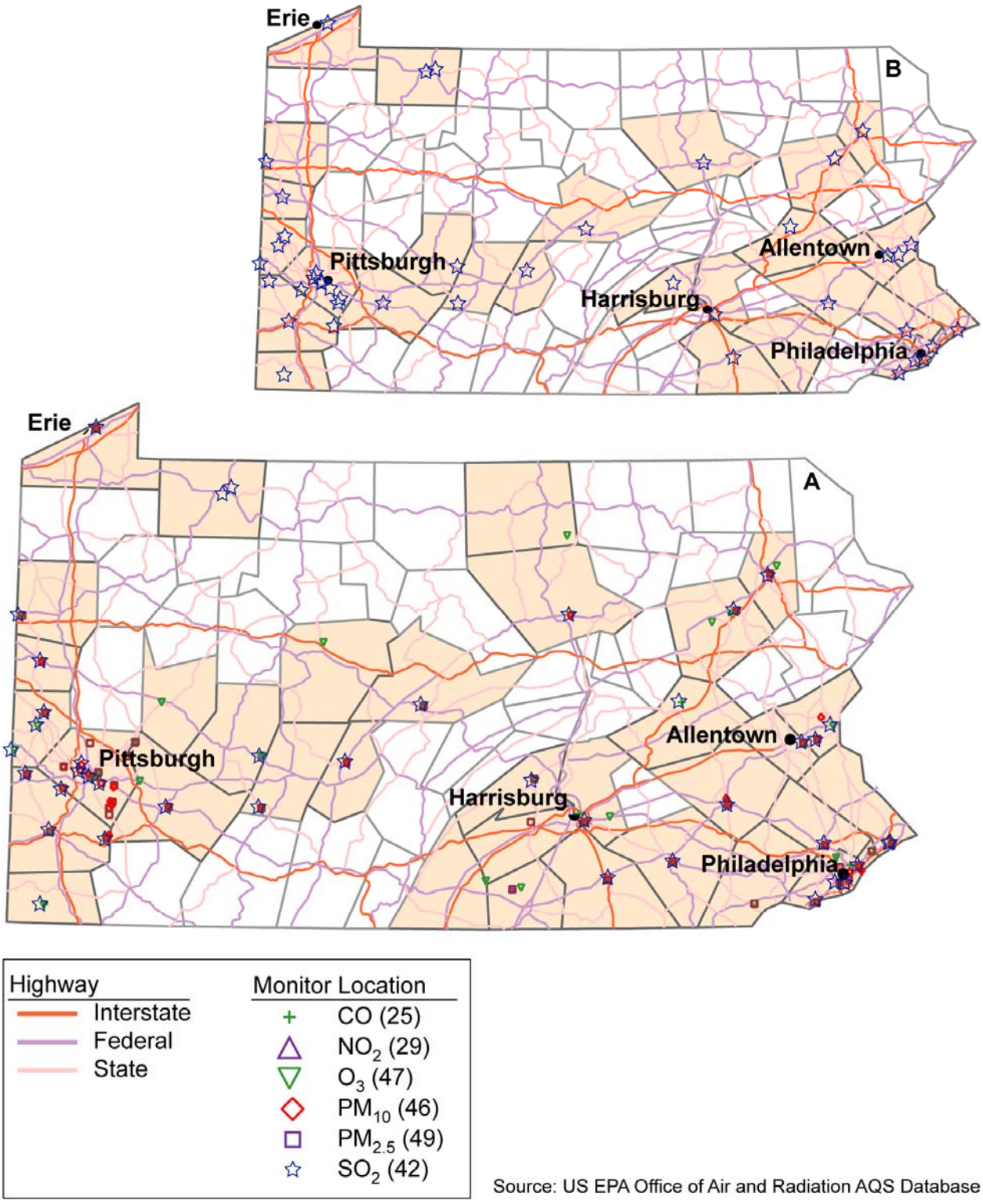


Figure 2-10. Criteria pollutant monitor locations (A) and SO_2 monitor locations (B), Arizona, 2005. Shaded counties have at least one monitor.



Source: US EPA Office of Air and Radiation AQS Database

Figure 2-11. Criteria pollutant monitor locations (A) and SO_2 monitor locations (B), Pennsylvania, 2005. Shaded counties have at least one monitor.

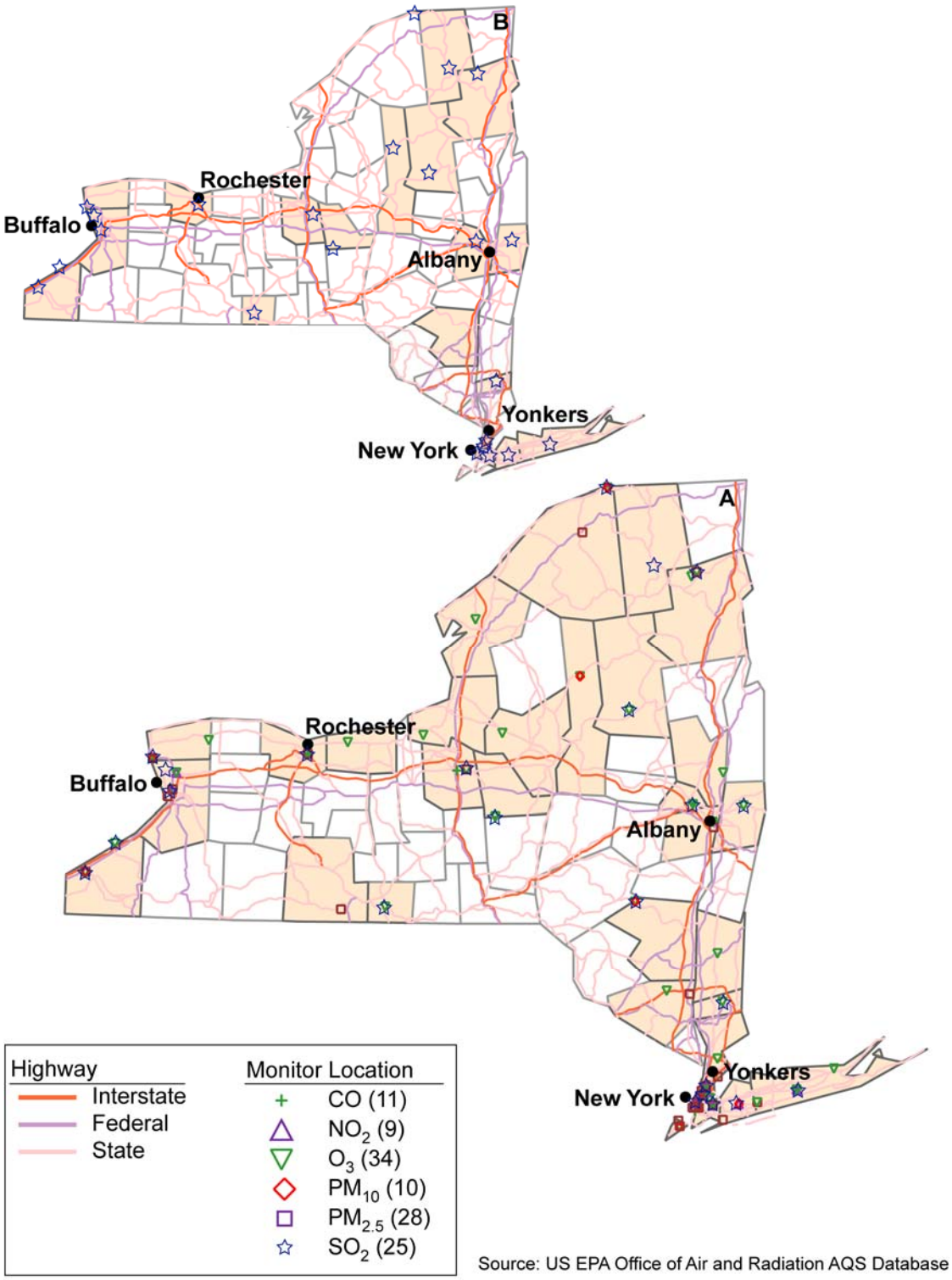


Figure 2-12. Criteria pollutant monitor locations (A) and SO_2 monitor locations (B), New York, 2005. Shaded counties have at least one monitor.

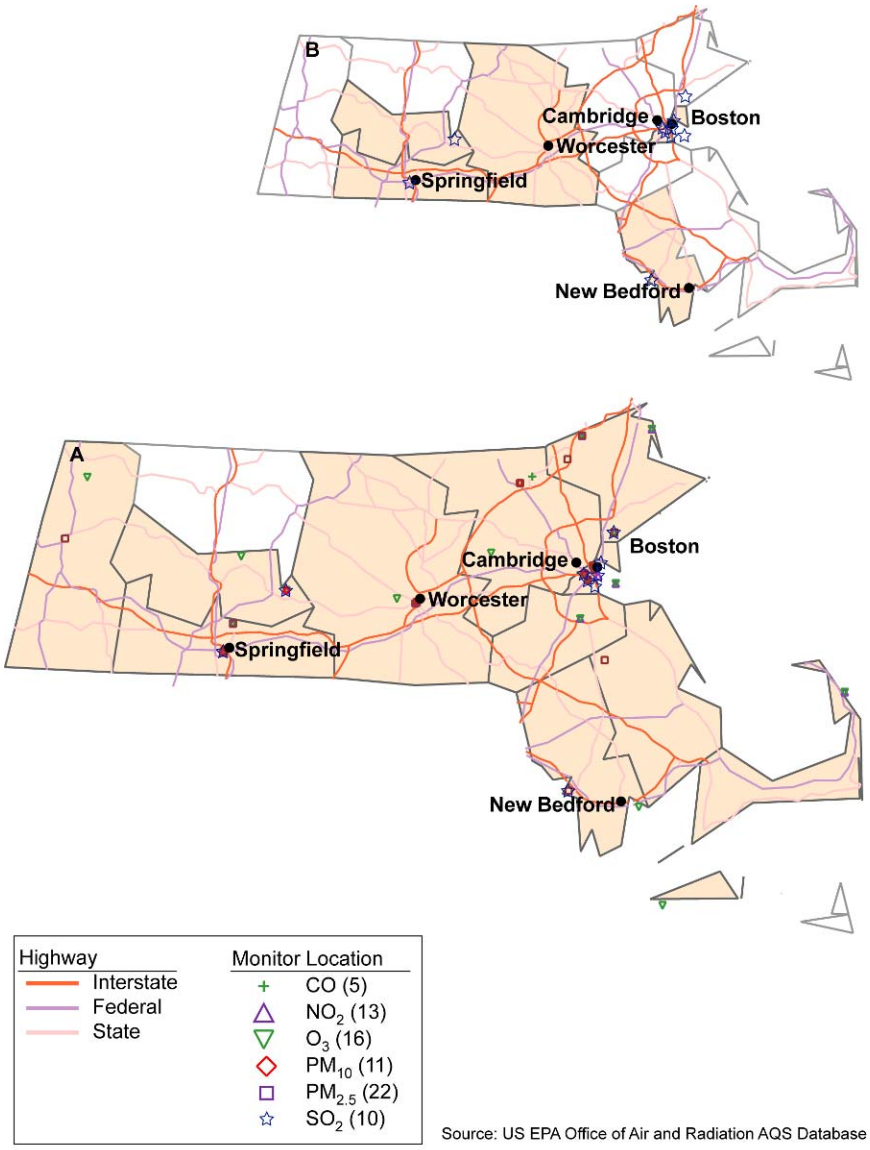


Figure 2-13. Criteria pollutant monitor locations (A) and SO_2 monitor locations (B), Massachusetts, 2005. Shaded counties have at least one monitor.

Table 2-5 lists the totals for all criteria air pollutant monitors (except Pb) in California, as well as the subset of these monitors in San Diego County. At each of the four sites where SO_2 was measured in San Diego county, NO_2, CO, PM_{10}, $PM_{2.5}$, and O_3 were also measured, with the exception of $PM_{2.5}$ at one site (AQS ID 060732007) in Otay Mesa, CA. Table 2-6 lists the totals for all criteria air pollutant monitors (except Pb) in Ohio, as well as the subset of monitors in Cuyahoga County. In Cuyahoga County, PM_{10} and $PM_{2.5}$ were measured at all four sites where SO_2 was also measured in 2005, but O_3 and CO were not measured at any of those four sites; NO_2 was only measured at one site (AQS ID 39050060) near Cleveland's city center and ~0.5 km from the intersection of Interstate Highways 77 and 90.

Table 2-5. Monitor counts for California and San Diego County, 2005.

	SO_2	NO_2	O_3	CO	PM_{10}	$PM_{2.5}$
California (all)	35	105	176	86	177	97
San Diego County	4	9	10	6	7	7

Table 2-6. Monitor counts for Ohio and Cuyahoga County, 2005.

	SO_2	NO_2	O_3	CO	PM_{10}	$PM_{2.5}$
Ohio (all)	31	4	49	15	49	49
Cuyahoga County	4	2	3	4	6	7

2.4.3. Ambient SO_2 Concentrations in Relation to SO_2 Sources

Figures 2-14 through 2-19 show the locations of SO_2 monitors in relation to SO_2 point sources from electricity generation for the Atlanta, Cincinnati, Cleveland, Los Angeles/Riverside, New York City/Philadelphia, and St. Louis MSAs. Information on point sources (i.e., fossil fueled electricity generating units and industrial point sources) for 2002 was obtained from the National Emissions Inventory (NEI) (EPA, 2006). Point sources were mapped for a particular region if they were contained by the MSA or if they were within 30 km of its boundary, and SO_2 monitors were mapped with buffer zones of 1, 5, 10, and 15 km constructed around the monitor locations. The figures show that the SO_2 monitors are placed in relative proximity to the majority of point sources of SO_2 with the exception of Atlanta, where most point sources are found outside the city center. In all cases, at least 1 monitor is in the vicinity of the most populated urban center and at least one is sited for background SO_2 concentrations.

SO_2 data collected from the State and Local Monitoring System (SLAMS) and National Air Monitoring System (NAMS) networks, like those illustrated in Figure 2-2 through Figure 2-7 show that the decline in SO_2 emissions from electric generating utilities has substantially improved air quality. No monitored exceedance of the SO_2 annual ambient air quality standard in the lower 48 States of the U.S. has been recorded between 2000 and 2005, according to the EPA Acid Rain Program (ARP) 2005 Progress Report (EPA, 2006b). EPA's trends data (http://www.epa.gov/airtrends/) reveal that the national composite avg SO_2 annual mean ambient concentration decreased by 48% from 1990 to 2005; the largest single-year reduction was 1994-95, the ARP's first operating year (EPA, 2006b). Figure 2-20 depicts data for SO_2 emissions in the contiguous United States (CONUS) during those years, with state-level totals.

These emissions data trends are consistent with the trends in the observed ambient concentrations from the Clean Air Status and Trends Network (CASTNet). Following implementation of the Phase I controls on ARP sources between 1995 and 2000, significant reductions in SO_2 and ambient SO_4^{2-} concentrations were observed at CASTNet sites throughout the eastern U.S.. The mean annual concentrations of SO_2 and SO_4^{2-} from CASTNet's long-term monitoring sites can be compared using two 3-year periods, 1989–1991 and 2003-2005, shown in Figure 2-21 for SO_2 and Figure 2-22 for SO_4^{2-}.

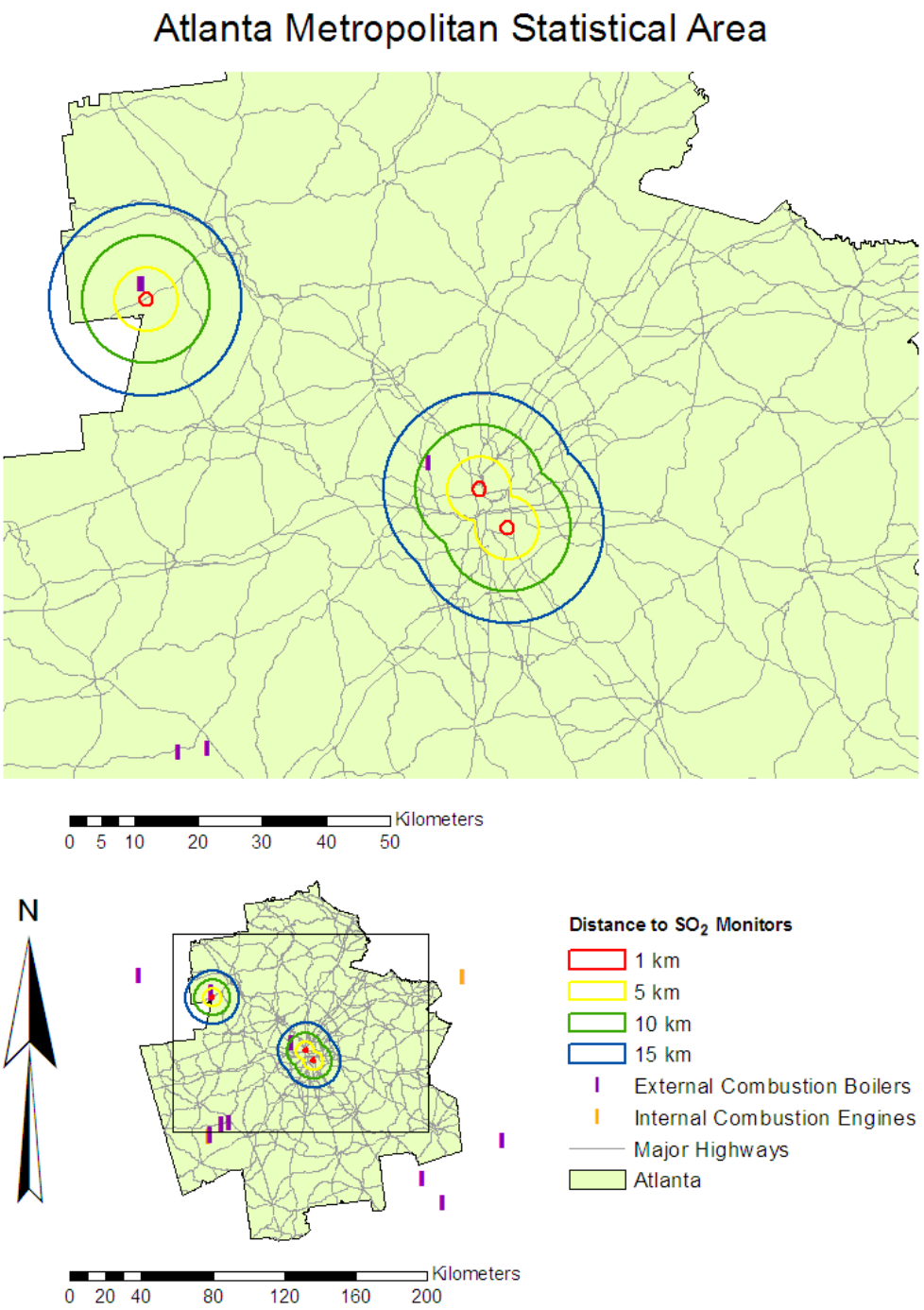


Figure 2-14. Location of SO_2 monitors within a 15 km buffer zone with respect to combustion sources and highways in the Atlanta, GA MSA.

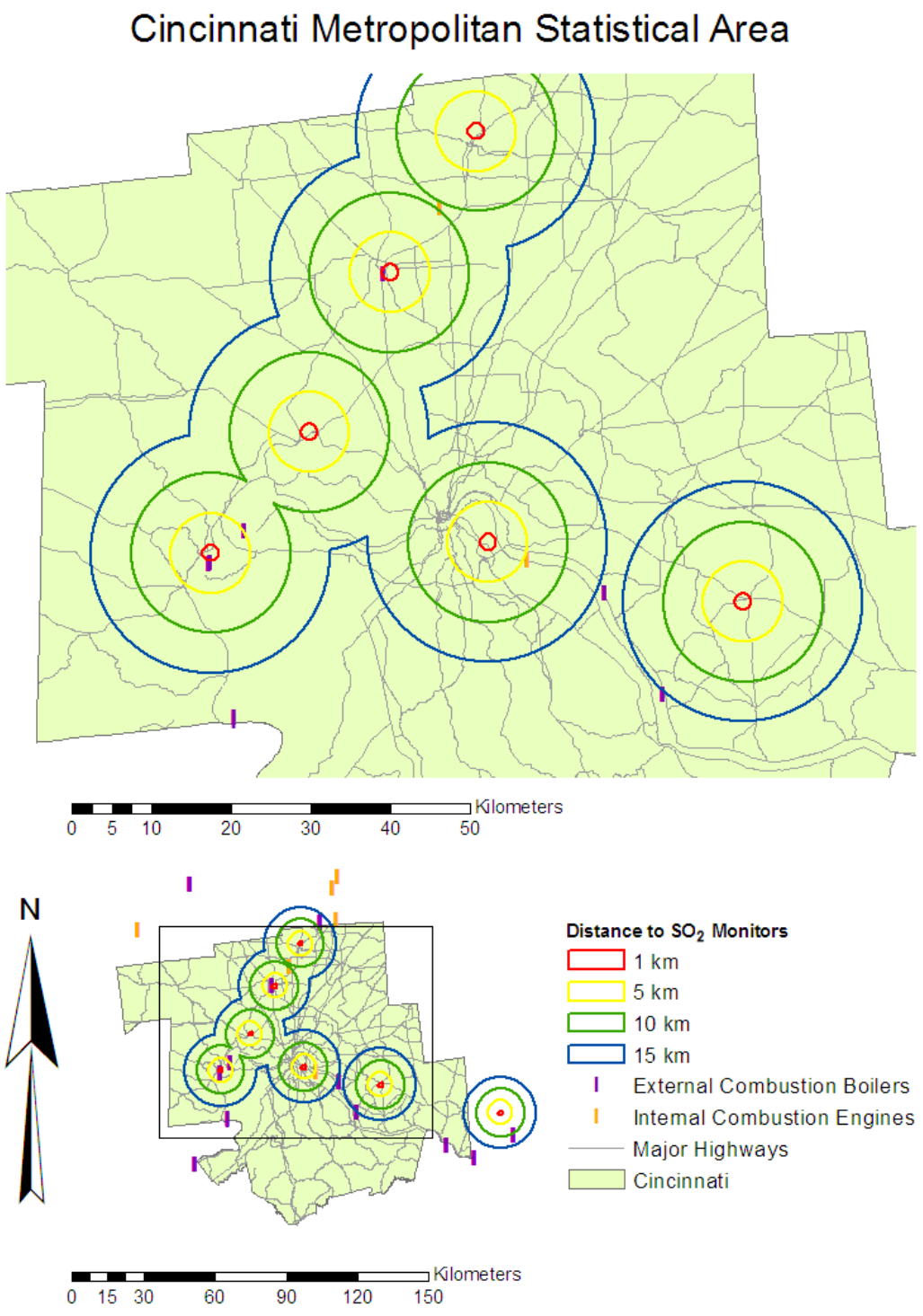


Figure 2-15. Location of SO_2 monitors within a 15 km buffer zone with respect to combustion sources and highways in the Cincinnati, OH MSA.

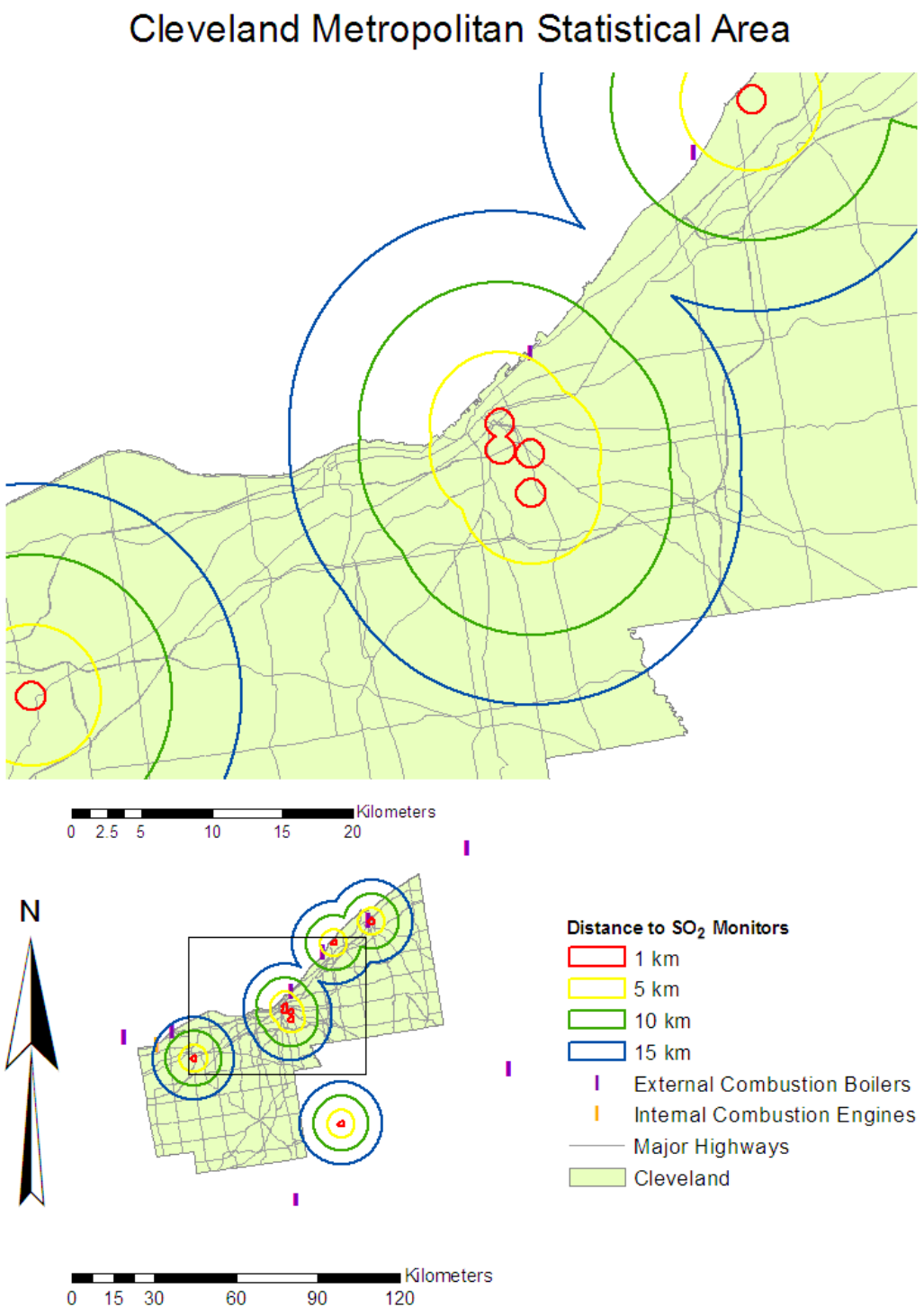


Figure 2-16. Location of SO_2 monitors within a 15 km buffer zone with respect to combustion sources and highways in the Cleveland, OH MSA.

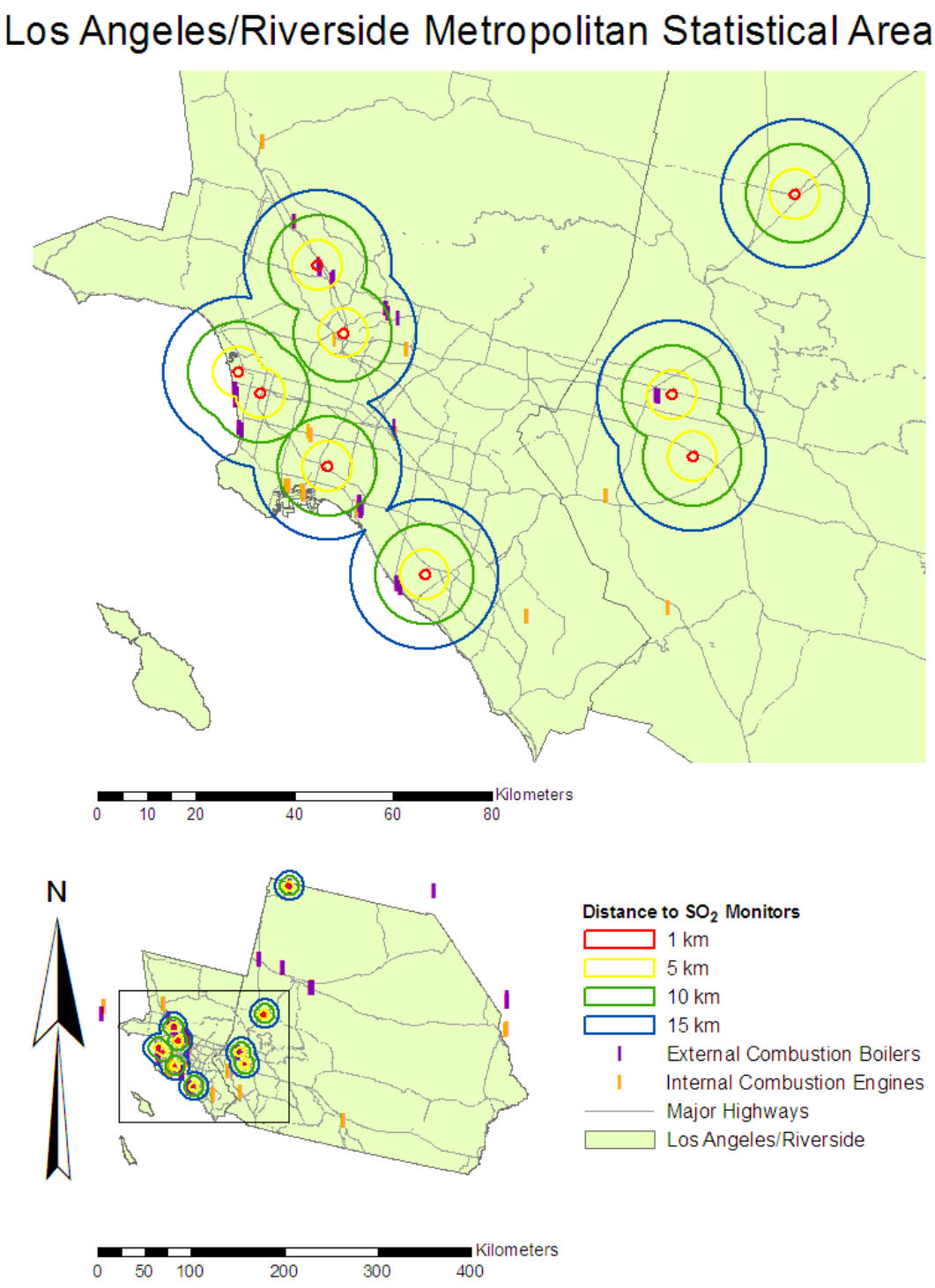


Figure 2-17. Location of SO_2 monitors within a 15 km buffer zone with respect to combustion sources and highways in the Los Angeles/Riverside, CA MSA.

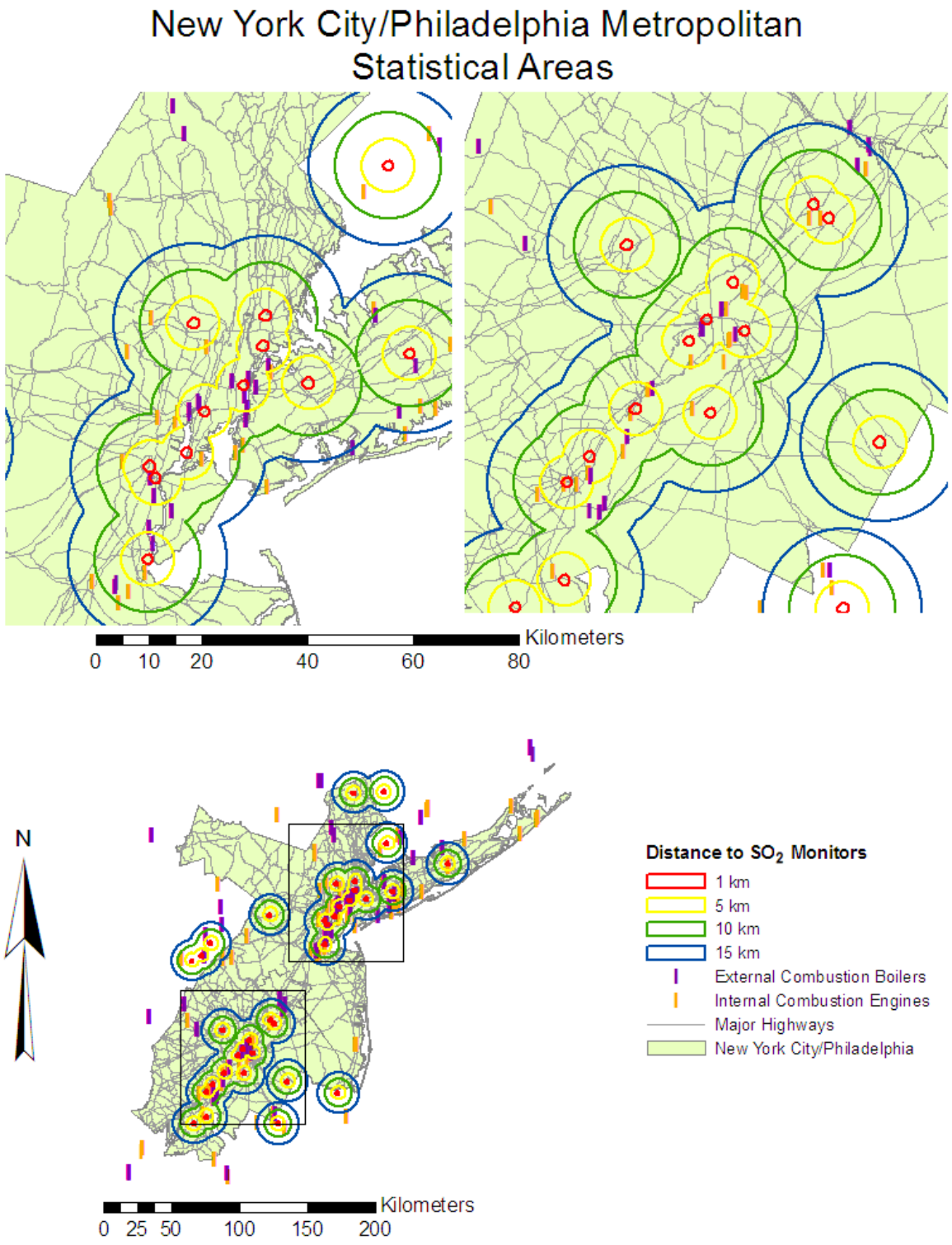


Figure 2-18. Location of SO_2 monitors within a 15 km buffer zone with respect to combustion sources and highways in the New York City, NY/Philadelphia, PA MSA.

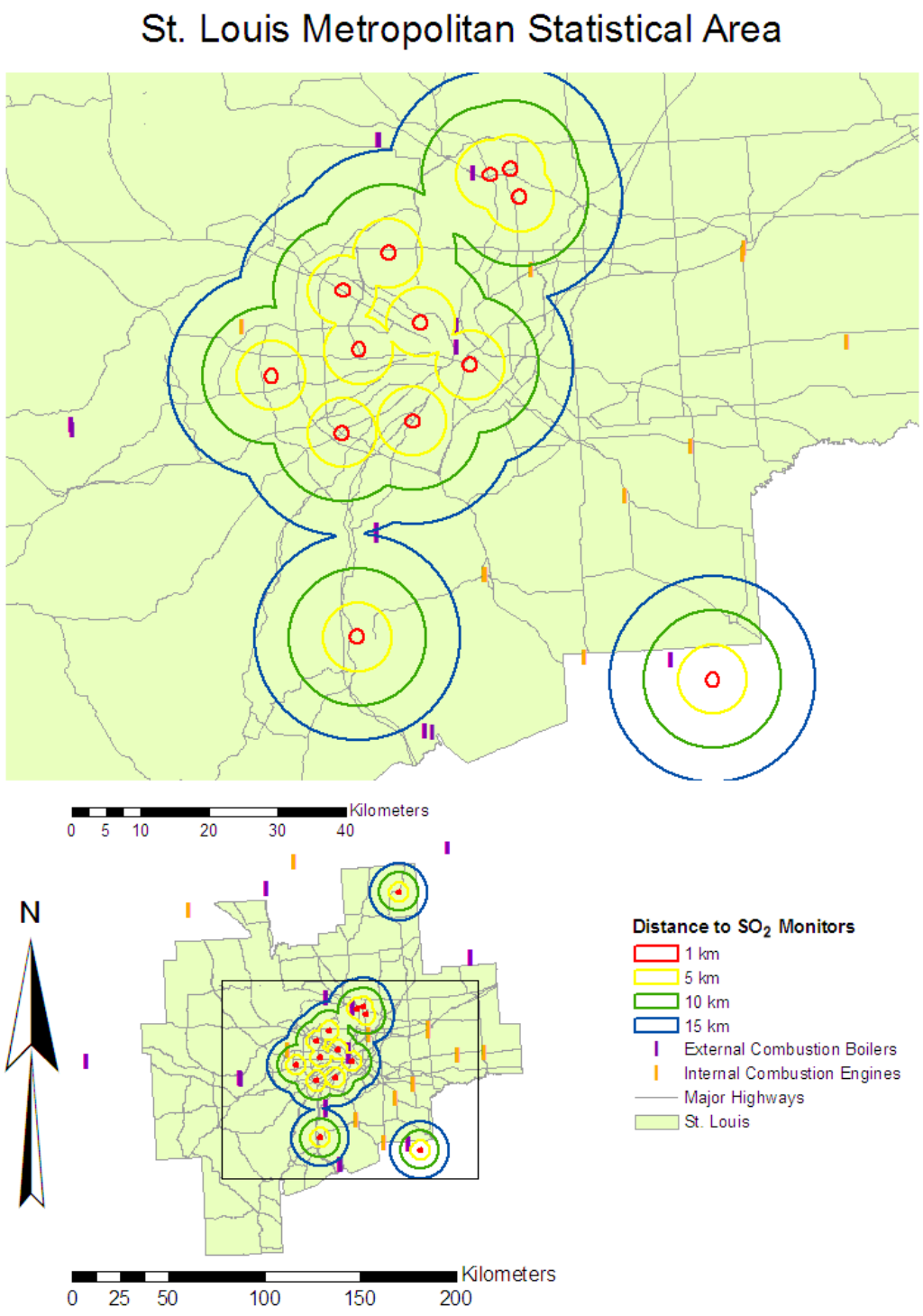
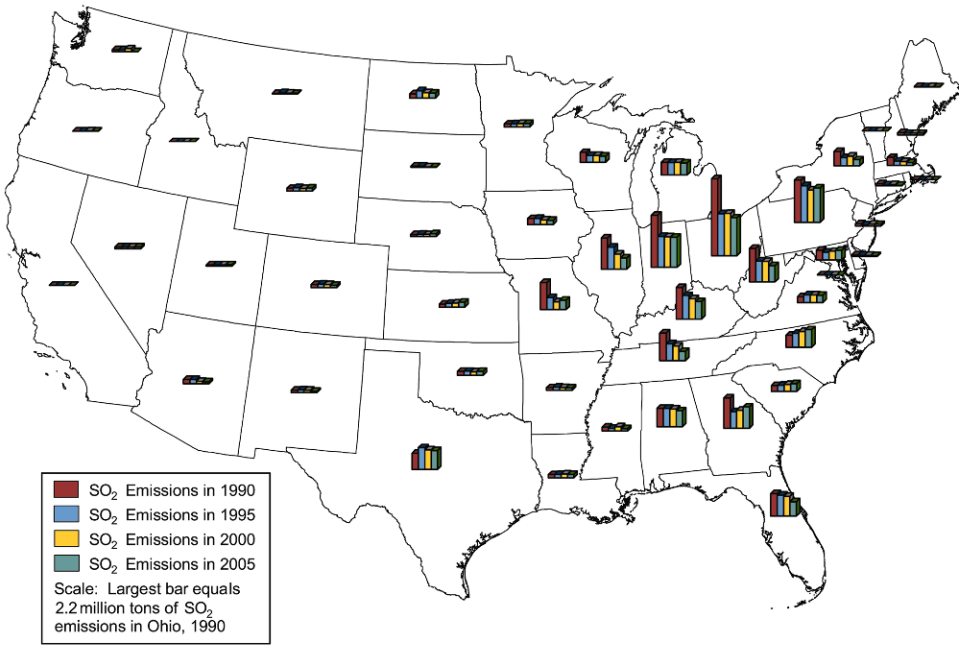
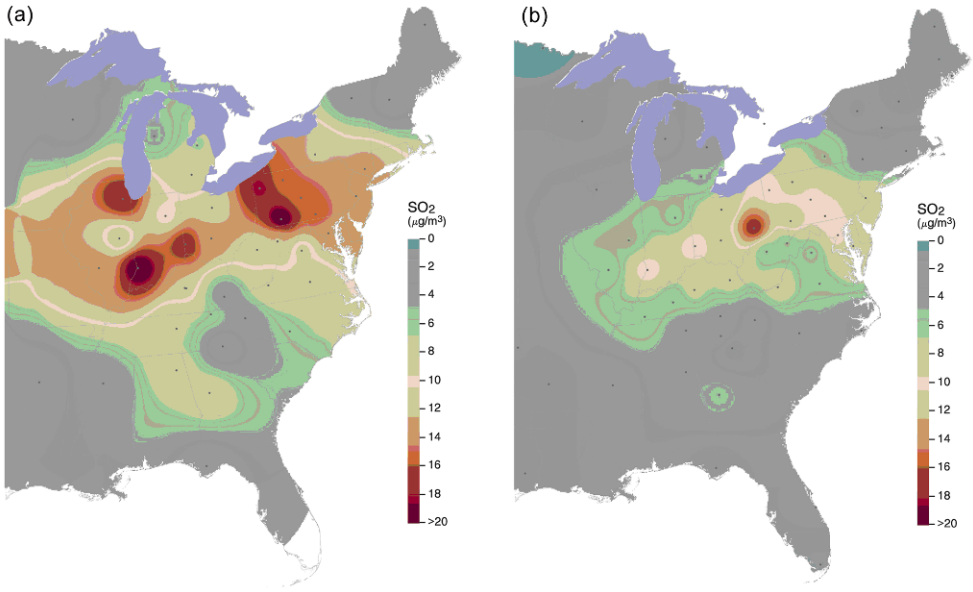


Figure 2-19 Location of SO_2 monitors within a 15 km buffer zone with respect to combustion sources and highways in the St. Louis, MO MSA.



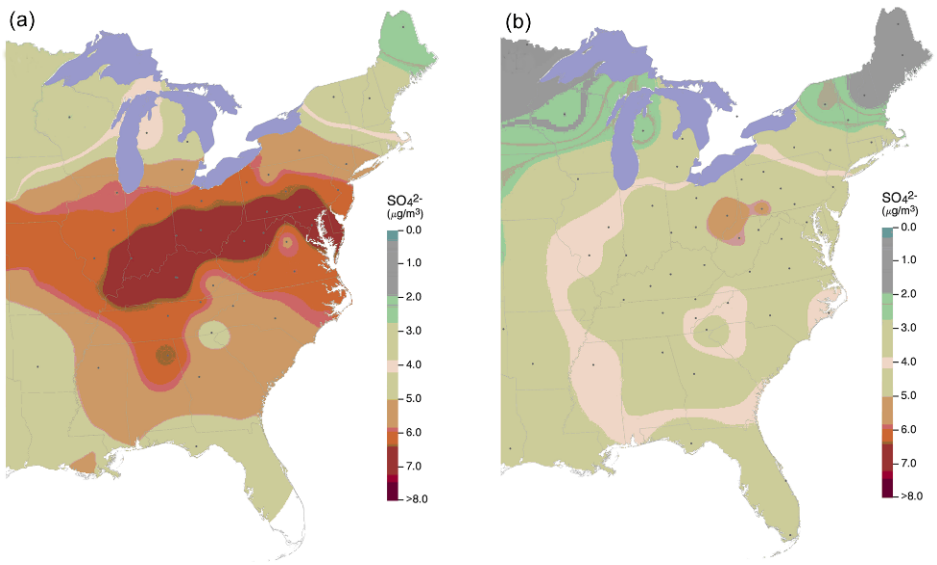
Source: Environmental Protection Agency Clean Air Markets Division http://www.epa.gov/airmarkets/index.html

Figure 2-20. State-level SO_2 emissions, 1990-2005.



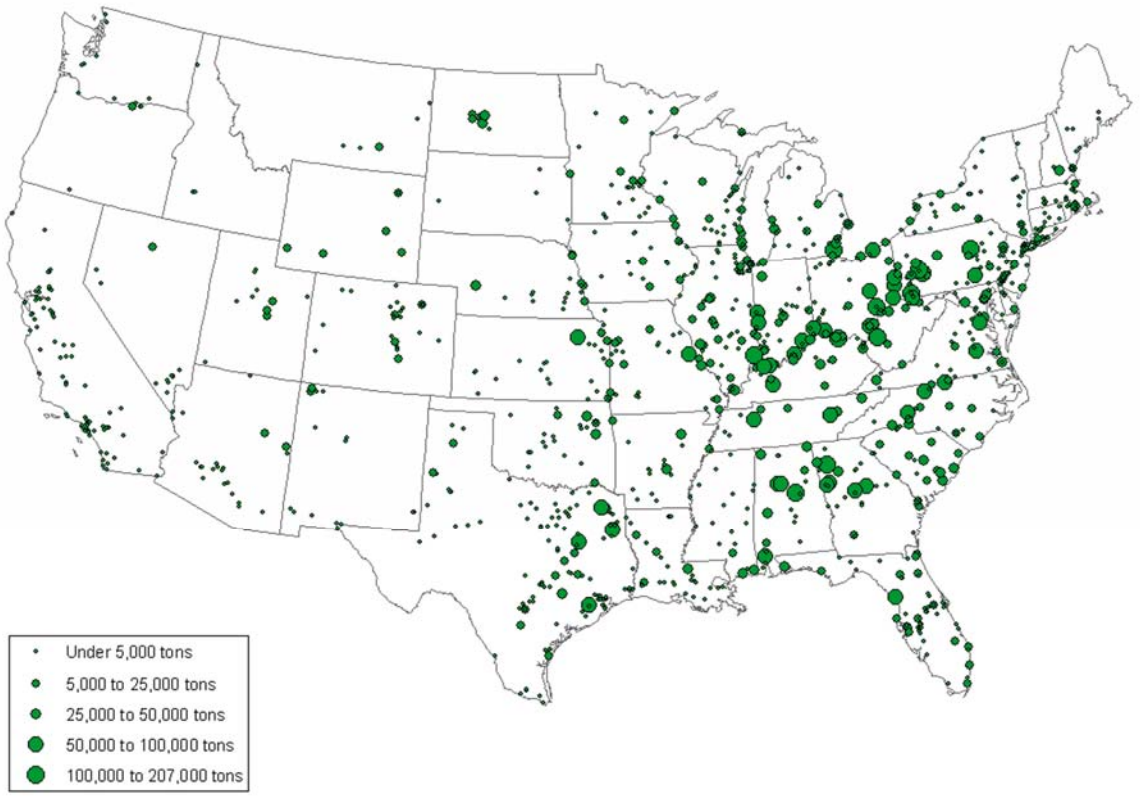
Source: U.S. EPA CASTNet

Figure 2-21. Annual mean ambient SO_2 concentration, 1989 through 1991 (A), and 2003 through 2005 (B).



Source: U.S. EPA CASTNet

Figure 2-22. Annual mean ambient SO_4^{2-} concentration, 1989 through 1991 (A), and 2003 through 2005 (B).



Source: Environmental Protection Agency, Clean Air Markets Division http://www.epa.gov/airmarkets/index.html

Figure 2-23. Annual mean ambient SO_2 emissions for Acid Rain Program cooperating facilities, 2006. Dots represent monitoring sites. Lack of shading for Southern Florida indicates lack of monitoring coverage.

From 1989 through 1991— the years prior to implementation of the ARP Phase I— the highest ambient mean concentrations of SO_2 and SO_4^{2-} were observed in western Pennsylvania and along the Ohio River Valley: > 20 µg/m^3 (~8 ppb) SO_2 and > 15 µg/m^3 SO_4^{2-}. These reductions are shown in Figure 2-21 and Figure 2-22, respectively. In the years since the ARP controls were enacted, both the magnitude of SO_4^{2-} concentrations and their areal extent have been significantly reduced, with the largest decreases again along the Ohio River Valley.

Figure 2-23 depicts the magnitude and spatial distribution of SO_2 emissions in 2006 from sources in the ARP for the CONUS. This depiction clearly shows the continuing predominance of SO_2 sources in the U.S. east of the Mississippi River with even stronger magnitude in the central Ohio River Valley, as evident in the smoothed concentration plots in Figure 2-21. As shown in Table 2-7, regional distributions of SO_2 and SO_4^{2-} concentrations averaged for 2003–2005 reflect this geospatial emissions source difference as well.

2.5. Environmental Concentrations of SO_X

2.5.1. Spatial and Temporal Variability of Ambient SO_2 Concentrations

SO_2 concentrations have been falling throughout all regions of the CONUS, as demonstrated by the CASTNet data reviewed above. In and around most individual CMSAs, the trends are also toward lower SO_2 levels. Table 2-7 shows that many annual and 1-h mean concentrations for the years 2003 through 2005 were consistently at or below the operating LOD of ~3 ppb for the standard sensitivity UV fluorescence SO_2 monitors deployed in the regulatory networks. Table 2-8 shows that the 1-h avg, 24-h avg, and aggregate mean value for the years 2003-2005 for inside and outside (all CMSAs) were operating just above the limit of detection (LOD) of ~ 3 ppb.

Table 2-7. Mean ambient concentrations of SO_2 and SO_4^{2-} in different regions of the U.S. averaged over 2003-2005.

Region	Concentration	
	SO_2 (ppb)	SO_4^{2-} (µg/m^3)
Mid-Atlantic	3.3	4.5
Midwest	2.3	3.8
Northeast	1.2	2.5
Southeast	1.3	4.1

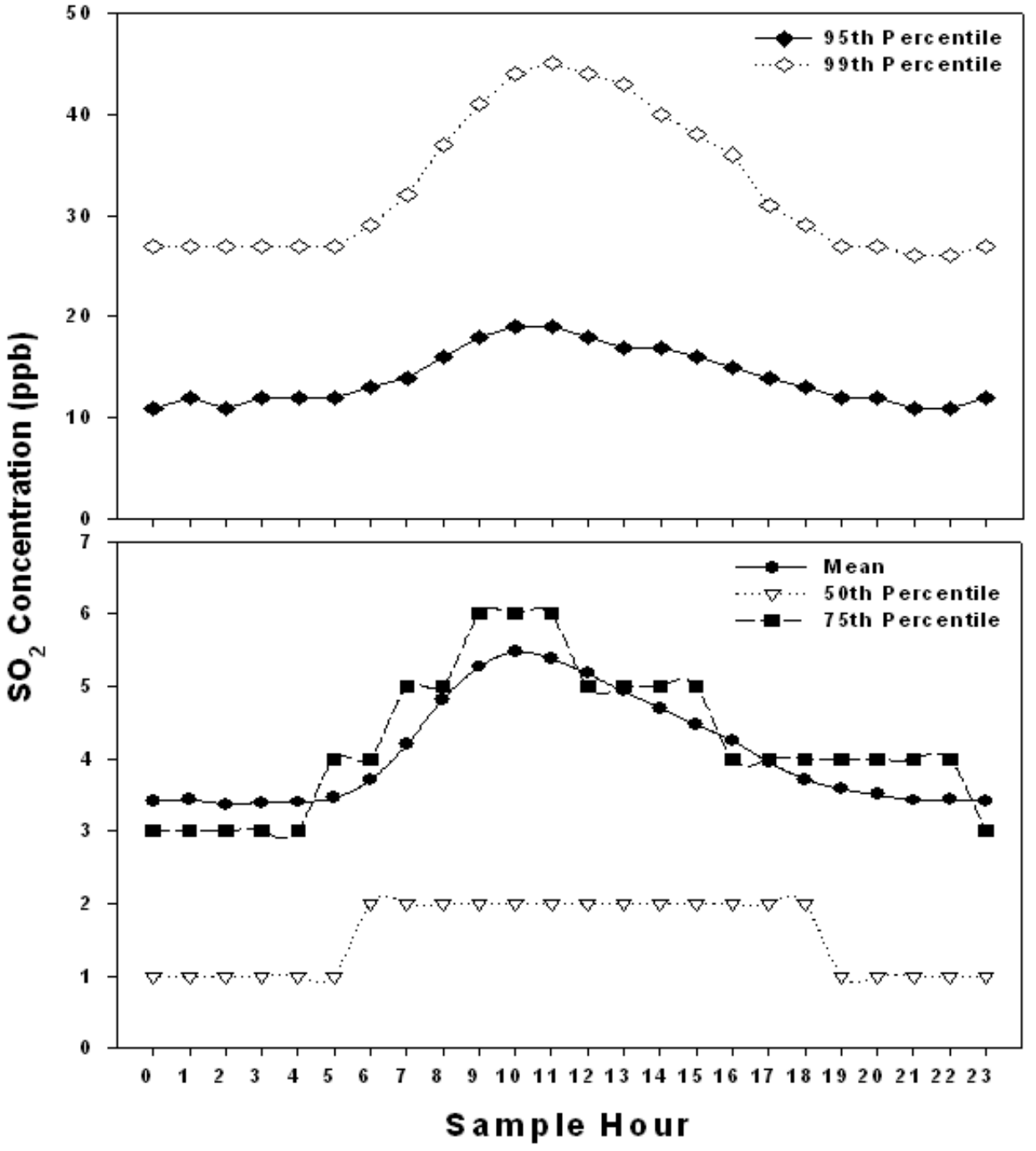
Table 2-8. Concentration distributions of SO_2 inside and outside CMSAs from 2003-2005. Values shown are in ppb.

Averaging Time Monitor Locations	Number of Samples	Mean	Percentiles											Max
			1	5	10	25	30	50	70	75	90	95	99	
1-H MAX CONCENTRATION														
Inside CMSAs	332405	13	1	1	1	3	4	7	13	16	30	45	92	714
Outside CMSAs	53417	13	1	1	1	1	2	5	10	13	31	51	116	636
1-H AVG CONCENTRATION														
Inside CMSAs	7408145	4	1	1	1	1	1	2	4	5	10	15	34	714
Outside CMSAs	1197179	4	1	1	1	1	1	2	3	3	7	13	36	636
24-H AVG CONCENTRATION														
Inside CMSAs	327918	4	1	1	1	1	2	3	5	6	10	13	23	148
Outside CMSAs	52871	4	1	1	1	1	1	2	3	4	8	12	25	123
ANNUAL AVG CONCENTRATION														
Inside CMSAs	898	4	1	1	1	1	2	4	5	6	8	10	12	15
Outside CMSAs	143	4	1	1	1	1	2	3	4	5	8	9	13	14
AGGREGATE 3-YR AVG CONCENTRATION, 2003-2005														
Inside CMSAs	283	4	1	1	1	2	3	3	5	5	8	10	12	14
Outside CMSAs	42	4	1	1	1	2	2	3	4	5	8	9	13	13

Figure 2-24 shows the composite diel variation in hourly SO_2 concentrations for the mean and selected percentile values from all monitors reporting SO_2 data into AQS. The AQS contains measurements of air pollutant concentrations in the 50 states plus the District of Columbia, Puerto Rico, and the Virgin Islands for the six criteria air pollutants and hazardous air pollutants.

Figure 2-24 shows hourly mean concentrations and the 50th, 75th, 95th and 99th percentile values from all monitors reporting data into AQS. All of these metrics show clear daytime maxima and nighttime minima. The magnitude of the day-night difference increases with increasing concentrations. Note: concentrations given in AQS are rounded to the nearest ppb, and thereby flatten the variability at lower concentrations, as shown in the lower panel of Figure 2-24. The day-to-night variability likely reflects the entrainment of SO_2 emitted by elevated point sources into the mixed layer that is growing by convection during the morning and early afternoon. The effect of higher concentration values on the means is shown by the 1 to 3 ppb difference between mean and 50th percentile values during the day.

The strong west-to-east increasing gradient in SO_2 emissions described above is well-replicated in the observed concentrations in the AQS data set. For example, Table 2-9 shows the mean annual concentrations from 2003–2005 for the 12 CMSAs with four or more SO_2 regulatory monitors. Values ranged from a reported low of ~1 ppb in Riverside, CA and San Francisco, CA to a high of ~12 ppb in Pittsburgh, PA and 14 pbb in Steubenville, OH, in the highest SO_2 source region.



Source: EPA AQS

Figure 2-24. Diel variation in SO_2 concentration across all monitoring sites reporting into AQS for 2005. The upper panel shows 95th, and 99th percentile values and the lower panel shows mean, 50th, and 75th percentile values.

Table 2-9. Range of mean annual SO_2 concentrations and Pearson correlation coefficients in urban areas having at least four regulatory monitors, 2003–2005.

CMSA (# Monitors)	Mean SO_2 Concentration (ppb)	Pearson Correlation Coefficient
Philadelphia, PA (10)	3.6 – 5.9	0.37 – 0.84
Washington, DC (5)	3.2 – 6.5	0.30 – 0.68
Jacksonville, FL (5)	1.7 – 3.4	−0.03 – 0.51
Tampa, FL (8)	2.0 – 4.6	−0.02 – 0.18
Pittsburgh, PA (10)	6.8 – 12	0.07 – 0.77
Steubenville, OH (13)	8.6 – 14	0.11 – 0.88
Chicago, IL (9)	2.4 – 6.7	0.04 – 0.45
Salt Lake City, UT (5)	2.2 – 4.1	0.01 – 0.25
Phoenix, AZ (4)	1.6 – 2.8	−0.01 – 0.48
San Francisco, CA (7)	1.4 – 2.8	−0.03 – 0.60
Riverside, CA (4)	1.3 – 3.2	−0.06 – 0.15
Los Angeles, CA (5)	1.4 – 4.9	−0.16 – 0.31

The Pearson correlation coefficients (r) for concentration data from multiple monitors taken as pairs in these CMSAs were generally very low for all cities, especially at the lower end of the observed concentration range. Some negative correlation coefficients were observed on the West Coast and Florida (see Table 2-9). This reflects strong heterogeneity in SO_2 ambient concentrations within a given CMSA and therefore indicates possibly different exposures of spatially distinct subgroups in these CMSAs. At higher concentrations, the r values were also higher. In some CMSAs, this heterogeneity may result from meteorological effects, whereby a generally well-mixed subsiding air mass containing one or more SO_2 plumes with relatively high concentration would be more uniformly spread than faster-moving plumes with lower concentrations. However, instrument error may also play a role because the highest r values, i.e., those >0.7, correspond to the highest SO_2 concentrations, i.e., >6 and > 10 ppb. Since the lowest SO_2 concentrations are at or below the operating LOD and demonstrate the lowest correlation across monitors that share at least some air mass characteristics most of the year, the unbiased instrument error in this range may be confounding interpretation of any possible correlation. This could be because the same actual ambient concentration would be reported differently by different monitors (with different error profiles) in the CMSA for this lowest concentration range.

To improve characterization of the extent and spatiotemporal variance of SO_2 concentrations within each of the CMSAs having four or more SO_2 monitors, the means, minima, and maxima were computed from daily mean data across all available monitors for each month for the years 2003 through 2005. Because many of these CMSAs with SO_2 monitors also reported SO_4^{2-}, it is possible to compute the degree of correlation between SO_2, the emitted species, and SO_4^{2-}, the most prominent oxidized product from SO_2. Although SO_4^{2-} values are averaged over all available data at each site, they are generally available at their monitoring sites on a schedule of only 1 in 3 days or 1 in 6 days. Furthermore, SO_2 and SO_4^{2-} monitors are not all co-located throughout the CMSAs. For each of the five example CMSAs in Figure 2-25 through Figure 2-29, monthly aggregated values are depicted for: (a) the monthly mean, minimum, and maximum SO_2 concentrations; (b) the monthly mean, minimum and maximum SO_4^{2-} concentrations; and (c) a scatterplot of SO_2 versus SO_4^{2-} concentrations.

In Steubenville, OH (Figure 2-25), the area of highest SO_2 concentrations of all 12 CMSAs with more than four monitors, all monthly mean SO_2 concentrations were substantially < 30 ppb, although max daily means in some months were often > 60 ppb, or even > 90 ppb. SO_4^{2-} data at Steubenville were insufficient to make meaningful comparisons, although the 12 months of available SO_4^{2-} data suggest no correlation with SO_2.

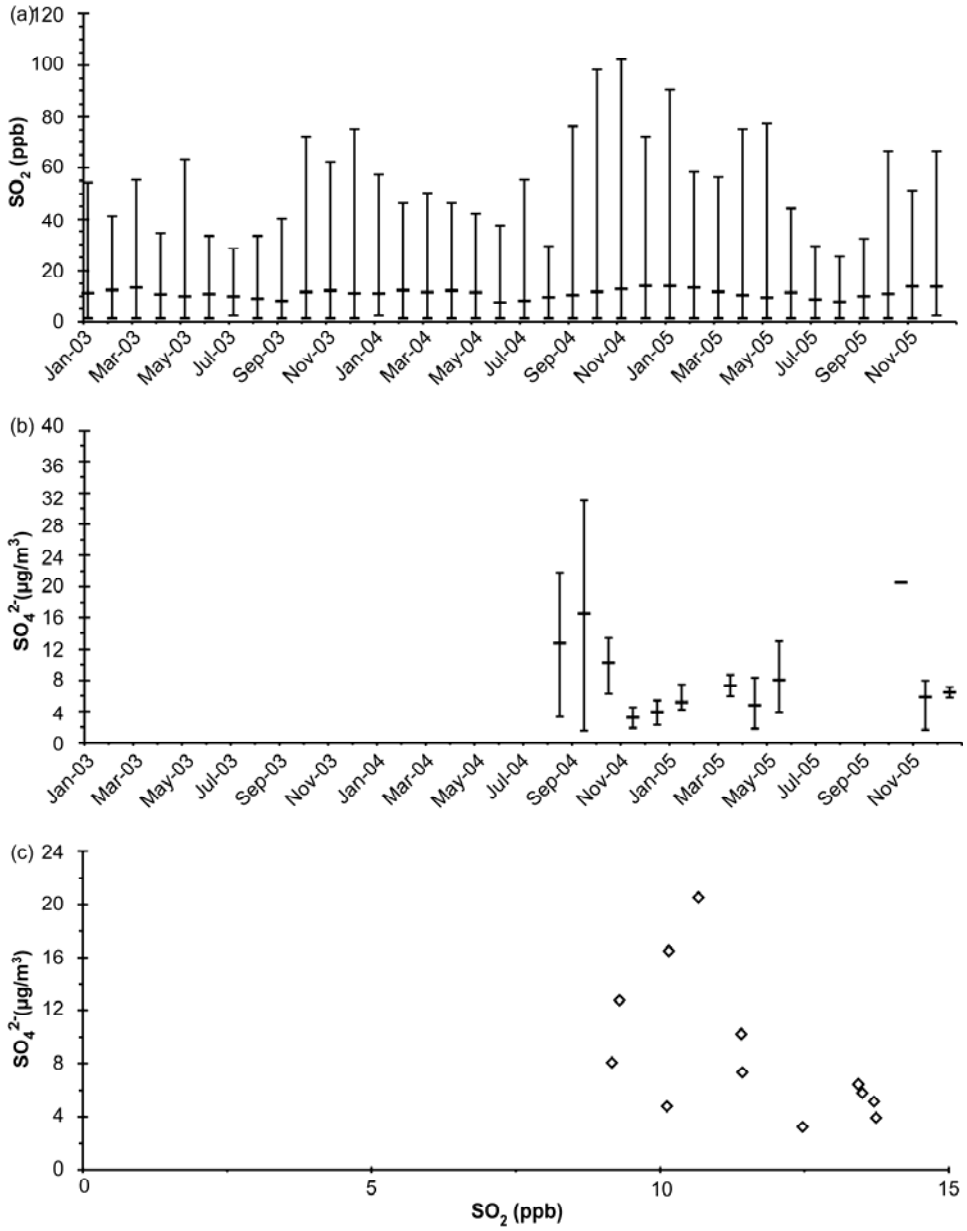


Figure 2-25. Steubenville, OH, 2003–2005. (a) Monthly mean, minimum, and maximum SO_2 concentrations. (b) Monthly mean, minimum, and maximum SO_4^{2-} concentrations. (c) Monthly mean SO_4^{2-} concentrations as a function of SO_2 concentrations.

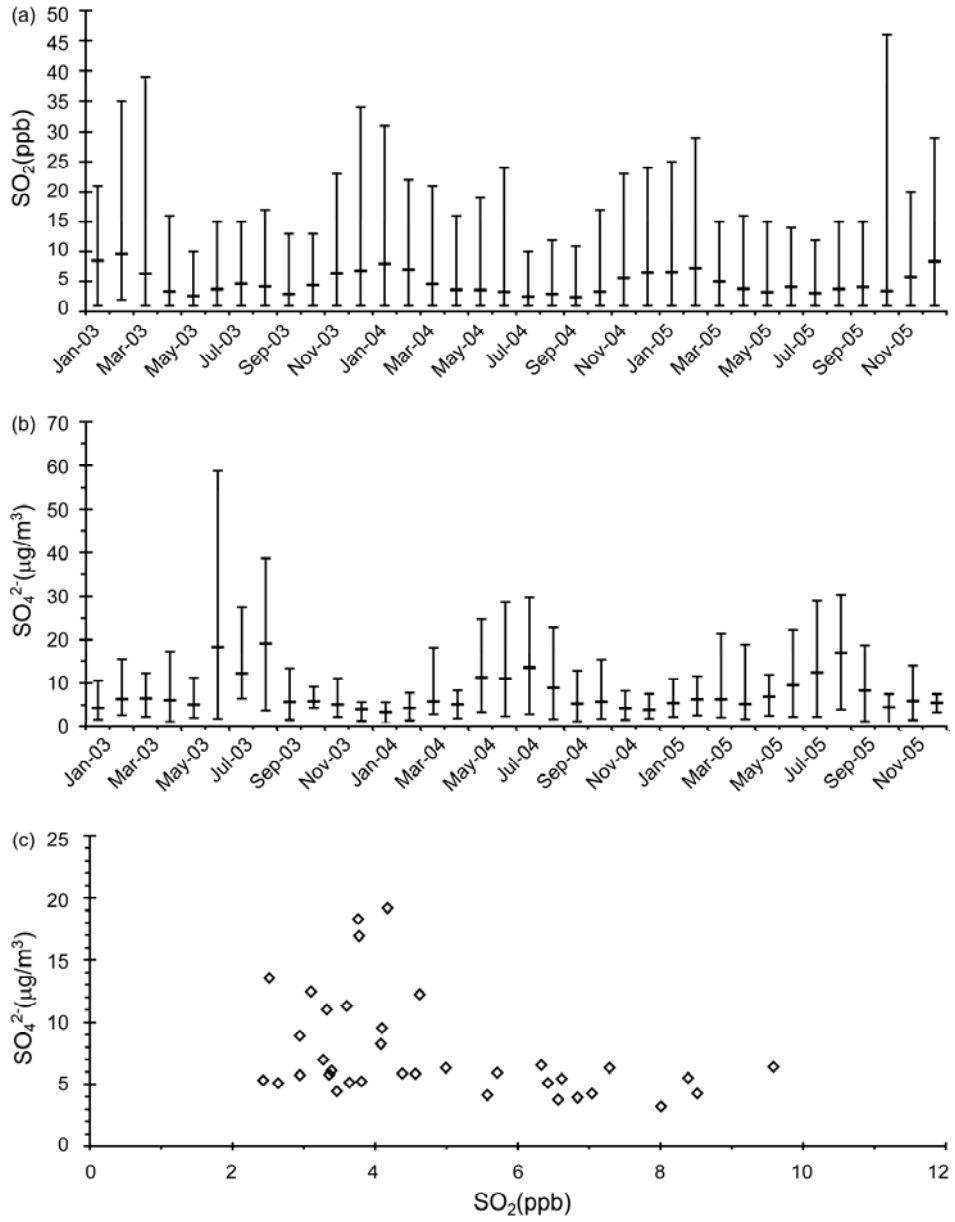


Figure 2-26. Philadelphia, 2003–2005. (a) Monthly mean, minimum, and maximum SO_2 concentrations. (b) Monthly mean, minimum, and maximum SO_4^{2-} concentrations. (c) Monthly mean SO_4^{2-} concentrations as a function of SO_2 concentrations.

SO_2 and SO_4^{2-} trends differ substantially in Philadelphia, PA (Figure 2-26) from those in Steubenville, OH. SO_2 in Philadelphia, PA (Figure 2-26). SO_2 is present at roughly one-half the monthly mean concentrations in Steubenville, OH, and demonstrates a strong seasonality with SO_2 concentrations peaking in winter. By contrast, SO_4^{2-} concentrations in Philadelphia (Figure 2-26) peak in the three summer months, with pronounced wintertime minima. This seasonal anticorrelation still contains considerable monthly scatter.

Los Angeles, CA (Figure 2-27), presents a special case since its size, power requirements, and role as a port city place a larger number of SO_2 emitters in or near the city than would otherwise be expected on the West Coast. Concentrations of SO_2 demonstrate weak seasonality in these 3 years, with

summertime means of ~3 to 4 ppb, and maxima generally higher than wintertime ones, although the highest means and maxima occur during the winter of 2004–2005. SO_4^{2-} at Los Angeles shows stronger seasonality, most likely because the longer summer days of sunny weather allow for additional oxidation of SO_2 to SO_4^{2-} than could happen in winter. Weak seasonal effects in SO_2 likely explain the complete lack of correlation between SO_2 and SO_4^{2-} here.

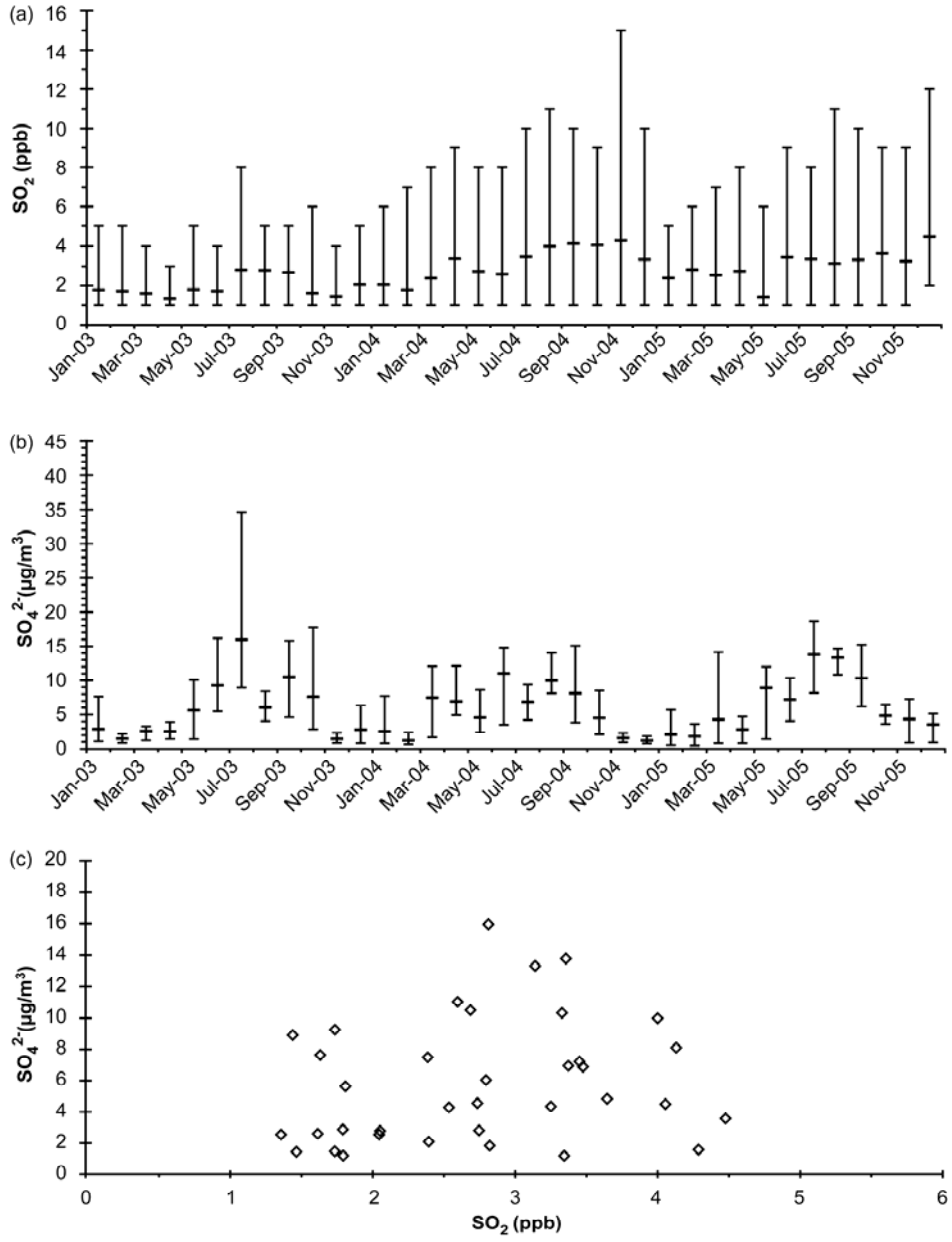


Figure 2-27. Los Angeles, 2003–2005. (a) Monthly mean, minimum, and maximum SO_2 concentrations. (b) Monthly mean, minimum, and maximum SO_4^{2-} concentrations. (c) Monthly mean SO_4^{2-} concentrations as a function of SO_2 concentrations.

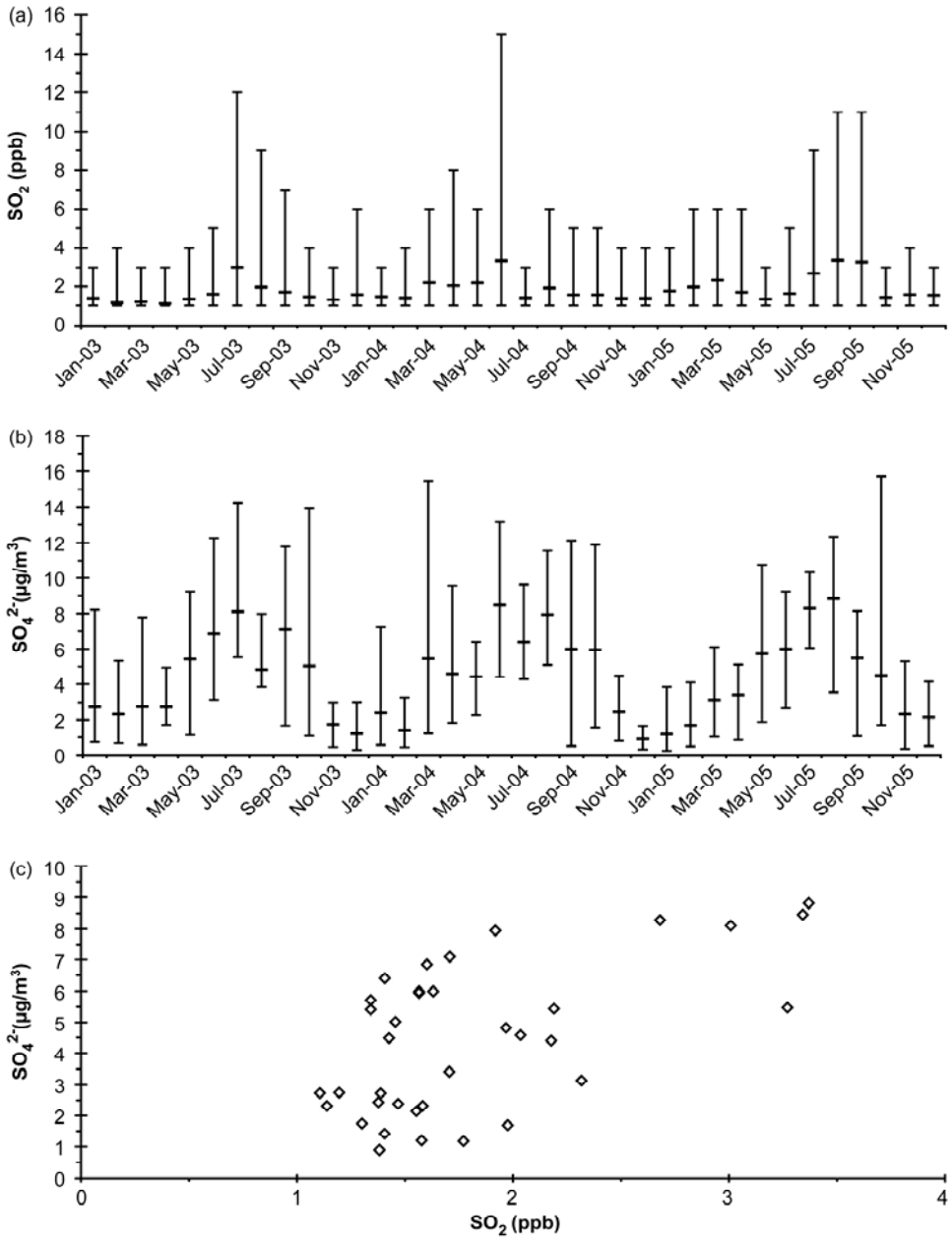


Figure 2-28. Riverside, CA, 2003–2005. (a). Monthly mean, minimum, and maximum SO_2 concentrations. (b) Monthly mean, minimum, and maximum SO_4^{2-} concentrations. (c) Monthly mean SO_4^{2-} concentrations as a function of SO_2 concentrations.

Riverside, CA, CMSA (Figure 2-28) presents the strongest example among the 12 areas examined for this study of correlation between SO_2 and SO_4^{2-}, though even here the coefficient of determination (R^2) value is merely 0.3. Seasonal peaks are obvious in summertime for SO_2 and SO_4^{2-}, both at roughly one-half the ambient concentrations seen in Los Angeles. This is very likely due to Riverside's geographic location just downwind of the regionally large electric generating utility sources near Los Angeles and the prevailing westerly winds in summer. Again, as with Los Angeles, the summertime peaks in SO_4^{2-} are most likely due to the combination of peaking SO_2 and favorable meteorological conditions allowing more complete oxidation.

Phoenix, AZ was the CMSA with the lowest monthly mean SO_2 and SO_4^{2-} concentrations examined here (Figure 2-29). In Phoenix, nearly all monthly mean SO_2 values were at or below the regulatory monitors' operating LOD of ~3 ppb. SO_4^{2-} concentrations were equivalently low, roughly one-half the concentrations seen in Riverside, CA. The monthly mean data show strong summertime peaks for even these very low-level SO_4^{2-} observations, which at ~1 to 3 μg/m^3, were generally one-half of those in Philadelphia. This suggests some seasonality in SO_2, though anticorrelated with SO_4^{2-}; however, the trend is very weak, as the correlation scatterplot shows.

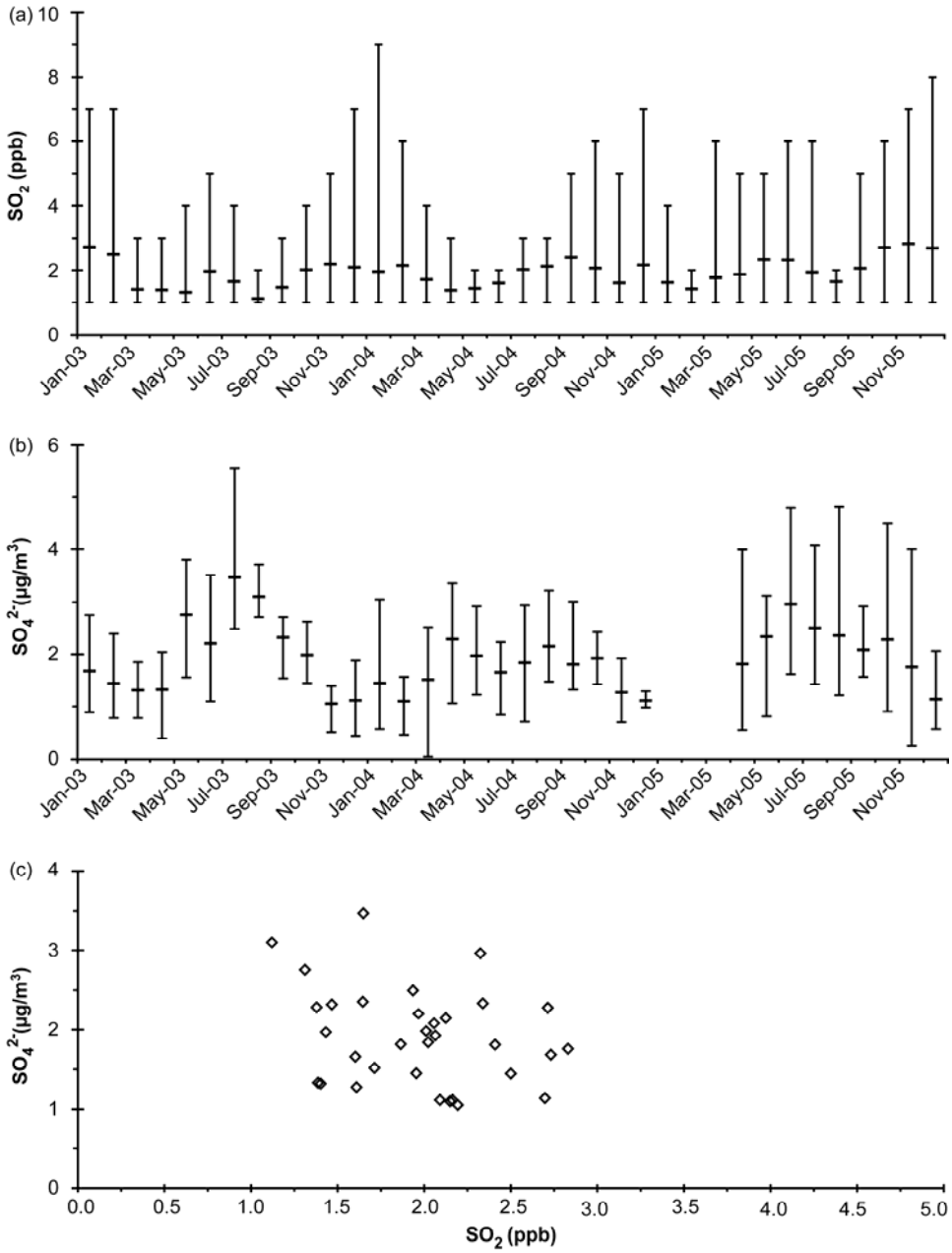


Figure 2-29. Phoenix, 2003–2005. (a) Monthly mean, minimum, and maximum SO_2 concentrations. (b) Monthly mean, minimum, and maximum SO_4^{2-} concentrations. (c) Monthly mean SO_4^{2-} concentrations as a function of SO_2 concentrations.

2.5.2. Five-Minute Sample Data in the Monitoring Network

Although the number of monitors across the CONUS varies somewhat from year to year, in 2006 there were ~500 SO_2 monitors in the NAAQS monitoring network (http://www.epa.gov/air/data/). The state and local agencies responsible for these monitors are required to report 1-h avg concentrations to the EPA AQS. However, a small number of sites, only 98 total from 1997 to 2007, and not the same sites in all years—voluntarily reported 5-min block avg data to AQS. Of these, only 16 reported all twelve 5-min avg in each hour at least part of the time between 1997 and 2007. The remainder reported only the maximum 5-min avg in each hour. See Table 2-10 and Table 2-11 for a breakdown of these monitoring locations and sampling periods, and Figure 2-30 for the distribution of these sites across the CONUS.

Table 2-10. Locations, counts, sampling periods and statistics for monitors reporting hourly maximum 5-min SO_2 values, 1997-2007.

State	Number of Counties	Number of Monitors	Number of Years	Years Operating	Mean	GM[1]	GSD[2]	50[3]	95[3]	99[3]	Max
AR	2	3	11	1997 - 2007	4	3	2	3	10	37	659
CO	1	1	10	1997 - 2006	8	4	3	4	29	57	216
DE	1	1	2	1997 - 1998	17	6	4	5	97	184	381
DC	1	1	6	2000 - 2007	9	6	2	6	23	42	482
FL	1	1	4	2002 - 2005	8	2	3	1	40	106	473
IA	6	9	5	2001 - 2005	4	2	3	1	12	45	307
LA	1	1	4	1997 - 2000	12	5	3	5	41	131	857
MO	7	14	11	1997 - 2007	9	3	3	2	32	146	4367
MT	1	7	10	1997 - 2006	8	3	4	2	35	77	843
NC	2	2	8	1997 - 2004	9	3	4	4	34	108	805
ND	11	19	11	1997 - 2007	3	1	2	1	11	54	499
PA	8	23	11	1997 - 2007	14	8	3	8	48	105	1099
SC	7	10	3	2000 - 2002	3	2	2	2	10	28	277
UT	1	1	2	1997 - 1998	3	2	2	1	9	21	209
WV	2	5	7	2001 - 2007	12	7	3	7	38	80	856

[1] Geometric mean
[2] Geometric standard deviation
[3] Percentile

Table 2-11. Locations, counts, sampling periods and statistics for monitors reporting all twelve 5-min SO_2 values, 1997-2007.

State	Number of Counties	Number of Monitors	Number of Years	Years Operating	Mean	GM[1]	GSD[2]	50[3]	95[3]	99[3]	Max
DC	1	1	1	2007	5	4	2	4	12	19	400
FL	1	1	4	2002 - 2005	4	2	3	1	18	62	473
MO	1	2	5	2003 - 2007	3	2	2	1	11	43	259
MT	1	4	1	2002	3	2	2	1	12	34	843
NC	1	1	4	1999 - 2002	5	2	3	1	22	77	805
PA	2	5	6	2002 - 2007	11	5	4	5	39	83	921
WV	2	2	5	2001 - 2005	9	5	3	5	29	58	508

[1] Geometric mean
[2] Geometric standard deviation
[3] Percentile

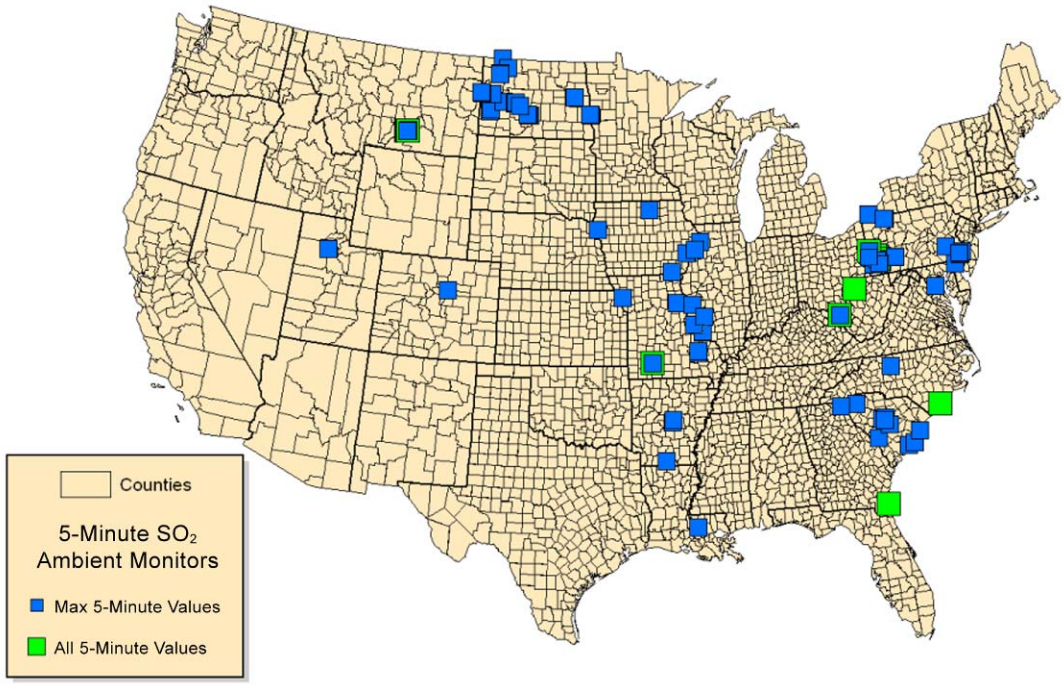


Figure 2-30. SO_2 monitors reporting maximum or continuous 5-min avg values for any period, 1997–2007.

EPA guidance on quality assurance practices for SO_2 monitoring by state/local monitoring agencies is aimed at ensuring adequate quality of 1-h SO_2 concentration data. Measurement of 5-min avg concentrations may involve quality assurance challenges that are not addressed by current EPA guidance. This possibility has not been specifically investigated to date, so the information presented here should be considered to be of uncharacterized uncertainty at this time. Furthermore, the voluntary nature of this

reporting results in irregular coverage in both space and time. For example, some sites reported data for some years while others did not. Because the 5-min data were reported voluntarily by the cooperating states from a subset of monitors in the national data network, no information is available to judge their degree of representativeness relative to the national network.

When maximum 5-min concentrations were reported, the absolute highest concentration over the ten-year period exceeded 4 ppm, but the 99th percentile of the maximum 5-min concentrations were all below 200 ppb. Medians from reported data ranged from 1 ppb to 8 ppb, and the avg for each maximum 5-min level ranged from 3 ppb to 17 ppb. Delaware, Pennsylvania, Louisiana, and West Virginia had mean values for maximum 5-min data exceeding 10 ppb. Among aggregated within-state data for the 16 monitors from which all 5-min avg data were reported, the median values ranged from 1 ppb to 5 ppb, and the means ranged from 3 ppb to 11 ppb. The highest reported concentration was 921 ppb, but the 99th percentile values for aggregated within-state data were all below 90 ppb. It should be emphasized that monitoring was not continual during the ten-year reporting period, and monitoring was not performed simultaneously among the sites. For these reasons, caution must be taken when comparing the distributions among the various sites.

Despite these limitations, distributions of the available 5-min data and comparisons with their respective 1-h avg can provide some insight into the temporal behavior of short-duration SO_2 concentrations at the monitoring stations where these data are available. Table 2-12 summarizes correlations between the maximum 5-min avg and the corresponding 1-h avg computed from the 5-min data for the monitors reporting all twelve 5-min avg. The correlations are high with only one monitor observing a correlation coefficient under 0.9.

Table 2-12. Pearson correlation coefficient between maximum 5-min and 1-h avg SO_2 concentrations at the 16 sites reporting all twelve 5-min SO_2 values.

State	Site ID	Correlation Coefficient
DC	110010041	0.87
FL	120890005	0.92
MO	290770026	0.92
MO	290770037	0.93
MT	301110066	0.95
MT	301110079	0.93
MT	301110082	0.93
MT	301110083	0.92
NC	371290006	0.91
PA	420030021	0.94
PA	420030064	0.95
PA	420030116	0.96
PA	420033003	0.95
PA	420070005	0.93
WV	540990002	0.95
WV	541071002	0.93

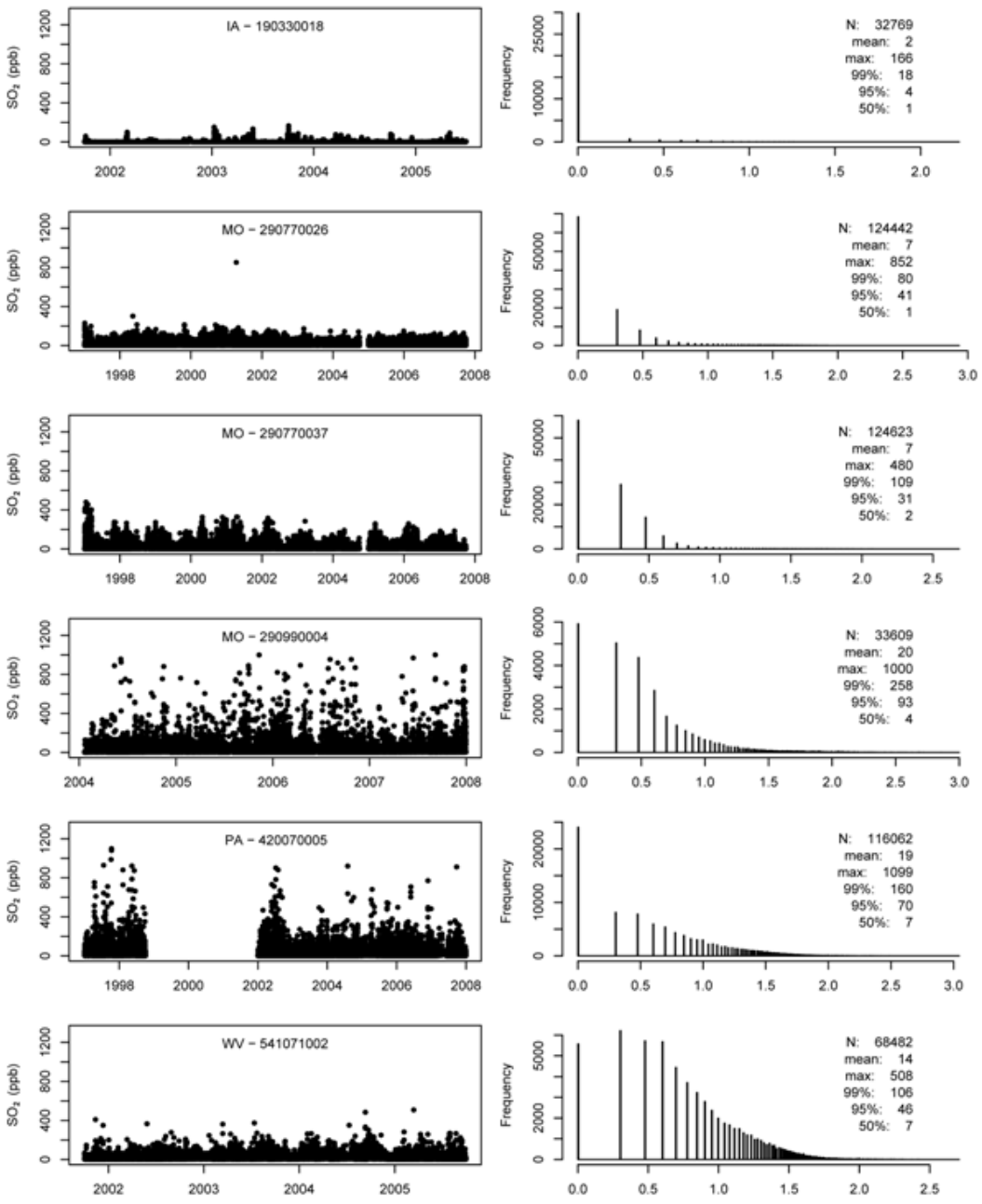


Figure 2-31. Time series and frequency distributions of voluntarily reported maximum 5-min SO_2 concentrations from 6 monitors located in Iowa, Missouri, Pennsylvania and West Virginia. Frequency distributions are shown in terms of the log of the concentration on the x-axis.

Figure 2-31 shows the time series and distribution of maximum 5-min SO_2 data per hour for six monitors located in Iowa (site ID = 190330018), Missouri (290770026, 290770037 and 290990004), Pennsylvania (420070005) and West Virginia (541071002). These sites were selected to represent the available 5-min data. The highest observed 5-min values for these six monitors range from 166 ppb at the Iowa monitor (Mason City, IA) to 1099 ppb at the Pennsylvania monitor (Beaver Co, PA). In general,

Figure 2-31 demonstrates that the higher range of mean values compared with the medians reflects a few high concentration events that skew the means upward with the mean concentration between 2 and 7 times greater than the median of these data.

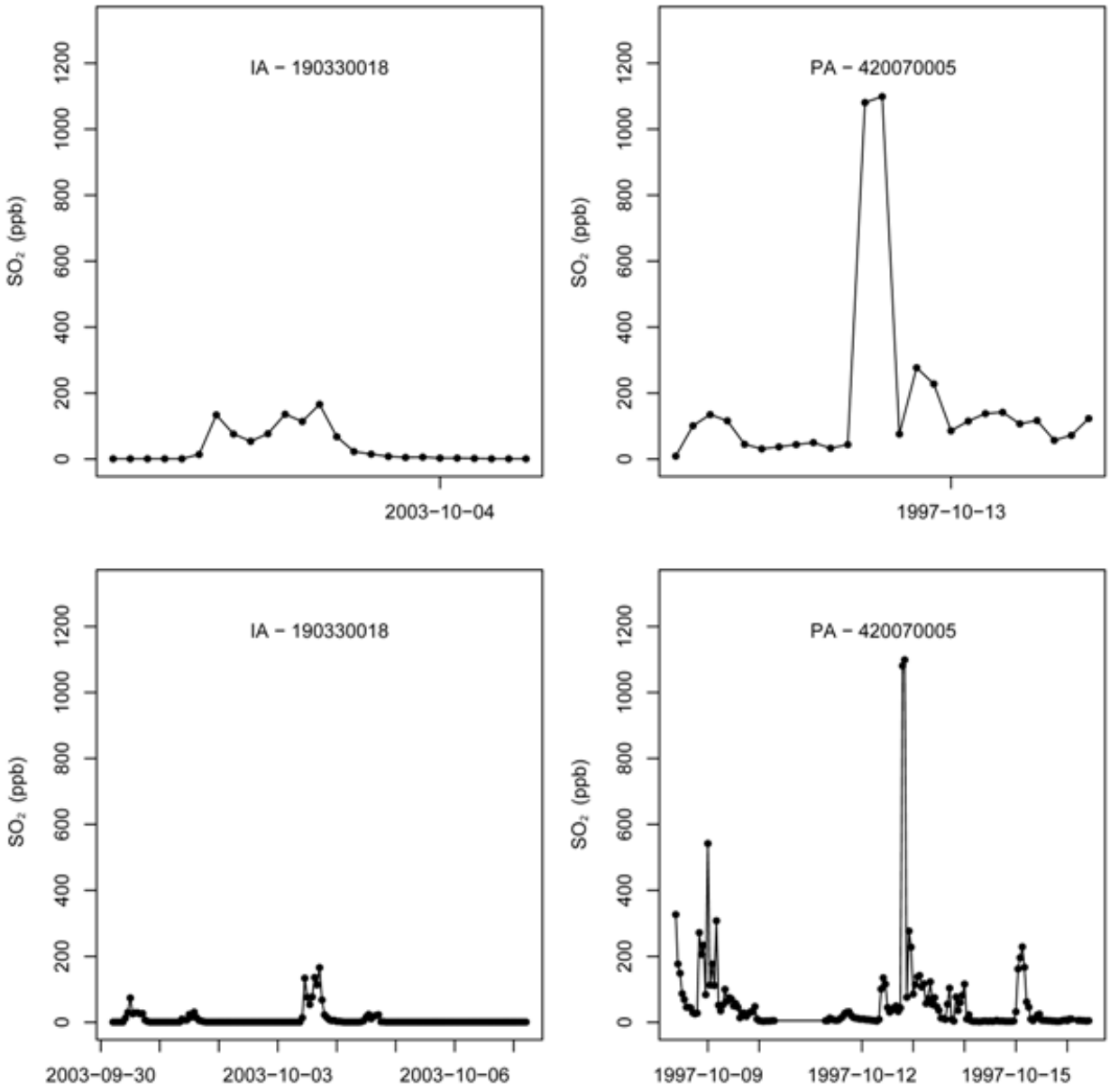


Figure 2-32. Time series of hourly maximum 5-min SO_2 data showing a 24 h (upper panels) and 1 week (lower panels) time window centered on the peak value for the two sites with the lowest (IA) and highest (PA) maximum values in the preceding figure.

Excursions of high 5-min concentrations should not be expected to be confined to one 5-min interval in any given hour as time scales for the meteorological conditions responsible for the excursions are much longer. During transport of emissions from their source to a receptor at the surface, turbulent

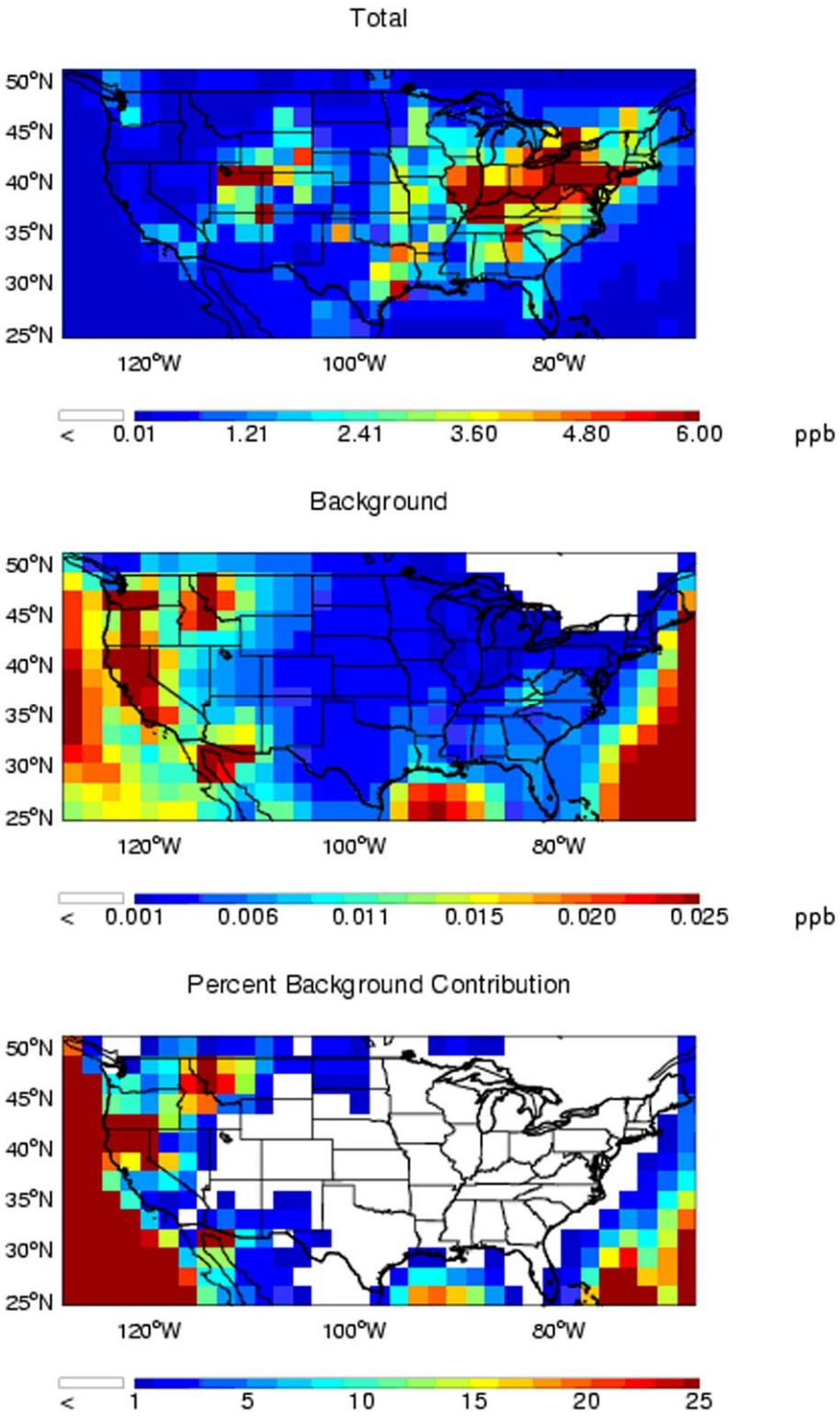
mixing and dilution of the plume occur, further extending the area at the surface that is affected. Figure 2-32 shows the time series of 5 min data centered on time of occurrence of the value (lower panel) for the two sites with the highest maximum value (PA) and lowest maximum value (IA) in the preceding figure. As can be seen for these two sites at least, high levels of SO_2 can be sustained at the surface for a few hours and the time for these excursions to affect the surface can differ from site to site and during different periods at the same site. Note also that these events do not occur in isolation as can be seen at the PA site, at which several excursions above the 200 ppb level occurred within a week. Further analysis would be required to determine characteristic time scales for the durations of these excursions across the U.S., using emissions and meteorological data.

2.5.3. Policy Relevant Background Contributions to SO_2 Concentrations

Background concentrations used for purposes of informing decisions about the NAAQS are referred to as PRB concentrations; those concentrations that would occur in the U.S. in the absence of anthropogenic emissions in continental North America (defined here as the U.S., Canada, and Mexico). PRB concentrations include contributions from natural sources everywhere in the world, and from anthropogenic sources outside these three countries. Background levels so defined facilitate separation of cases where pollution levels can be controlled by U.S. regulations (or through international agreements with neighboring countries), from cases where pollution is generally uncontrollable by the U.S.. EPA assesses risks to human health and environmental effects from SO_2 levels in excess of PRB concentrations.

Contributions to PRB concentrations include natural emissions of SO_2 and photochemical reactions involving reduced sulfur compounds of natural origin, as well as their long-range transport from outside of North America from any source. As an example, transport of SO_2 from Eurasia across the Pacific Ocean or the Arctic Ocean would carry PRB SO_2 into the U.S. Annex B contains a schematic diagram showing the major photochemical processes involved in the sulfur cycle, including natural sources of reduced sulfur species from anaerobic microbial activity in wetlands and volcanic activity. Volcanoes and wildfires are the major natural source of SO_2. Biogenic emissions from agricultural activities are not considered in the formation of PRB concentrations. Discussions of the sources and estimates of emissions are given in Annex Section B.6.

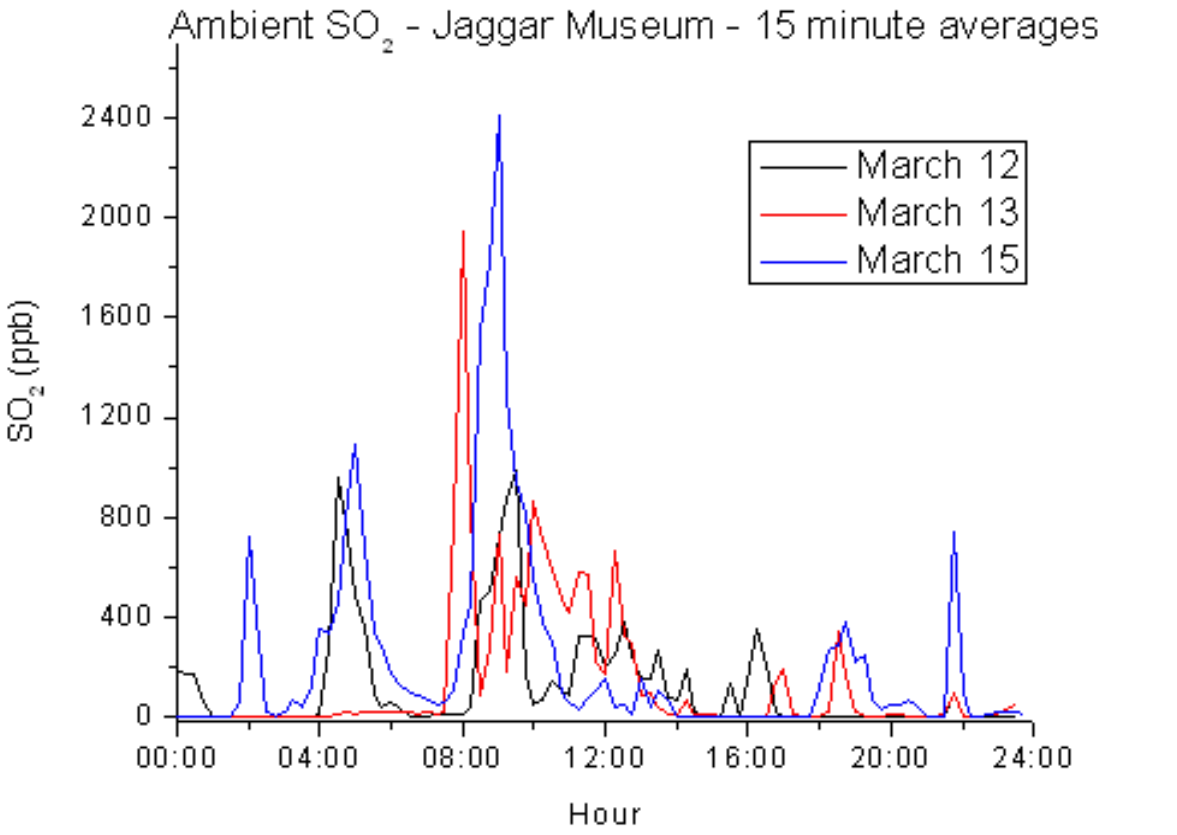
The MOZART-2 global model of tropospheric chemistry (Horowitz et al., 2003) is used to estimate the PRB contribution to SO_2 concentrations. The model setup for the present-day simulation, i.e., including all sources in the U.S., Canada, and Mexico, was published in a series of papers from a recent model inter-comparison (Dentener et al., 2006a; van Noije et al., 2006). MOZART-2 is driven by the National Oceanic and Atmospheric Administration's National Center for Environmental Prediction (NOAA/NCEP) meteorological fields and the International Institute for Applied Systems Analysis (IIASA) 2000 emissions at a resolution of $1.9° \times 1.9°$ with 28 σ (sigma) levels in the vertical and includes gas- and aerosol-phase chemistry. Results shown in Figure 2-33 are for the meteorological year 2001. An additional PRB simulation was conducted in which continental North American anthropogenic emissions were set to zero.



Source: NOAA Geophysical Fluid Dynamics Laboratory.

Figure 2-33. Annual mean model-predicted concentrations of SO_2 (ppb).

The role of PRB in contributing to SO_2 concentrations in surface air is examined first. Figure 2-33 shows the annual mean predicted SO_2 concentrations in surface air in the simulation including all sources, or the "base case" (top panel); the PRB simulation (middle panel); and the percentage contribution of the background to the total base case SO_2 (bottom panel). Maximum concentrations in the base case simulation, > 5 ppb, occur along the Ohio River Valley (upper panel). Background SO_2 concentrations are orders of magnitude smaller, below 10 parts per trillion (ppt) over much of the U.S. (middle panel). Maximum PRB concentrations of SO_2 are 30 ppt. In the Northwest where there are geothermal sources of SO_2, the contribution of PRB to total SO_2 is 70 to 80%, however absolute SO_2 concentrations are still of the order of ~2 ppb or less. With the exception of the West Coast where volcanic SO_2 emissions cause high PRB concentrations, PRB contributes < 1% to present-day SO_2 concentrations in surface air (bottom panel).



Source: National Park Service

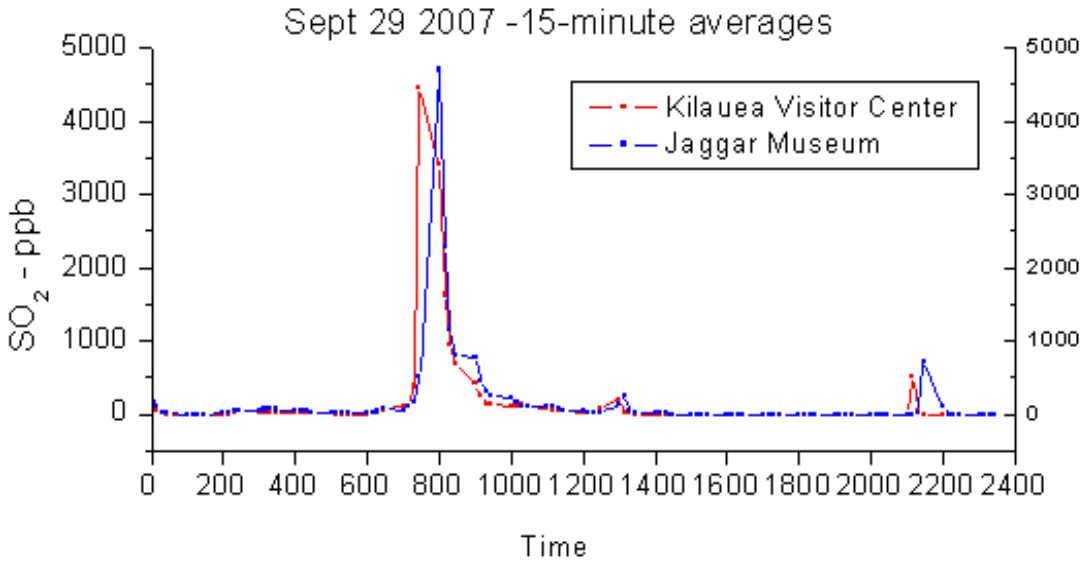
Figure 2-34. 15-min avg ambient SO_2 concentrations measured at 1 Hawaii Volcanoes National Park monitoring site (Jaggar Museum), March 12, 13, and 15, 2007.

When estimating background concentrations, it is instructive to consider measurements of SO_2 at relatively remote monitoring sites, i.e., sites located in sparsely populated areas not subject to obvious local sources of pollution. Berresheim et al. (1993) used a type of atmospheric pressure ionization mass spectrometer (APIMS) at Cheeka Peak, WA (48.30EN 124.62EW, 480 m asl) in April 1991 during a field study for DMS oxidation products. SO_2 concentrations ranged between 20 and 40 ppt. Thornton et al. (2002) have also used an APIMS with an isotopically labeled internal standard to determine background

SO_2 levels. SO_2 concentrations of 25 to 40 ppt were observed in northwestern Nebraska in October, 1999 at 150 m above ground using the National Center for Atmospheric Research (NCAR)'s C-130 research aircraft. These data are comparable to remote central South Pacific convective boundary layer SO_2 data (Thornton, 1999).

As noted earlier, volcanic sources of SO_2 in the U.S. are found in the Pacific Northwest, Alaska, and Hawaii. The greatest potential domestic effects from volcanic SO_2 occurs on the island of Hawaii. Nearly continuous venting of SO_2 from Mauna Loa and Kilauea produces SO_2 in high concentrations (see Figure 2-34 and Figure 2-35) at two National Park sites near the Kilauea caldera and the nearby east rift zone. The latter emits several times as much SO_2 as the Kilauea caldera. The two measurement sites within the National Park are < 3 km from the summit emission source and ~10 km from the east rift source and are affected by the two sources during southerly and easterly winds. A number of communities and population centers are within the same distance from the east rift gas source that affects these two monitoring sites. When the normal trade wind flows are disrupted, emissions from the sources can be brought directly to these various communities. Since these communities are located at a similar distance from the large east rift emission source as the National Park monitoring stations, it is probable that these communities experience SO_2 concentrations as high as those measured within Hawaii Volcanoes National Park.

Since 1980, the Mount St. Helens volcano (46.20°N, 122.18°W, summit 2549 m asl) in the Washington Cascade range has been a variable source of SO_2. Its major effects came in the explosive eruptions of 1980, which primarily affected the northwestern U.S. The Augustine volcano near the mouth of the Cook Inlet in southwestern Alaska (59.363°N, 153.43°W, summit 1252 m asl) has emitted variable quantities of SO_2 since its last major eruptions in 1986. Volcanoes in the Kamchatka peninsula in far eastern Siberia do not particularly affect the surface concentrations in northwestern North America. Overall, the background contribution to SO_2 over the U.S. is relatively small, with a max PRB of 0.030 ppb SO_2, except for areas with volcanic activity.



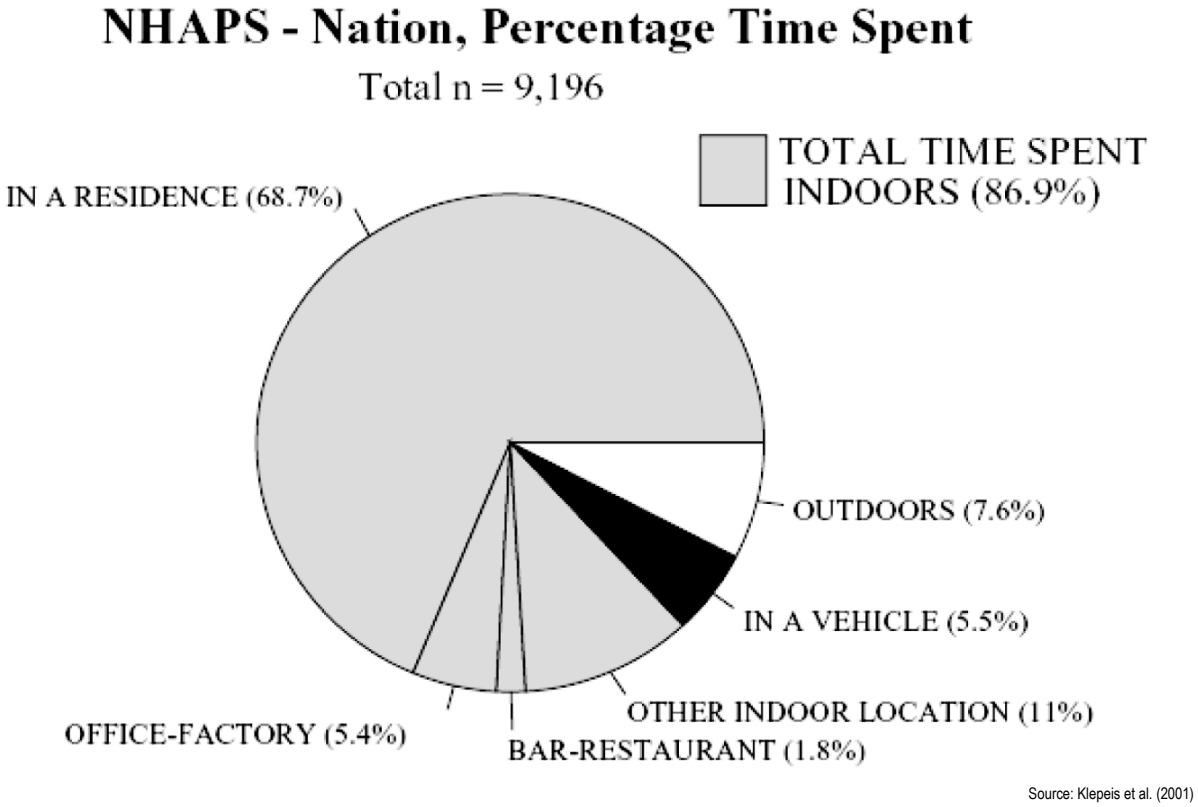
Source: National Park Service

Figure 2-35. 15-min avg ambient SO_2 concentrations measured at 2 Hawaii Volcanos National Park monitoring sites on September 29, 2007.

2.6. Issues Associated with Evaluating SO_2 Exposure

2.6.1. General Considerations for Personal Exposure

Human exposure to an airborne pollutant consists of contact between the human and the pollutant at a specific concentration for a specified period of time. People spend various amounts of time in different microenvironments characterized by different pollutant concentrations. The integrated exposure of a person to a given pollutant is the sum of the exposures over all time intervals for all microenvironments. Figure 2-36 represents a composite average of activity patterns across all age groups in the U.S., based on data collected in the National Human Activity Pattern Survey (NHAPS) (Klepeis et al., 2001). The demographic distribution of the respondents was designed to be similar to that of overall U.S. Census data. Different cohorts, e.g., the elderly, young and middle-aged working adults, and children exhibit different activity patterns.



Source: Klepeis et al. (2001)

Figure 2-36. Percentage of time spent in various environments in the U.S.[1]

[1] For example, the cohort of working adults between the ages of 18 and 65 yr represents ~50% of the population. Of this total, about 60% work outside the home, spending ~24% (40 h/168 h) of their time in factory/office environments. Thus, this cohort is likely to spend considerably more time in offices and factories than shown in the figure (5.4%), which reflects the entire population, and is also likely to spend less time in a residence than small children or the elderly.

In a given microenvironment, the ambient component of a person's microenvironmental exposure to a pollutant is determined by the following physical factors:

- ambient concentration C_a
- air exchange rate a_i
- pollutant specific penetration coefficient P_i
- pollutant specific decay rate k_i
- fraction of time an individual spends in the microenvironment y_i

These factors are in turn affected by the following exposure factors:

- environmental conditions, such as weather and season
- dwelling conditions such as: proximity to sources; the amount of natural ventilation (e.g., open windows and doors, and the "draftiness" of the dwelling); and the ventilation system
- personal activities (e.g., the time spent cooking, commuting, or exercising [See Section 2.7.1])
- indoor sources and sinks of a pollutant

Microenvironmental exposures can also be influenced by the individual-specific factors such as age, gender, health or socioeconomic status (SES).

A person's exposure to a pollutant, such as SO_2, can be represented by:

$$E_T = \sum_{i=l}^{n} C_i t_i$$

Equation 2-1

where E_T is an individual's total personal exposure for a specific time period, n is the total number of microenvironments encountered, C_i is the average concentration, and t_i is the time spent in the ith microenvironment. A person's exposure can be characterized as: an instantaneous exposure, a peak exposure such as might occur during a short-term event such as cooking, an average exposure, or an integrated exposure over all environments encountered. These distinctions are important because health effects caused by long-term low-level exposures may differ from those caused by short-term peak exposures.

An individual's total exposure (E_T) can also be represented by:

$$E_T = E_a + E_{na} = \{y_o + \sum_i y_i \, [P_i a_i/(a_i + k_i)] \, \} C_a + E_{na} = \{y_o + \sum_i y_i F_{inf_i}\} C_a + E_{na}$$

Equation 2-2

subject to the constraint

$$y_o + \sum_i y_i = 1$$

Equation 2-3

where E_a is the ambient component of personal exposure, E_{na} is the nonambient component of personal exposure, y_o is the fraction of time spent outdoors, and y_i is the fraction of time spent in microenvironment i. F_{inf_i}, P_i, a_i, and k_i are the infiltration factor, penetration coefficient, air exchange rate, and decay rate, respectively for microenvironment i. In the case where an exposure occurs mainly in one microenvironment, Equation 2-2 may be approximated by Equation 2-4 where y is the fraction of time spent outdoors, and α is the ratio of personal exposure from a pollutant of ambient origin to the pollutant's ambient concentration (or the ambient exposure factor). Other symbols have the same definitions as in Equations 2-2 and 2-3.

$$E_T = E_a + E_{na} = \{y + (1-y)[Pa/(a+k)]\}C_a + E_{na} = \alpha C_a + E_{na}$$

Equation 2-4

If concentrations in a single microenvironment are considered, then Equation 2-4 can be reduced to

$$C_{me} = C_a + C_{na} = [Pa/(a+k)]C_a + S/[V(a+k)]$$

Equation 2-5

where C_{me} is the concentration in a microenvironment, C_a and C_{na} are the contributions to C_{me} from ambient and nonambient sources, S is the microenvironmental source strength, and V is the volume of the microenvironment. (Bracketed symbols are same as Equation 2-2.) In this equation, it is assumed that microenvironments do not exchange air with each other but only with the ambient environment.

Microenvironments in which people are exposed to air pollutants such as SO_2 typically include residential indoor environments, other indoor locations, near-traffic outdoor environments, other outdoor locations, and in vehicles, as shown in Figure 2-36. Indoor combustion sources such as gas stoves and space heaters need to be considered when evaluating exposures to SO_2. However, in the U.S., the only important indoor sources of SO_2 are kerosene heaters, which are not widely used. Exposure characterization is improved when microenvironment-level exposures are considered to estimate the ambient component of personal exposure and to describe the relationship between ambient air pollution exposures and health outcomes.

Time-activity diaries, completed by study participants, are used to compile activity patterns for input to exposure models and assessments. The EPA's National Exposure Research Laboratory (NERL) has consolidated the majority of the most significant human activity databases into one comprehensive database called the Consolidated Human Activity Database (CHAD). Eleven different human activity pattern studies were evaluated to obtain over 22,000 person-days of 24-h human activities in CHAD (McCurdy et al., 2000). These data can be useful in assembling population cohorts to be used in exposure modeling and analysis.

In general, the relationship between personal exposures and ambient concentrations is modified by pollutant behavior in microenvironments. During infiltration, ambient pollutants can be lost through chemical and physical processes. Therefore, the ambient component of a pollutant's microenvironmental concentration is less than its ambient concentration, and can be represented as the product of the ambient concentration and the infiltration factor (F_{inf} or α [if people spend 100% of their time indoors]). In addition, exposure to nonambient, microenvironmental sources modifies the relationship between personal exposures and ambient concentrations.

In practice, it is extremely difficult to characterize community exposures by measurements of each individual's personal exposures. Instead, the distribution of personal exposures in a community, or the population exposure, is simulated by extrapolating measurements of personal exposure using various techniques or by stochastic, deterministic or hybrid exposure modeling approaches such as APEX, SHEDS, and MENTOR (see Annex Section C.2 for a description of modeling methods). Variations in community-level personal exposures are determined by cross-community variations in ambient pollutant concentrations and the physical and exposure factors mentioned above. These factors also determine the strength of the association between population exposure to SO_2 of ambient origin and ambient SO_2 concentrations.

Of major concern is the ability of SO_2 measured by ambient monitors to serve as a reliable indicator of personal exposure to SO_2 of ambient origin. The key question is what errors are associated with using SO_2 measured by ambient monitors as a surrogate for personal exposure to ambient SO_2 and/or its oxidation products in epidemiologic studies. There are three aspects to this issue: (1) ambient and personal sampling issues; (2) the spatial variability of ambient SO_2 concentrations as related to exposures; and (3) the associations between ambient concentrations and personal exposures as influenced by

exposure factors, e.g., indoor sources and time spent indoors and outdoors. Items (1) and (3) are discussed individually in the following sections; item (2) was discussed previously in Section 2.4.2.

2.6.2. Methods Used for Monitoring Personal Exposure

Three basic methods of analysis have been used as personal exposure monitors (PEMs) to measure personal exposure to SO_2. The Harvard-EPA annular denuder system (HEADS) was initially developed to measure particles and acid gases simultaneously (Brauer et al., 1999; Koutrakis et al., 1988b). The aerosol is initially sampled at 10 L/min through an impactor that is attached to an annular denuder to remove particles. Subsequently, the aerosol is sampled through an annular denuder coated with sodium carbonate (Na_2CO_3). This denuder is used to trap SO_2, nitric acid (HNO_3), and nitrous acid (HNO_2). Following sampling, the denuder is extracted with ultrapure water and analyzed by ion chromatography. Collection efficiencies of SO_2 in the denuder are typically around 0.993, which compares well with predicted values.

For a study conducted in Baltimore, MD, Chang et al. (2000) developed and employed a personal roll-around system (RAS), which is an active sampling system designed to measure short-term personal exposure concentrations of several atmospherically relevant species, including SO_2. For the measurement of SO_2, the RAS employed an NO_2/SO_2 sorbent denuder worn on a vest by the study participant. The hollow glass denuder, encased in an aluminum jacket, is coated with triethanolamine (TEA) for the collection of SO_2 and NO_2, and aerosol is sampled through the denuder at 100 cc/min. Following sampling, the denuder can be extracted and analyzed for SO_2 concentrations by ion chromatography. The detection limit for 1-h sampling of SO_2 was reported to be 62 ppb, which resulted in many of the 1-h samples being below the LOD.

The most commonly employed SO_2 PEM method for personal exposure studies is the passive badge sampler. A personal multipollutant sampler has been developed to measure particulate and gaseous pollutants simultaneously (Demokritou et al., 2001). A single elutriator, operating at 5.2 L/min, is employed to sample particulate pollutants. A passive SO_2 badge is attached diametrically to the elutriator, which has been coated with Teflon to minimize reactive gas losses. The passive badge sample is coated with TEA for the collection of SO_2 and NO_2. Because wind speed can affect the collection rate of the passive badge sampler, this system employs a constant face velocity across the passive badge sampler. For 24-h sampling times, the estimated limit of detection (LOD) for SO_2 is 5 ppb.

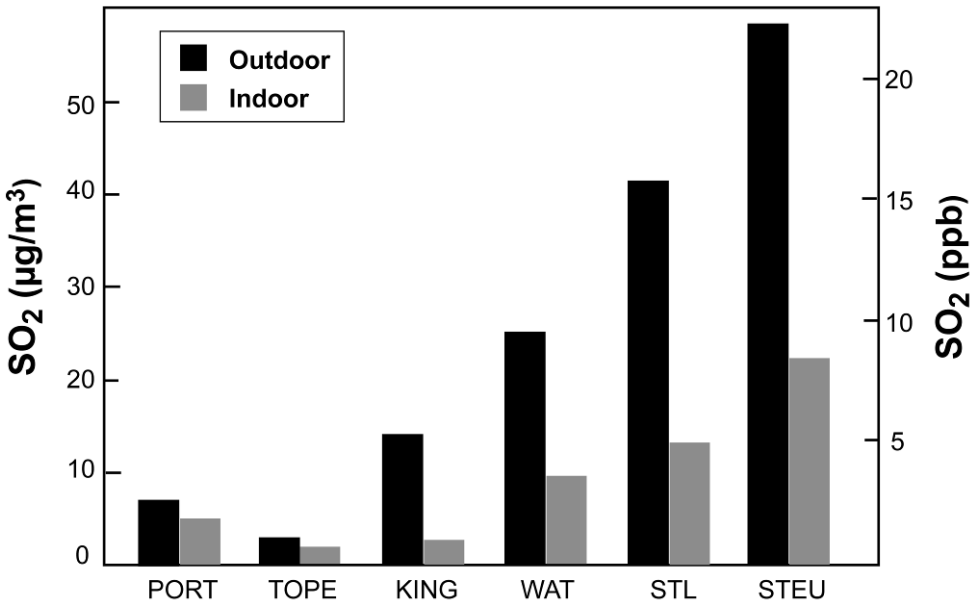
Currently, limits exist for using PEM systems to measure personal exposure to SO_2. Because SO_2 concentrations have been declining annually in the U.S., little focus has been placed on improving the methods of analysis. LODs for SO_2 PEMs (~5-10 ppb for 24-h sampling) are often greater than the concentrations of SO_2 that are typically observed in urban ambient environments. However, much lower detection limits can be achieved by extending the sampling time (Kasper-Giebl et al., 1999). Personal exposure monitoring studies often suffer from having many of the daily SO_2 samples (e.g., 30 to 70%) collected below the sampler's LOD (see Table 2-14 and Table 2-15). Because of these issues, current methods cannot characterize hourly or shorter exposures and their relationship to ambient concentrations unless these values are in the range of several tens to hundreds of ppb.

2.6.3. Relationship between Personal Exposure and Ambient Concentration

Because SO_2 concentrations have declined markedly over the past few decades, relatively few recent personal exposure studies have focused on SO_2. Another consideration is that current indoor and outdoor levels in many areas are often beneath detection limits for passive personal SO_2 monitors.

2.6.3.1. Indoor Versus Outdoor SO_2 Concentrations

Several studies in the U.S., Canada, Europe, and Asia have examined the relationships of indoor, outdoor, and personal concentrations of SO_2 to ambient SO_2 concentrations. Perhaps the most comprehensive set of indoor-outdoor data was obtained by Spengler et al. (1979) during the Harvard Six Cities Study. These data are shown in Figure 2-37. 24-h ambient and indoor SO_2 concentrations were measured every sixth day for 1 yr in a minimum of 10 homes or public facilities for each of the cities studied.



Source: Adapted from Spengler et al. (1979)

Figure 2-37. Average annual indoor and outdoor SO_2 concentrations for each of the six cities included in the Harvard six-cities study analysis. PORT = Portage, WI / TOPE = Topeka, KS / KING = Kingston, TN / WAT = Watertown, MA / STL = St. Louis, MO / STEU = Steubenville, OH.

As can be seen from Table 2-13, a wide range is found in the ratio of indoor to outdoor concentrations among the different studies. These differences among studies could be due in part to differences in building characteristics (e.g., forced ventilation, building age, and building function such as residences, schools, or other public buildings), in activities affecting air exchange rates, and in analytical capabilities. In several studies, high values for R^2 were found, suggesting that indoor levels were largely driven by outdoor levels. A few studies found higher levels of SO_2 indoors than outdoors in some samples. This situation could have arisen if there were indoor sources or as a result of analytical measurement issues. One would expect to find lower concentrations indoors than outdoors because SO_2 is consumed by reactions on indoor surfaces, especially those that are moist. Chao (2001) acknowledged this point but could not account for the findings of this study. It was noted that two samples had unusually high indoor to outdoor ratios and that the mean ratios would have been much lower otherwise. Winter-summer differences in the indoor:outdoor ratio are consistent with seasonal differences in air exchange rates, as noted by Brauer et al. (1991).

Table 2-13. Relationships of indoor to outdoor SO_2 concentrations.

Study	Location	Indoor to Outdoor Ratio (# samples)	Notes
Spengler et al. (1979)	Portage, WI	0.67 (349)	One year during Harvard Six Cities Study. West-Gaeke method.
	Topeka, KS	0.50 (389)	
	Kingston, TN	0.08 (425)	
	Watertown, MA	0.33 (486)	
	St. Louis. MO	0.31 (543)	
	Steubenville, OH	0.39 (499)	
Stock et al. (1985)	Houston, TX	0.54 (2425)	May to October, continuous FRM for indoor and outdoor.
Meranger and Brule (1987)	Antigonish, NS, Canada	0.84 (8)	Early spring, 1 wk avg in 1 house with oil furnace, FPD-TA
Brauer et al. (1989)	Boston, MA	0.23 (24)	Summer, HEADS
Li and Harrison (1990)	Essex, UK	0.22	Summer
Brauer et al. (1991)	Boston, MA	0.39 (geom. mean) (29), $R^2 = 0.89$	Summer, HEADS
		0.05 (geom. mean) (23), $R^2 = 0.73$	Winter, HEADS
Chan et al. (1994)	Taipei, Taiwan	0.24 (15)	Summer, PS
		0.23 (37)	Winter, PS
Lee et al. (1999b)	Hong Kong	0.92, $R^2 = 0.56$	Winter, PF
Patterson and Eatough (2000)	Lindon, UT	0.027 ± 0.0023, $R^2 = 0.73$	Winter, ADS, all samples
Kindzierski and Sembaluk (2001)	Boyle, Alberta, Canada	0.12 (12)	Late Fall, PS
	Sherwood Park, Alberta, Canada	0.14 (13)	
Chao (2001)	Hong Kong	1.01 ± 0.78 (10)	Summer. Windows mainly kept closed, PS
Kindzierski and Ranganathan (2006)	Fort McKay, Alberta, Canada	0.35 (30)	Fall. All indoor levels < LOD and set =1/2 LOD, PS

FPD-TA = Flame Photometric Detection-Thermal Analysis
HEADS = Harvard-EPA Annular Denuder System
PS = passive sampler
PF = pulsed fluorescence
FRM = Federal Reference Method
ADS = Annular Denuder System

Indoor, or nonambient, sources of SO_2 could complicate the interpretation of associations between personal exposure to ambient SO_2 in exposure studies. The source of indoor SO_2 is combustion of sulfur-containing fuels, and higher levels are expected when emissions are poorly vented. Brauer et al. (2002b) noted that only one study (Biersteker et al., 1965) conducted inferential analyses of potential determinants of exposure to indoor SO_2 levels. In the Biersteker et al. study, conducted in the Netherlands, indoor levels increased with oil, coal, and gas heating, as well as smoking in homes and increased outdoor levels.

Triche et al. (2005) measured SO_2 levels in homes in which secondary heating sources (fireplaces, kerosene heaters, gas space heaters, and wood stoves) were used. They found elevated indoor levels of SO_2 when kerosene heaters were in use. Median levels of SO_2 when kerosene heaters were used (6.4 ppb) were much higher than when they were not in use (0.22 ppb). The maximum SO_2 level associated with kerosene heater use was 90.5 ppb. They did not find elevated SO_2 levels when the other secondary heating sources were in use.

2.6.3.2. Relationship of Personal Exposure to Ambient Concentration

A few studies have evaluated the association of personal SO_2 exposure to ambient concentrations (Brauer et al., 1989; Chang et al., 2000; Sarnat et al., 2000; 2001; 2005; 2006a). However, no studies have characterized the relationship between community avg exposures and ambient concentrations of SO_2. Some of these personal exposure studies were conducted under the Health Effects Institute's Characterization of Particulate and Gas Exposures of Sensitive Subpopulations Living in Baltimore and Boston research plan (Koutrakis et al., 2005). However, the focus of many of these studies has been exposure to particles with acid gases included to evaluate confounder or surrogate issues.

Table 2-14 summarizes the longitudinal correlation coefficients between personal SO_2 exposures and ambient concentrations of SO_2, and Table 2-15 shows the pooled correlation coefficients. Most of the studies examined lack the ability to quantify 24-h avg personal SO_2 exposures as a result of the low ambient SO_2 concentrations and the limitations of passive sampling, except two studies conducted by Brauer et al. (1989) and Sarnat et al. (2006a) in which the sampling systems can adequately quantify 24-h personal exposures.

Brauer et al. (1989) determined the slope of the regression line between personal and ambient concentrations to be 0.13 ± 0.02, $R^2 = 0.43$, based on 44 measurements made in Boston, MA during the summer of 1988. This study had the highest proportion of personal samples above the detection limit among the studies considered and the best regression fit between personal exposure and ambient concentrations. Most if not all of the data points obtained using the HEADS appeared to be above the working detection limits as defined by the authors in their publications (Brauer et al., 1989; Koutrakis et al., 1988b). Note that calculating detection limits in this way could result in lower apparent detection limits than if field blanks were used. The authors reported significance at the $p < 0.001$ level for the slope but not the intercept. Since the stationary monitoring site was located at an elevation of 250 m above street level, the use of data from this ambient monitoring site will overestimate personal exposure, as the concentration of SO_2 increases with height because it is emitted mainly by elevated point sources. Indeed, the ambient concentrations are about a factor of two higher than the concentrations measured outside residences. Sarnat et al. (2006a) reported that ambient SO_2 was observed to be significantly associated with personal SO_2 exposure concentrations during the fall (slope = 0.08 for overall population) in a study in Steubenville, OH. The authors also observed the effect of ventilation on the association between personal exposure concentrations and ambient concentrations (slope = 0.07 for subjects in buildings with low ventilation rates, and 0.13 for subjects in buildings with high ventilation rates).

The associations between personal exposure and ambient concentration cannot be examined in the other studies because almost all the personal exposure concentrations were beneath detection limits. For example, Chang et al. (2000) tested a new personal active sampling device (a RAS with a TEA-based denuder) on volunteer participants to measure hourly personal exposure to SO_2. However, the method detection limit was too high for SO_2 (62 ppb for 1-h sampling) to generate a robust SO_2 exposure dataset to perform further analysis, and so the authors did not use the SO_2 data.

Table 2-14. Association between personal exposure concentration and ambient concentration (longitudinal correlation coefficients).

Study	Study Design	Season	Mean Conc. (ppb)	Statistics	Comments
Sarnat et al. (2000)	Longitudinal, Baltimore, 20 senior, healthy, nonsmoking people (avg age 75), summer of 1998 and winter of 1999, 1 day averaged sample, for 12 consecutive days for each subject; four to six subjects were measured concurrently during each 12-day monitoring period.	Winter	Ambient: 6.6 – 10.2 Personal: -0.8 – 1.2	Slope: NR Intercept: NR Correlation Coefficient (r): -0.75 to 0.65 with a median of 0.02 (14 subjects)	The LOD for 24-h sampling was 6.5 ppb. All personal samples were below LOD.
Sarnat et al. (2001)	Longitudinal, Baltimore, 56 seniors, schoolchildren, and people with COPD, summer of 1998 and winter of 1999, 14 of 56 subjects participated in both sampling seasons; all subjects were monitored for 12 consecutive days (24-h avg samples) in each of the one or two seasons, with the exception of children who were measured for 8 consecutive days during the summer.	Winter	Ambient: 4 – 17 Personal: -2 – 3	Slope: -0.05 (N=487 with 45 subjects) Intercept: 0.54* (N=487 with 45 subjects) r = -0.75 to 0.6 with a median of -0.1 (45 subjects)	1) Concentrations are estimated from Figure 1 in the paper. 2) Correlation coefficients are estimated from Figure 2 in the paper. 3) LOD was referred to Sarnat et al. (2000), which was 6.5 ppb. Therefore, all personal samples were below LOD.
Sarnat et al. (2005)	Longitudinal, Boston, 43 seniors and schoolchildren, summer of 1999 and winter of 2000, Similar study design as Sarnat et al. (2001).	Summer	Ambient: 2.8 – 4.5 Personal: 0.3 – 0.5	Slope: 0.00 (N-335) Intercept: NR r = -0.60 to 0.70 with a median of 0.00, (Sample size: NR)	1) Correlation coefficients are estimated from Figure 1 in the paper. 2) LOD was 2.3 ppb, and 96.5% of personal samples were below LOD.
		Winter	Ambient: 4.9 – 10.7 Personal: -0.3 – 1.9	Slope: -0.02 (N = 299) Intercept: NR r = -0.55 to 0.60 with a median of 0.10 (Sample size NR)	1) Correlation coefficients are estimated from Figure 1 in the paper. 2) LOD was 3.2 ppb, and 95.4% of personal samples were below LOD.

NR: not reported
* $p \leq 0.05$

In the context of determining the effects of ambient pollutants on human health, the association between the ambient component of personal exposures and ambient concentrations is more relevant than the association between personal total exposures (ambient component + nonambient component) and ambient concentrations. As described in Equations 2-2 and 2-4, personal total exposure can be decomposed into two parts: an ambient and a nonambient component. Usually, the ambient component of personal exposure is not directly measureable. However, it can be estimated by exposure models, or the personal total exposure can be regarded as the personal exposure of ambient origin if there are no indoor or nonambient sources. It is expected that the association between ambient concentrations and the ambient component of personal exposures would be stronger than the association between ambient concentrations and personal total exposures as long as the ambient and nonambient component of personal total exposure are independent. None of the studies examined indoor sources. However, indoor sources are not expected to be present for SO_2. The correlation coefficients between personal ambient SO_2

exposures and ambient SO_2 concentrations in different types of exposure studies are relevant to different types of epidemiologic studies.

Table 2-15. Association between personal exposure concentration and ambient concentration (pooled correlation coefficients).

Study	Study Design	Season	Mean Conc. (ppb)	Statistics	Comments
Brauer et al. (1989)	Pooled, Boston, study population was NR, the number of participants was estimated to be 48, July and August of 1988 for 24 days, 1 day averaged sample, two subjects were monitored each day.	Summer	Ambient: 2.5 – 9.5 Personal: 0.4 – 1.8	Slope: 0.13* (N=44) Intercept: Not significant R^2: 0.43	1) Concentrations estimated from Figure 2 in the paper. 2) Central site monitor was 250 m above the ground level. 3) LOD for personal samples was ~0.19 ppb based on the method of determining the LOD for an active sampling system.
Sarnat et al. (2006a)	Steubenville, 15 senior subjects, summer and fall of 2000, two consecutive 24-h samples were collected for each subject for each wk, 23 wks total. Correlation coefficients were calculated in the pooled data set.	Summer	Ambient: 2.7 ± 3.9 Personal: 1.5 ± 3.3	Slope: 0.03 (N=106) Intercept: NR R^2: 0.00	LOD was 5.5 ppb; 53.5% of personal samples were below LOD.
		Fall	Ambient: 5.4 ± 9.6 Personal: 0.7 ± 1.9	Slope: 0.08* (N=152) Intercept: NR R^2: 0.15	LOD was 3.8 ppb, and 31.6% of personal samples were below LOD.

* significant at $\alpha = 0.05$ level

There are three types of correlations generated from different study designs and ways to analyze the data from exposure studies: longitudinal, "pooled," and daily-avg correlations (U.S. EPA, 2004). Longitudinal correlations[1] are calculated when data from a study includes measurements over multiple days for each subject (longitudinal study design). Longitudinal correlations describe the temporal relationship between daily personal SO_2 exposure or microenvironment concentration and daily ambient SO_2 concentration for the same subject. The longitudinal correlation coefficient can differ between subjects (i.e., each person may have a different correlation coefficient). The distribution of correlations for each subject across a population could be obtained with this type of data (e.g., Sarnat et al., 2000; 2001; 2005). A longitudinal correlation coefficient between the ambient component of personal exposures and ambient concentrations is relevant to the panel epidemiologic study design. In Table 2-14, most longitudinal studies reported the association between personal total exposures and ambient concentrations for each subject. For some subjects the associations were strong and for some subjects the associations were weak. The weak personal and ambient associations do not necessarily mean that ambient

[1] $r_{ax_i} = \frac{\sum_j \left(x_{ij} - \overline{x_i}\right)\left(a_j - \overline{a}\right)}{(n-1)s_{x_i} s_a}$ where "r" is the longitudinal correlation coefficient between personal exposure and ambient concentration, "a" represents the ambient concentration, "x" represents exposure, "i" represents the ith subject, "j" represents the jth measurement (with the averaging time ranging from two days to two weeks for SO_2 measurement), "s" represents the standard deviation, and "n" in the longitudinal studies is the number of measurements for each subject. The ambient concentration a_j could be measured by one ambient monitor or the average of several ambient monitors.

concentrations are not a good surrogate for personal exposures, because the weak associations could have resulted from the day-to-day variation in the nonambient component of total personal exposure. These types of correlations can have a substantial effect on the value of the resultant correlation coefficient. Mage et al. (1999) showed that very low correlations between personal exposure and ambient concentrations could be obtained when people with very different nonambient exposures are pooled, even though their individual longitudinal correlations are high.

Pooled correlations[1] are calculated when a study involves one or only a few measurements per subject and when different subjects are studied on subsequent days. Pooled correlations combine individual-subject/individual-day data for the calculation of correlations. Pooled correlations describe the relationship between daily personal SO_2 exposure and daily ambient SO_2 concentration across all subjects in the study (e.g., Brauer et al., 1989; Sarnat et al., 2006a).

Daily-avg correlations[2] are calculated by averaging exposure across subjects for each day. Daily-avg correlations then describe the relationship between the daily avg exposure and daily ambient pollutant concentration. This type of correlation (i.e., the association between the ambient component of community avg exposures and ambient concentrations) is more directly relevant to community time-series studies, in which ambient concentrations are used as a surrogate for community avg exposure to pollutants of ambient origin. However, exposure of the population to SO_2 of ambient origin has not been reported in any of the studies examined.

Not only does the exposure study design determine the meaning of the correlation coefficients in the context of exposure assessment in epidemiologic studies, but the type of correlation calculation also affects the strength of the association between personal exposures and ambient concentrations. The strength of the association between personal exposures with ambient and/or outdoor concentrations for a population is determined by variations in several physical factors: indoor or other local sources, air exchange rate, penetration, decay rate of the pollutant in different microenvironments, and the time people spend in different microenvironments with different pollutant concentrations. For different types of correlation coefficients, the components of the variance of these physical factors are different, and therefore the strength of different types of correlation coefficients is different. Longitudinal correlation coefficients reflect the *interpersonal* variations of these physical factors. Pooled correlation coefficient reflect both *inter*- and *intra*- personal variations of these physical factors. For the association between community avg exposures and ambient concentrations, *interpersonal* variations of these physical factors are reduced by averaging personal exposures across a community. Therefore, the strength of the associations between personal exposures and ambient concentrations may not be directly comparable, although these associations are determined by the same set of physical factors (but affected in different ways).

Since correlations are standardized quantities that depend on multiple features of the data not only is the linear "relatedness" (covariance) of the two quantities important in a correlation, but so is the variability of each. That variability can be affected by exposure factors in various ways. In the following assessments, the effects of these physical factors on the strength of correlation coefficients are primarily

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[1] $r_{ax} = \frac{\sum_{i,j}(x_{ij} - \bar{x})(a_j - \bar{a})}{(n-1)s_x s_a}$ where "*r*" is the pooled correlation coefficient and "*n*" is the number of paired measurements of exposure and ambient concentration, and all other symbols are defined the same way as those in the longitudinal correlation coefficient.

[2] $r_{a\bar{x}} = \frac{\sum_{j}(\bar{x_j} - \bar{x})(a_j - \bar{a})}{(n-1)s_{\bar{x}_j} s_a}$, where "*r*" is the daily-average correlation coefficient and "*n*" is the number of measurement period, during each of which the exposure for all subjects are measured, and all other symbols are defined the same way as those in the longitudinal correlation coefficient.

examined *within* a study, and the purpose of the inter-study comparison is to examine the consistency of the effects across different types of studies.

The strength of the associations between personal exposures and ambient concentrations could also be affected by the quality of the data collected during the exposure studies. There are at least six aspects associated with the quality of the data: method precision, method accuracy (compared with FRM), percent of data above method detection limits (based on field blanks), completeness of the data collection, sample size, and soundness of the quality assurance/quality control procedures. Unfortunately, not all studies reported the six aspects of the data quality issue. The fraction of data below the detection limit might be a concern for some studies (Sarnat et al., 2000; 2001; 2005). Correlation coefficients would be biased low if data used in their calculation are below detection limits. Sampling interferences associated with both ambient (see Section 2.3) and personal sampling (see Section 2.6.2) could also affect data quality. Therefore, caution must be exercised when interpreting the results in Table 2-14 and Table 2-15. Sarnat et al. (2001; 2005; 2006a) examined the associations between ambient SO_2 concentrations and ambient or personal co-pollutant concentrations. Sarnat et al. (2001) reported that during the winter of 1999, ambient SO_2 was significantly associated ($p < 0.05$) with personal exposure to fine particulate matter ($PM_{2.5}$) (slope = − 0.24), personal exposure to SO_4^{2-} (slope = − 0.03), and personal exposure to $PM_{2.5}$ of ambient origin (slope = − 0.16). However, it should be noted that all the slopes are negative perhaps as the result of measurement error. Sarnat et al. (2005) reported that significant associations between ambient SO_2 and either personal exposures or ambient concentrations of other pollutants were found for personal SO_4^{2-} (winter, slope = 0.06); (summer, slope = 0.39); personal $PM_{2.5}$ (summer, slope = 1.68), ambient SO_4^{2-} (winter, slope = 0.19); and ambient $PM_{2.5}$ (winter, slope = 0.80). In Sarnat et al. (2006a), ambient SO_2 was observed to be significantly associated with ambient $PM_{2.5}$, ambient SO_4^{2-}, and ambient elemental carbon (EC) during the fall (R^2 = 0.22, 0.33, and 0.34 respectively). It was significantly associated with personal $PM_{2.5}$ during the summer, and personal SO_4^{2-} and personal EC during the fall (R^2 = 0.07, 0.06, and 0.05 respectively).

Of significant concern is the ability of currently available techniques for monitoring either personal exposures or ambient concentrations to measure SO_2 concentrations that are typically found in most urban environments. In some studies, most data might be beneath detection limits. This is especially true for personal exposure and indoor data. Indeed, in one study (Chang et al., 2000), the investigators had to discard data for SO_2 because the values were mostly beneath detection limits. In the study of Kindzierski and Ranganathan (2006), all indoor concentration data were beneath detection limits. In Sarnat et al. (2000), ~70% of personal measurements were beneath detection limits, and ~33% of personal measurements returned apparent negative concentration values. In such situations, associations between ambient concentrations and personal exposure are inadequately characterized. When personal exposure concentrations are above detection limits, a reasonably strong association is observed between personal exposures and ambient concentrations.

2.6.4. Exposure Errors in Epidemiologic Studies

This assessment considered the errors that result from using the ambient concentration of an air pollutant as an exposure indicator rather than using the actual personal exposure to that air pollutant in the epidemiologic statistical analysis. Such errors change both the health effects estimate, expressed as the relative risk factor, β, and the standard error of β. There are many assumptions made in going from the available measurement of a pollution indicator to an estimate of the personal exposure. The importance of these assumptions and their effect on β depend on the type of epidemiologic study.

The considerations of exposure error for SO_2 are simplified compared to those for NO_2 and PM. The only experimental measure available is the ambient concentration of SO_2. In addition, indoor and other non-ambient sources of SO_2 are not thought to be important in population studies, lessening concerns about the possible influence of exposures other than to ambient SO_2. However, because SO_2 is

rapidly removed by interaction with surfaces (more slowly than O_3 but more rapidly than NO_2 or PM), the ratio of indoor concentrations to outdoor concentrations will be lower, and perhaps more variable than in the case of NO_2, PM and CO (which is relatively un-reactive with surfaces).

2.6.4.1. Community Time-Series Studies

This section applies primarily to studies on the association of daily avg SO_2 concentrations with daily measures of mortality or morbidity in a community. The following three exposure issues are of primary concern with respect to SO_2 time-series epidemiologic analysis: (1) the relationship of the measured concentration of SO_2 to the true concentration; (2) the relationship of day-to-day variations in the concentrations of SO_2, as measured at a central monitoring site, with the corresponding variations in the avg concentration of SO_2 over the geographic area from which the health measurements are drawn; and (3) the relationship of the community avg concentration of SO_2 to the avg personal exposure to ambient SO_2. These three issues are described below.

Relationship of Measured SO_2 to the True Concentration

Since there is always a random component to instrumental measurement error, the correlation of the measured SO_2 with the true SO_2, on either a 24-h or 1-h basis, will be less than 1. Sheppard et al. (2005) indicate that instrument error in the individual or daily avg concentrations have "the effect of attenuating the estimate of α." Zeger et al. (2000) suggest that instrument error has both Berkson and non-Berkson error components. However, the authors state that the "instrument error in the ambient levels is close to the Berkson type." In order for this error to cause substantial bias in β, the error term (the difference between the true concentrations and the measured concentrations) must be strongly correlated with the measured concentrations. Zeger et al. (2000) suggest that, "further investigations of this correlation in cities with many monitors are warranted." Averaging across multiple unbiased ambient monitors in a region should reduce the instrument measurement error (Sheppard et al., 2005; Wilson and Brauer, 2006; Zeger et al., 2000). There are concerns about the precision and accuracy of the ambient concentration measurements because SO_2 concentrations are much lower now than when the SO_2 standards were first promulgated. Typical ambient concentrations of SO_2 in the contiguous U.S. are nearly all at or beneath the detection limit of the monitors currently used in the regulatory network. Thus, greater relative error is most often observed at the lower ambient concentrations compared to the less frequent higher concentration exposures, as might occur because of plume downwash near local point sources or entrainment of plumes downwind from large power plants or smelters. It is unclear how uncertainties in the true concentrations of SO_2, i.e., instrument measurement error, will change β.

Relationship of Day-to-day Variations in the Ambient Concentration of SO_2 to Variations in the Community Average

There has been little analysis of the spatial variation of SO_2 across communities. SO_2 emissions arise mainly from coal fired power plants (see Annex Table B-4). Newer power plants and smelters in the U.S. are no longer located within urban centers. However, some older power plants and industrial facilities are located in many urban areas, especially in the Midwest and Northeast. Downwash from the plumes emitted from these facilities can contribute to elevated levels of SO_2 at the surface in these cities. However, it is anticipated that SO_2 will behave largely as a regional pollutant in most areas.

Site-to-site correlations of SO_2 concentrations, as shown for several cities in Table 2-9 vary from very low to very high values. This suggests that the concentration of SO_2, measured at any given monitoring site, may not be highly correlated with the avg community concentration in some areas. There are a number of possible reasons for these findings: local sources that cause the SO_2 to be unevenly distributed spatially; a monitoring site being chosen to represent a nearby source; terrain features that

divide the community into several sub-communities that differ in the spatial and temporal pattern of pollution; and errors in the measurement of the low concentrations of SO_2 present at most sites. To the extent that the correlation of the ambient concentration with the community avg concentration is < 1, β will be reduced. Similarly, β will be reduced if there are subareas of the community where the correlation between the local avg concentrations and the concentrations measured at the ambient monitoring site is < 1. If concentrations in an area of a community impacted by plumes from local SO_2 sources might be higher than, and not well-correlated with, the concentrations at the ambient monitor, and if such high concentrations affect a sizable portion of the population exposed to emissions from a local source, that community might not be suitable for time-series epidemiologic analyses. On the other hand, if the plume impacts the ambient monitor, the high concentration of SO_2 not accompanied by a corresponding high effect in the entire community will bias β toward the null.

An additional complication will arise if location near a source is correlated with sensitivity. For example, if poverty causes sensitivity due to poor nutrition, and land prices decline the closer one gets to a major source, then exposure and sensitivity will be correlated. If the day to day variations in the concentrations due to the source are correlated with the day to day variations in the ambient concentrations used in the epidemiologic analysis, β will be increased above the β that would be found if the exposure and sensitivity were not correlated. However, it is more likely that the variations in the concentrations related to the source are not correlated with the ambient concentrations. In this case the health effects from the source SO_2 would not contribute to β and β would be decreased compared to a uniform distribution of sensitivity.

Relationship of Community Average Concentration of SO_2 to Average Personal Exposure to Ambient SO_2

People spend much of their time indoors, and in the absence of indoor sources, indoor concentrations are lower than outdoor concentrations. This is very likely the case with SO_2, since the only known significant indoor source of SO_2 in the U.S. is the use of kerosene heaters, which is not thought to be widespread enough to influence population studies. Differences in infiltration factors among homes can also result in differences among individuals' personal exposures. It is necessary to consider how this difference between the ambient concentration, which is used in epidemiologic analyses, and the personal ambient exposure (which includes exposure to the full outdoor concentration while outdoors and exposure of only a fraction of the outdoor concentrations while indoors) will affect the calculated β. Personal exposure to ambient SO_2 is given by $Ea = \alpha \bullet C_a$ where E_a is exposure to ambient SO_2, α is the ambient exposure factor with values between 0 and 1, and *Ca* is the ambient SO_2 concentration as measured at a community monitoring site. Zeger et al. (2000) noted that for community time-series epidemiology, which analyzes the association between health effects and potential causal factors at the community scale rather than the individual scale, it is the correlation of the daily avg ambient concentrations with the daily *community average* personal exposures that is important, not the correlation between the daily avg ambient concentrations and *the individual* personal exposures. Thus, as mentioned in Section 2.6.3, the low correlation between daily avg ambient concentrations and individual personal exposures, as frequently found in pooled panel exposure studies, is not relevant to community time-series epidemiologic analysis. Unfortunately, no studies provide adequate information about the community avg personal exposure to SO_2.

There has also been concern with the variation of α. Zeger et al. (2000) suggested (for PM) that variations in the individual daily values of α would be a Berkson error and would not change the point estimate of β, although such variations would increase the standard error of β. Sheppard et al. (2005) used simulations to confirm this for nonreactive pollutants. However, such variations increase the standard error. Day-to-day variations in the population avg fraction of ambient exposure will not change the point estimate of β unless the population avg fraction of ambient exposure is correlated with seasonal trends in ambient concentration, according to Sheppard et al. (2005).

In the case of a correlation of location near a source with sensitivity, the health effects of the higher concentrations will be attributed to the avg concentration and β will be increased. A similar but lesser effect on β will occur anytime there are high concentrations resulting from localized sources that are not included in the long-term avg concentration and that vary from city to city.

Both Zeger et al. (2000) and Sheppard et al. (2005) show that if β^A is the health effect parameter that would be obtained with a time-series analysis using the ambient exposure and β^C is the health effect parameter that would be obtained with a time-series analysis using the ambient concentration, then $\beta^C = \alpha \bullet \beta^A$. Thus, time-series studies yield different parameters depending on whether they use concentration or exposure. However, the two parameters are related by α.

2.6.4.2. Short-Term Panel Studies

Panel epidemiology refers to studies that follow a relatively small number of subjects for a relatively short time. Panel studies typically examine the association between symptoms or health outcomes of individuals and either ambient concentrations or personal exposures. Personal exposures to SO_2 usually are not measured. Rather, ambient concentrations are more often used in panel studies. Similar types of exposure error as discussed for community time series apply to panel studies.

The ambient exposure factor (α) may differ for each person and each day leading to error in the exposure estimate. If a panel is composed of subjects who live in similar housing and have similar activity pattern, and the study is limited to a single season, the variation in α over time and individual subjects may be small. However, if the panels are composed of more diverse subjects or extend for more than one season, values of α may be quite variable. Such variability will affect the estimate of exposure for each subject.

2.6.4.3. Long-Term Cohort Studies

For long-term exposure epidemiologic studies, concentrations are integrated over time periods of a year or more and usually for spatial areas the size of a city, county, or metropolitan statistical area (MSA), although integration over smaller areas may be feasible. These studies focus on spatial variations in concentrations. Health effects are then regressed in a statistical model against the avg concentrations in the series of cities (or other areas). In time-series studies, a constant difference between the measured and the true concentration (instrument offset) will not affect β, nor will variations in the daily average α or the daily avg nonambient exposure, unless the variations are correlated with the daily variations in concentrations. However, in long-term exposure epidemiologic studies, if instrument measurement errors, long-term avg values of α, or long-term averages of nonambient exposure differ for different cities (or other areas used in the analysis), the city-to-city long-term ambient SO_2 concentrations will not be perfectly correlated with the long-term avg exposure to either ambient or total SO_2. This lack of correlation would be expected to bias the point estimate of β.

2.6.4.4. Summary of Evaluation of Exposure Error in Epidemiologic Studies

Exposure error caused by using ambient concentrations of SO_2 as a surrogate for exposure to ambient SO_2 affect β in different ways, depending upon the type of epidemiologic study. In community time-series and short-term panel epidemiologic studies, the nonambient source component of personal exposure and the variation in the ambient exposure factor caused by building ventilation practices and personal behaviors generally will not change the estimate of β. But, the spatial variation of SO_2 or the representativeness of the ambient monitor might bias the estimate of β toward null. Therefore, β observed in SO_2 community time-series or panel epidemiologic studies would be stronger and less uncertain if exposure errors had been adjusted and/or controlled. In long-term cohort epidemiologic studies,

instrument measurement errors, factors that influence exposure to ambient SO_2, or long-term averages of nonambient exposure may differ for different cities, which may bias the estimate of β, but the extent and direction of this bias is unclear.

2.7. Dosimetry of Inhaled Sulfur Oxides

This section is intended to present an overview of general concepts related to the dosimetry of SO_2 in the respiratory tract. Dosimetry of SO_2 refers to the measurement or estimation of the amount of SO_2 or its reaction products reaching and persisting at specific respiratory tract and systemic sites after exposure. One of the principal effects of inhaled SO_2 is that it stimulates bronchial epithelial irritant receptors and initiates a reflexive contraction of smooth muscles in the bronchial airways. The compound most directly responsible for health effects may be the inhaled SO_2, and/or its chemical reaction products. Complete identification of the causative agents and their integration into SO_2 dosimetry is a complex issue that has not been thoroughly evaluated. Few studies have investigated SO_2 dosimetry in the interval since the 1982 AQCD and the 1986 Second Addendum.

2.7.1. Respiratory Gas Deposition

The major factors affecting the transport and fate of gases and aerosols in the respiratory tract are: the morphology of the respiratory tract; the physiochemical properties of the mucus and surfactant layers; respiratory functional parameters such as tidal volume, flow rate, and route of breathing; physicochemical properties of the gas; and the physical processes that govern gas transport. Physicochemical properties of SO_2 relevant to respiratory tract uptake include its solubility and diffusivity in epithelial lining fluid (ELF), as well as its reaction-rate with ELF constituents. Henry's law relates the gas phase and liquid phase interfacial concentrations at equilibrium, and is a function of temperature and pressure. Henry's law shows that the amount of SO_2 in the aqueous phase is directly proportional to the partial pressure or concentration of SO_2 in the gas phase. Although the solubility of most gases in mucus and surfactant is not known, the Henry's law constant is known for many gases in water. Inversely proportional to solubility, the Henry's law constant for SO_2 is 0.048 (mole/liter) air / (mole/liter) water at 37° C and 1 atm. For comparison, the value for O_3 is 6.4 under the same conditions (Kimbell and Miller, 1999). In general, the more soluble a gas is in biological fluids, the more rapid and proximal its absorption will be in the respiratory tract. When the partial pressure of SO_2 on mucosal surfaces exceeds that of the gas phase, such as during expiration, some desorption of SO_2 from the ELF may be expected.

Because SO_2 is highly soluble in water, it is expected to be almost completely absorbed in the nasal passages of both humans and laboratory animals under resting conditions. The dosimetry of SO_2 can be contrasted with the lower solubility gas, O_3, for which the predicted tissue doses (O_3 flux to liquid-tissue interface) are very low in the trachea and increase to a maximum in the terminal bronchioles or first airway generation in the pulmonary region (see Chapter 4, U.S. EPA, 2006b). Similar to O_3, the nasal passages remove SO_2 more efficiently than the oral pathway (Brain, 1970; Melville, 1970; Nodelman and Ultman, 1999). With exercise, the pattern of SO_2 absorption shifts from the upper airways to the tracheobronchial airways in conjunction with a shift from nasal to oronasal breathing and increased ventilatory rates. As a result of its effect on delivery and uptake, mode of breathing is also recognized as an important determinant of the severity of SO_2-induced bronchoconstriction. The greatest responses occur during oral breathing followed by oronasal breathing, and the smallest responses were observed during nasal breathing.

Andersen et al. (1974) measured the nasal absorption of SO_2 (25 ppm) in 7 volunteers during inspiration at an avg inspired flow of 23 L/min (i.e., eucapnic hyperpnea [presumably] to simulate light

exertion). These investigators reported that the oropharyngeal SO_2 concentration was below their limit of detection (0.25 ppm), implying that at least 99% of SO_2 was absorbed in the nose of subjects during inspiration. Speizer and Frank (1966) also measured the absorption of SO_2 (16.1 ppm) in 7 healthy subjects at an avg ventilation of 8.5 L/min (i.e., at rest). They reported that 14% of the inhaled SO_2 was absorbed within the first 2 cm into the nose. The concentration of SO_2 reaching the pharynx was below the limit of detection, suggesting that at least 99% was absorbed during inspiration. Melville (1970) measured the absorption of SO_2 (1.5 to 3.4 ppm) during nasal and oral breathing in 12 healthy volunteers. Total respiratory tract absorption of SO_2 was significantly greater ($p < 0.01$) during nasal than oral breathing (85 versus 70%, respectively) and was independent of the inspired concentration. Melville (1970) did not report respired flow rates, so the effect of flow on the SO_2 absorption could not be discerned. However, it may be noted that the total respiratory absorption during nasal breathing reported by Melville (1970) was clearly less than the nasal absorption reported by both Andersen et al. (1974) and Speizer and Frank (1966). The disparity in nasal absorption between these studies is, in part, due to desorption of SO_2 during expiration as discussed in Section 2.7.3.

Frank et al. (1969) and Brain (1970) investigated the oral and nasal absorption of SO_2 in the surgically isolated upper respiratory tract of anesthetized dogs. Radiolabeled SO_2 ($^{35}SO_2$) at the concentrations of 1, 10, and 50 ppm was passed separately through the nose and mouth at the steady unidirectional flows of 3.5 and 35 L/min for 5 min. The nasal absorption of SO_2 (1 ppm) was 99.9% at 3.5 L/min and 96.8% at 35 L/min. The oral absorption of SO_2 (1 ppm) was 99.56% at 3.5 L/min, but only 34% at 35 L/min. The nasal absorption of SO_2 at 3.5 L/min increased with concentration at 1, 10, and 50 ppm and was reported to be 99.9, 99.99, and 99.999%, respectively. This increase in absorption with concentration was hypothesized to be due to increased mucus secretion and increased nasal resistance at the higher SO_2 concentrations. The increased mucus was thought to provide a larger reservoir for SO_2 uptake. The increased nasal resistance may increase turbulence in the airflow and, thereby, decrease the boundary layer between the gas and liquid phases. Dissimilar to the nose, SO_2 absorption in the mouth decreased from 99.56 to 96.3% when the concentration was increased from 1 to 10 ppm at 3.5 L/min. Frank et al. (1969) noted that the aperture of the mouth may vary considerably, and that this variation may affect SO_2 uptake in the mouth. Although SO_2 absorption was dependent on inhaled concentration, the rate and route of flow had a greater effect on the magnitude of SO_2 absorption in the upper airways.

Strandberg (1964) studied the uptake of SO_2 in the respiratory tract of rabbits. A tracheal cannula with two outlets was utilized to allow sampling of inspired and expired air, and SO_2 absorption was observed to depend on inhaled concentration. The absorption during maximal inspiration was 95% at high concentrations (100 to 700 ppm), reflecting an increased SO_2 removal in the extrathoracic (ET) region, whereas it was only 40% at low concentrations (0.05 to 0.1 ppm). On expiration, the total SO_2 absorbed (i.e., inspiratory removal in the ET region plus removal in the lower airways) was 98% at high concentrations and only 80% at the lower concentrations.

Amdur (1966) examined changes in airway resistance in guinea pigs due to SO_2 exposure. Guinea pigs were exposed for 1-h to 0.1 to 800 ppm SO_2 during natural unencumbered breathing or to 0.4 to 100 ppm while breathing through a tracheal cannula. At concentrations of 0.4- to 0.5 ppm SO_2, route of administration did not affect the airway resistance response, whereas at concentrations of > 2 ppm, the responses were greater in animals exposed by tracheal cannula. Based on the concentration-dependent absorption of SO_2 in the ET region observed by Strandberg (1964), Amdur (1966) concluded that the airway resistance responses at low-exposure concentrations were independent of method of administration, because the lung received nearly the same concentration with or without the cannula as evidenced by minimal ET absorption.

More recently, Ben-Jebria et al. (1990) investigated the absorption of SO_2 in excised porcine tracheae. Absorption was monitored over a 30-min period following the introduction of SO_2 (0.1 to 0.6 ppm, inlet concentration) at a constant flow (2.7 to 11 L/min). The data were analyzed using diffusion-reactor theory. An overall mass transfer coefficient (KSO_2) was determined and separated into its contributions due to gas (convection and diffusion) and tissue phase (diffusivity, solubility, and reaction rates) resistances. SO_2 in the liquid phase was assumed to form HSO_3^- rapidly, in proportion with the gas

phase SO_2 concentration. HSO_3^- then diffused down the concentration gradient into the tissues where it reacted irreversibly with biochemical substrates. Initially, KSO_2 was limited only by gas phase resistance, but it decreased exponentially over the first 5 to 10 min of SO_2 exposure to a smaller steady-state value that was due to tissue resistance to SO_2 absorption. The initial and steady-state KSO_2 values were found to be independent of inlet SO_2 concentration, i.e., for a given flow, the fractional absorption of SO_2 did not depend on SO_2 concentration. An increased K_{SO2} (initial and steady-state) was observed with an increasing flow that was thought to be due to a decrease in the boundary layer near the walls of the trachea for radial SO_2 transport. This is in agreement with Aharonson et al. (1974), who also reported that the transfer rate coefficient for SO_2 increases with increasing flow. However, the initial molar flux of SO_2 across the gas-tissue interface appears to increase purely as a function of the increase in mass transport occurring with increasing flow (see Figure 5 in Ben-Jebria et al., 1990). Given that the steady-state KSO_2 remained stable during the 10 to 30 min of exposure and that no SO_2 leakage through the tissue was identified, the authors concluded that there was an irreversible sink for SO_2 within the tissue.

Mathematical modeling specific to the regional respiratory uptake of SO_2 is unavailable for humans and laboratory animals. More generally, the influence of age on gas dosimetry in humans during light activity (on average) was examined by Ginsberg et al. (2005) using the U.S. EPA reference concentration methodology (U.S. EPA, 1994a). For a highly soluble gas, such as SO_2, they predicted that the majority of gas uptake would occur in the ET region and that the fractional uptake in these airways would be modestly greater in a 3-month-old infant than an adult. The rate of gas uptake per surface, however, in the ET region and large bronchial airways was not markedly different between infants and adults. The smaller bronchial airways of adults were predicted to receive a greater dose (i.e., uptake per unit time and surface area) relative to infants, although the majority of the inhaled SO_2 would be removed proximal to these airways.

In summary, inhaled SO_2 is readily absorbed in the upper airways of both humans and laboratory animals. During nasal breathing, the majority of available data suggests 95% or greater SO_2 absorption occurs in the nasal passages, even under ventilation levels comparable to exercise. Somewhat less SO_2 is absorbed in the oral passage than in the nasal passages. The difference in SO_2 absorption between the mouth and the nose is highly dependent on respired flow rates. With an increase in flow from 3.5 to 35 L/min, nasal absorption is relatively unaffected, whereas oral absorption is reduced from 100 to 34%. Thus, the rate and route of breathing have a great effect on the magnitude of SO_2 absorption in the upper airways and so the penetration of SO_2 to the lower airways. Overall, the available data clearly show that the pattern of SO_2 absorption that shifts from the upper airways to the tracheobronchial airways in conjunction with a shift from nasal to oronasal breathing and associated increased ventilatory rates in exercising humans. Mode of breathing is also recognized as an important determinant of the severity of SO_2 induced bronchoconstriction, with the greatest responses occurring during oral breathing followed by oronasal breathing and the smallest responses observed during nasal breathing.

2.7.2. Particles and Sulfur Oxide Mixtures

As already discussed, inhaled SO_2 is readily absorbed in the upper airways, particularly during nasal breathing. It has been suggested that SO_X may become absorbed to particles and subsequently transported to more distal lung regions. Depending on atmospheric conditions, SO_2 can be transformed to secondary sulfate particles and acid aerosols (H_2SO_4) and can adsorb onto particulate matter (see Section 2.2). Jakab et al. (1996) observed that the conversion of SO_2 to SO_4^{2-} on the surface of carbon black aerosols was dependent on high relative humidity ($\geq$ 85%) and SO_2 concentration. These investigators suggested that fine carbon black particles can be an effective vector for delivery of SO_4^{2-} to the peripheral lung. This is not believed to be a mechanism for bringing sulfite into the deep lung. Other studies investigating the effects of SO_2 coated aerosols are briefly discussed in Section 3.1.4.7.

Sulfate aerosols are hygroscopic and grow in the respiratory tract. The implications of hygroscopic growth on deposition have been reviewed extensively by Morrow (1986) and Hiller (1991). 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 (aerodynamic diameter), the influence of hygroscopicity would be to increase total deposition with a shift in regional deposition from the distal to larger proximal airways; for smaller particles deposition would tend to decrease. A thorough review of respiratory deposition and clearance of particulate matter is available elsewhere (U.S. EPA, 1996, 2004). The intent herein was to briefly mention some issues specific to SO_x.

2.7.3. Distribution and Elimination of SO_X

When SO_2 contacts the fluids lining the airway, it dissolves into the aqueous fluid and forms hydrogen (H^+) ions and bisulfite (HSO_3^-) and sulfite (SO_3^{2-}) anions (ATS, "Health effects of outdoor air pollution. Committee of the Environmental and Occupational Health Assembly of the American Thoracic Society," 1996). The majority of anions are expected to be present as HSO_3^- at a concentration proportional to the gas phase concentration of SO_2 (Ben-Jebria et al., 1990). Because of the chemical reactivity of these anions, various reactions are possible, leading to the oxidation of SO_3^{2-} to SO_4^{2-} (see Section 12.2.1, U.S. EPA, 1982). Clearance of SO_3^{2-} from the respiratory tract may involve several intermediate chemical reactions and transformations. Gunnison and Benton (1971) identified *S*-sulfonate in blood as a reaction product of inhaled SO_2. Following inhalation of SO_2, the clearance half-time of 4.1 days for *S*-sulfonate in rabbits has been reported (Gunnison and Palmes, 1973).

Some SO_2 is also removed by desorption of from the respiratory tract. Desorption is expected when the partial pressure of SO_2 in airway lining fluids exceeds that of the air. Speizer and Frank (1966) found that on expiration, 12% of the SO_2 absorbed during inspiration was desorbed into the expired air. During the first 15 min after the 25- to 30-min SO_2 exposure, another 3% was desorbed. In total, 15% of the amount of SO_2 originally inspired and absorbed was desorbed from the nasal mucosa. Frank et al. (1969) reported that up to 18% of the SO_2 was desorbed within ~10 min after exposure.

Chapter 3. Integrated Health Effects

This integrated discussion is structured to provide a coherent framework for the assessment of health risks associated with human exposure to ambient SO_2 in the U.S.. The main goals of this chapter are: (1) to integrate newly available epidemiologic, human clinical, and animal toxicological evidence with consideration of key findings and conclusions from the 1982 AQCD for Sulfur Oxides and First Addendum (U.S. EPA, 1982), 1986 Second Addendum (U.S. EPA, 1986b), and 1994 Supplement to the Second Addendum, (U.S. EPA, 1994c); and (2) to draw conclusions about the causal role of SO_2 in relation to a variety of health effects. These causal determinations utilize the framework outlined in Chapter 1.

This chapter is organized to present morbidity and mortality associated with short-term exposures to SO_2, followed by morbidity and mortality associated with long-term exposures. Human clinical studies examining the effect of peak exposures (less than 1-h, generally 5-10 min) of SO_2 on respiratory symptoms and lung function are discussed first. Later sections describe the findings of epidemiologic studies that examine the association between short-term (generally 24-h avg) and long-term (generally months to years) ambient SO_2 exposure and health outcomes, such as respiratory symptoms in children and asthmatics, emergency department (ED) visits and hospital admissions for respiratory and cardiovascular diseases, and premature mortality. The human clinical and epidemiologic evidence are presented with relevant animal toxicological data, when available.

The evaluation of epidemiologic evidence involves consideration of sources of uncertainty, as discussed in Chapter 1, including exposure error, potential confounders or effect modifiers, statistical modeling issues, publication bias, and multiple testing. Efforts have been made to assess the impact of these uncertainties in the evaluation of the epidemiologic literature. For example, in studies examining multiple single-day lag models, the pattern of association across the various lags was evaluated. Additional focus was placed on results from distributed and moving avg lags as they are able to examine multiday effects. Both single- and multiple-pollutant models were considered and examined for robustness of results. Additional analyses of multiple model specifications for adjustment of temporal or meteorological trends were regarded as sensitivity analyses. Further, the evaluation of the epidemiologic evidence also considered study population and sample size, with particular emphasis placed on multicity studies that by their very nature can reduce uncertainty related to publication bias. Other factors considered were study location (North America versus other regions), meaningfulness and validity of the health endpoint measurements, and appropriateness of the statistical analyses methods used. These considerations led to emphasis of certain studies in the chapter text, tables, and figures.

Animal toxicological studies may provide further evidence for the potential mechanism of an observed effect; however, most of these studies have been conducted at concentrations vastly exceeding current ambient conditions. In discussing the mechanisms of SO_X toxicity, studies conducted under atmospherically relevant conditions are emphasized whenever possible; studies at higher levels are also considered, due to species-to-species differences and potential differences in sensitivity between study subjects and especially susceptible human populations.

This chapter focuses on important recent scientific studies, with emphasis on those conducted at or near current ambient concentrations. Given their respective strengths and limitations, evidence from human clinical, epidemiologic, and animal toxicological studies was considered in order to evaluate the causality of SO_X–health effects associations. The annexes supplement the information included here by presenting more details of the literature.

3.1. Respiratory Morbidity Associated with Short-Term Exposure

3.1.1. Summary of Findings from the Previous Review

The majority of the SO_2 human clinical studies discussed in the 1982 AQCD for SO_X evaluated respiratory effects of SO_2 exposure in healthy adults, with some limited data from clinical studies of adults with asthma. SO_2-related respiratory effects such as increased airway resistance and decreased forced expiratory volume in 1 s (FEV_1) were observed in healthy individuals at concentrations > 1.0-5.0 ppm, and in asthmatics at concentrations < 1.0 ppm. The 1986 Second Addendum (U.S. EPA, 1986b) and 1994 Supplement to the Second Addendum (U.S. EPA, 1994c) reviewed several additional controlled studies involving both healthy and asthmatic individuals. In general, these studies found no pulmonary effects of SO_2 exposure in healthy subjects exposed to concentrations ≤ 1.0 ppm (Bedi et al., 1984; Folinsbee et al., 1985; Kulle et al., 1984; Stacy et al., 1983). However, in exposures of asthmatic adults, respiratory effects were observed following short-term exposures (5-10 min) to levels < 1.0 ppm (Balmes et al., 1987; Horstman et al., 1986; Linn et al., 1987).

Only a few epidemiologic studies reviewed in the 1982 AQCD were useful in determining the concentration-response relationship of respiratory health effects from short-term exposure to SO_2. The most notable study was by Lawther et al. (1970), which examined the association between air pollution and worsening health status in bronchitic patients residing in London, England. It was concluded in the 1982 AQCD that worsening of health status among chronic bronchitic patients was associated with daily black smoke (BS) levels of 250-500 $\mu g/m^3$ in the presence of SO_2 levels in the range of 191-229 ppb. In the 1986 Second Addendum, additional studies investigated morbidity associated with short-term exposure to SO_2. The most relevant study was by Dockery et al. (1982), which examined pulmonary function in school children in Steubenville, OH, as part of the Harvard Six Cities Study. This study found that small but statistically significant reversible decrements in forced vital capacity (FVC) and forced expiratory volume in 0.75 s ($FEV_{0.75}$) were associated with increases in 24-h avg concentrations of total suspended particles (TSP) at levels ranging up to 220-420 $\mu g/m^3$ and SO_2 at levels ranging up to 107-176 ppb. However, it was impossible to separate the relative contributions of TSP and SO_2, and no threshold level for the observed effects could be discerned from the wide range of exposure levels.

Epidemiologic evidence for an association between SO_2 and respiratory morbidity, as indicated by increased use of ED facilities or increased hospital admissions for respiratory diseases, was also reported in the 1982 AQCD. Overall, these results suggested increased upper respiratory tract morbidity during episodic marked elevations of PM or SO_2 (400-500 ppb), especially among older adults. The 1982 AQCD further concluded that the studies reviewed provided essentially no evidence for an association between asthma attacks and acute exposures at typical ambient PM or SO_2 levels in the U.S. (the mean annual avg SO_2 concentrations from 1972 to 1977 was approximately 6 ppb, with 90th percentile values ranging from 15 to 20 ppb).

The 1982 AQCD reported numerous effects on the respiratory system in animals exposed to SO_2. Effects were generally observed at levels exceeding those found in the ambient environment, and included morphological changes, altered pulmonary function, lipid peroxidation, and changes in host lung defenses. The immediate effect of acute SO_2 exposure in animals was increased pulmonary resistance to airflow, a measure of bronchoconstriction. Bronchoconstriction was reported to be the most sensitive indicator of lung function effects.

Collectively, the human clinical, epidemiologic, and animal toxicological, studies provided biological plausibility and coherent evidence of an adverse effect of ambient SO_2 on respiratory health. Since the 1982 AQCD, 1986 Second Addendum, and 1994 Supplement to the Second Addendum, additional studies have been conducted to determine the relationship between short-term exposures to

ambient SO_2 and adverse respiratory health effects, including respiratory symptoms, lung function, airway inflammation, airway hyperresponsiveness (AHR), lung host defenses, and ED visits and hospitalizations for respiratory causes. The epidemiologic, human clinical, and animal toxicological evidence on the effects of SO_2 on these various endpoints are discussed below. The findings of the previous review are integrated below with the current literature.

3.1.2. Potential Mode of Action for Respiratory Health Effects

The 1982 AQCD (U.S. EPA, 1982) gave background information on the biochemistry of SO_2, chemical reactions of bisulfite (HSO_3^-), metabolism of SO_2, and the activating or inhibiting effects of bisulfite on various enzymes. SO_2 readily dissolves in water, rapidly becoming hydrated to form sulfurous acid, which at physiological pH substantially dissociates to form bisulfite and sulfite (SO_3^{2-}) ions. In vitro studies have shown that SO_2 and/or bisulfite readily react with nucleic acids, proteins, lipids, and other classes of biomolecules. Bisulfite participates in three important types of reactions with biomolecules: sulfonation (sulfitolysis), autooxidation with generation of free radicals, and addition to cytosine. Products of sulfonation reactions have been shown to be long-lived in vivo and may be highly reactive. Products of autooxidation may be responsible for the initiation of lipid peroxidation, which, among other effects, could damage plasma membranes. In addition, bisulfite can react with nucleic acids to convert cytosine to uracil, thus resulting in mutational events. A principal mechanism of detoxification of SO_2 (and sulfite/bisulfite) occurs through the enzymatic activity of sulfite oxidase, resulting in the production of sulfate. Sulfite oxidase is a molybdenum-containing enzyme, and the 1982 AQCD noted that depleting its activity in an animal model through a low-molybdenum diet supplemented with the competitive inhibitor tungsten resulted in a significant lowering of the LD_{50} for intraperitoneally injected bisulfite. It was also noted that while in vitro exposure to SO_2 or sulfite/bisulfite had been shown to either activate or inhibit a variety of enzymes, no such effects had yet been demonstrated for in vivo exposure.

As discussed in the 1982 AQCD, the immediate effect of acute SO_2 exposure in animals is bronchoconstriction. Reactions of SO_2 with respiratory tract fluids can result in the production of bisulfite, sulfite, and a lowering of the pH, which may be involved in the bronchoconstrictive response. It is now widely appreciated that bronchoconstriction following SO_2 exposure is mediated by chemosensitive receptors in the tracheobronchial tree. Rapidly activating receptors (RARs) and sensory C-fiber receptors found at all levels of the respiratory tract are sensitive to irritant gases such as SO_2 (Coleridge and Coleridge, 1994; Widdicombe, 2006). Activation of these vagal afferents stimulates central nervous system reflexes resulting in bronchoconstriction, mucus secretion, mucosal vasodilation, cough, apnea followed by rapid shallow breathing, and effects on the cardiovascular system such as bradycardia and hypotension or hypertension (Coleridge and Coleridge, 1994; Widdicombe and Lee, 2001; Widdicombe 2003).

Early experiments demonstrated that SO_2-induced reflexes were mediated by cholinergic parasympathetic pathways involving the vagus nerve and inhibited by atropine (Grunstein et al., 1977; Nadel et al., 1965a; 1965b). Bronchoconstriction was found to involve smooth muscle contraction since β-adrenergic agonists such as isoproterenol reversed the effects (Nadel et al., 1965a; 1965b). Histamine was also thought to be involved in SO_2-induced bronchoconstriction (U.S. EPA, 1982).

More recent experiments in animal models conducted since 1982 have demonstrated that both cholinergic and noncholinergic mechanisms may be involved in SO_2-induced effects. In two studies utilizing bilateral vagotomy, vagal afferents were found to mediate the immediate ventilatory responses to SO_2 (Wang et al., 1996), but not the prolonged bronchoconstrictor response (Barthelemy et al., 1988). Other studies showed that atropine failed to block SO_2-induced bronchoconstriction, and that a local axon reflex resulting in C-fiber secretion of neuropeptides (i.e., neurogenic inflammation) was responsible for the effect (Atzori et al., 1992; Hajj et al., 1996). Neurogenic inflammation has been shown to play a key role in animal models of airway inflammatory disease (Groneberg et al., 2004).

In humans, the mechanisms responsible for SO_2-induced bronchoconstriction are not fully understood. In non-asthmatics, near complete attenuation of bronchoconstriction has been demonstrated using the anticholinergic agents atropine and ipratropium bromide (Snashall and Baldwin, 1982; Tan et al., 1982; Yildirim et al., 2005). However, in asthmatics, these same anticholinergic agents (Field et al., 1996; Myers et al., 1986), as well as short- and long-acting $\beta 2$-adrenergic agonists (Gong et al., 1996; Linn et al., 1988), theophylline (Koenig et al., 1992), cromolyn sodium (Myers et al., 1986), nedocromil sodium (Bigby and Boushey, 1993) and leukotriene receptor antagonists (Gong et al., 2001; Lazarus et al., 1997) only partially blocked SO_2-induced bronchoconstriction (see Annex Table D-1, (U.S. EPA, 1994c). That none of these therapies have been shown to completely attenuate the effects of SO_2 implies the involvement of both parasympathetic pathways and inflammatory mediators in asthmatics. Strong evidence of this was borne out in a study by Myers et al. (1986), in which asthmatic adults were exposed to SO_2 following pretreatment with cromolyn sodium (a mast cell stabilizer), atropine (a muscarinic receptor antagonist), and the two medications together. While both treatments individually provided some protection against the bronchoconstrictive effects of SO_2, there was a much stronger and statistically significant effect following concurrent administration of the two medications.

It has been proposed that inflammation contributes to the enhanced sensitivity to SO_2 seen in asthmatics by altering autonomic responses (Tunnicliffe et al., 2001), enhancing mediator release (Tan et al., 1982) and/or sensitizing C-fibers and RARs (Lee and Widdicombe, 2001). Whether local axon reflexes also play a role in SO_2-induced bronchoconstriction in asthmatics is not known (Groneberg et al., 2004; Lee and Widdicombe, 2001; Widdicombe, 2003). However, differences in respiratory tract innervation between rodents and humans suggest that C-fiber mediated neurogenic inflammation may be unimportant in humans (Groneberg et al., 2004; Widdicombe and Lee, 2001; 2003).

3.1.3. Respiratory Effects Associated with Peak (5-10 min) Exposure

SO_2-induced respiratory effects among exercising asthmatics are well-documented, and have been consistently observed following peak exposures (defined here as 5-10 min exposures to relatively high concentrations, e.g., 0.2-1.0 ppm) (Balmes et al., 1987; Bethel et al., 1985; Horstman et al., 1986; 1988; Linn et al., 1984; 1987; 1988; 1990; Schachter et al., 1984; Sheppard et al., 1981). SO_2-induced decrements in lung function have been observed in asthmatics at concentrations as low as 0.1 ppm when SO_2 is administered via mouthpiece (Koenig et al., 1990; Sheppard et al., 1981). However, these exposures cannot be directly compared to exposures occurring among freely breathing subjects as a larger fraction of administered SO_2 reaches the tracheobronchial airways during oral breathing (see Section 2.7.1, Kirkpatrick et al., 1982; Linn et al., 1983a). Since the publication of the 1994 Supplement, several additional human clinical studies have been published that provide supportive evidence of SO_2-induced decrements in lung function and increases in respiratory symptoms among exercising asthmatics (see Annex Table D-2). Descriptions of older studies were presented in the 1994 Supplement, and are not described in great detail in this document. However, based in part on recent guidance from the American Thoracic Society (ATS) regarding what constitutes an adverse health effect of air pollution (ATS, 2000), key older studies described in the 1994 Supplement were reviewed and analyzed along with studies published since 1994. In their official statement, the ATS concluded that an air pollution-induced shift in a population distribution of a given health-related endpoint (e.g., lung function in asthmatic children) should be considered adverse, even if this shift does not result in the immediate occurrence of illness in any one individual in the population. The ATS also recommended that transient loss in lung function with accompanying respiratory symptoms attributable to air pollution should be considered adverse. However, it is important to note that symptom perception is highly variable among asthmatics even during severe episodes of asthmatic bronchoconstriction. An asymptomatic decrease in lung function may pose a significant health risk to asthmatic individuals as it is less likely that these individuals will seek treatment (Eckert et al., 2004; Fritz et al., 2007). Therefore, whereas the conclusions in the 1994 Supplement were

based on SO_2 exposure concentrations which resulted in large decrements in lung function along with moderate to severe respiratory symptoms, the current review of data from human clinical studies focused on moderate to large SO_2-induced decrements in lung function along with respiratory symptoms ranging from mild (perceptible wheeze or chest tightness) to severe (breathing distress requiring the use of a bronchodilator).

3.1.3.1. Respiratory Symptoms

The 1994 Supplement to the Second Addendum described in detail several studies that evaluated respiratory symptoms following controlled human exposures to SO_2. Briefly, following 5-min exposures to 0, 0.2, 0.4, and 0.6 ppm SO_2 during moderate to heavy levels of exercise ($\dot{V}_E$ = 48 L/min), Linn et al. (1983b) reported that the severity of respiratory symptoms (i.e., cough, chest tightness, throat irritation) among asthmatics increased with increasing SO_2 concentration. Relative to clean air exposures, exposures to SO_2 resulted in statistically significant increases in respiratory symptoms at concentrations of 0.4 and 0.6 ppm. In a subsequent study, Linn et al. (1987) observed a significant effect of SO_2 on respiratory symptoms in asthmatics who were engaged in slightly lower levels of exercise ($\dot{V}_E$ = 40 L/min) for a duration of 10 min. Clear increases in respiratory symptoms were observed at concentrations of 0.6 ppm, with 43% of asthmatic subjects experiencing SO_2-induced symptoms. Some evidence of SO_2-induced increases in respiratory symptoms was also demonstrated at concentrations as low as 0.4 ppm, with 15% of subjects experiencing symptoms (Smith, 1994). It was also observed that these symptoms abated < 1 h after exposure. Balmes et al. (1987) reported that 7 out of 8 asthmatic adults developed respiratory symptoms, including wheezing and chest tightness, following 3-min exposures to 0.5 ppm SO_2 via mouthpiece during eucapnic hyperpnea ($\dot{V}_E$ = 60 L/min).

Additional human clinical studies published since the 1994 Supplement to the Second Addendum have provided support for previous conclusions regarding the effect of peak exposures to SO_2 on respiratory symptoms. In a human clinical study of SO_2-sensitive asthmatics, Gong et al. (1995) reported that respiratory symptoms (i.e., shortness of breath, wheeze, and chest tightness) increased with increasing SO_2 concentration (0, 0.5, and 1.0 ppm SO_2) following exposures of 10 min with varying levels of exercise. It was also observed that exposure to 0.5 ppm SO_2 during light exercise evoked a more severe symptomatic response than heavy exercise in clean air. Trenga et al. (1999) observed a significant correlation between decreases in FEV_1 and increases in respiratory symptoms following 10 min exposures via mouthpiece to 0.5 ppm SO_2.

3.1.3.2. Lung Function

In controlled exposures of healthy human subjects to SO_2, respiratory effects including increased respiration rates, decrements in peak flow, bronchoconstriction, and increased airway resistance have been observed at concentrations > 1 ppm (Abe, 1967; Amdur et al., 1953; Andersen et al., 1974; Frank et al., 1962; Lawther, 1955; 1975; Sim and Pattle, 1957; Snell and Luchsinger, 1969). SO_2-induced decrements in lung function can be potentiated by increasing ventilation rate, either through eucapnic hyperpnea or by performing exercise during exposure. This effect is likely due to an increased uptake of SO_2 resulting from both the increase in minute ventilation as well as a shift from nasal breathing to oronasal breathing.

It has been clearly established that subjects with asthma are more sensitive to the respiratory effects of SO_2 exposure than healthy individuals without asthma. Asthmatic individuals exposed to SO_2 concentrations as low as 0.2-0.3 ppm for 5-10 min during exercise have been shown to experience moderate or greater bronchoconstriction, measured as an increase in specific airway resistance (sRaw) of $\geq$ 100% or decrease in FEV_1 of $\geq$ 15% after correction for exercise-induced responses in clean air (Bethel et al., 1985; Linn et al., 1983b; 1984; 1987; 1988; 1990). It has been consistently demonstrated that these

decrements in lung function are more pronounced following exposures to higher concentrations of SO_2 (0.4-0.6 ppm), with a greater fraction of asthmatics affected (Linn et al., 1983b; 1987; 1988; 1990; Magnussen et al., 1990; Roger et al., 1985). Gong et al. (1995) demonstrated a concentration-response relationship between SO_2 and lung function by exposing 14 unmedicated, SO_2-sensitive asthmatics to 0, 0.5, and 1 ppm SO_2 under 3 different levels of exercise. It was shown that increasing SO_2 concentration had a greater effect on sRaw and FEV_1 than increasing exercise level. In some cases, bronchoconstrictive responses to SO_2 can occur in as little as 2 min after the start of exposure (Balmes et al., 1987; Horstman et al., 1988). SO_2-induced decrements in lung function appear to be transient, and the magnitude of effect has not been observed to increase with repeat exposures. There is evidence of a diminished response to SO_2 when repeat exposures (10 min) occur within 5 h of the initial exposure. However, when exposure to SO_2 occurs during a 30-min period with continuous exercise, the response to SO_2 develops rapidly and is maintained throughout the 30-min exposure (Kehrl et al., 1987; Linn et al., 1984; 1987). Although the majority of human clinical studies have been conducted at 20-25°C and 70-85% relative humidity, there is some evidence that the respiratory effects of SO_2 are exacerbated when exposure occurs in cold or dry ambient conditions (Bethel et al., 1984; Linn et al., 1985b).

Since some of the studies involving asthmatic subjects have used change in sRaw as the endpoint of interest while others measured changes in FEV_1 or both, a comparison of FEV_1 and sRaw based on data from Linn et al. (1987, 1990) was provided in the 1994 Supplement to the Second Addendum. Based on simple linear interpolation of the data from these two studies, a 100% increase in sRaw corresponded to a 12 to 15% decrease in FEV_1 and a 200% increase in sRaw corresponded to a 25 to 30% decrease in FEV_1.

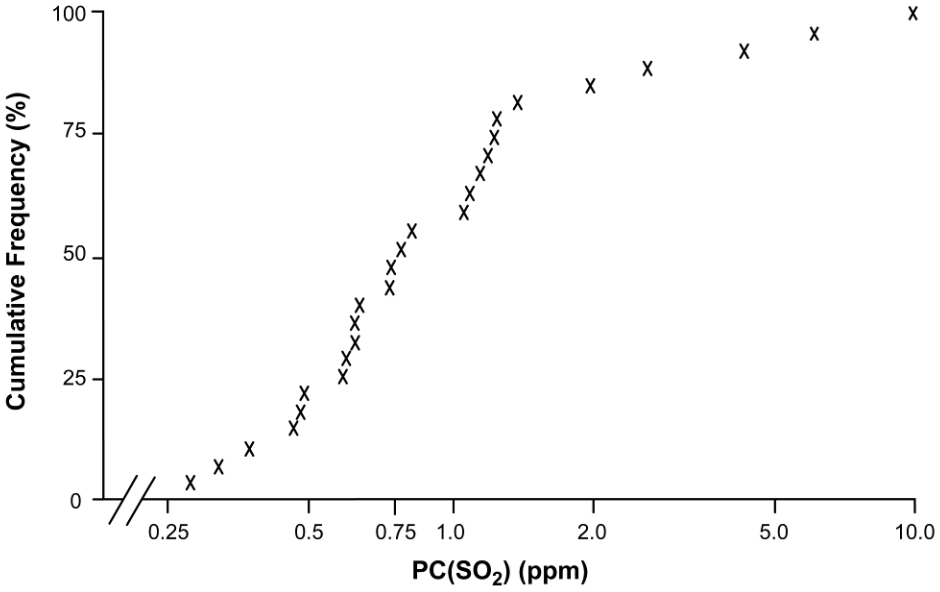
One of the aims of the Linn et al. (1987) study was to determine how the intensity of response varied with asthma severity or status. In this study, 24 normal, 21 atopic (but not asthmatic), 16 mild asthmatic, and 24 moderate/severe asthmatic subjects were exposed to SO_2 concentrations between 0 and 0.6 ppm. While the moderate/severe asthmatics experienced greater decrements in lung function than mild asthmatics following exposure to clean air during exercise, their increases in response to increasing SO_2 concentrations were similar to those of the mild asthmatic group. Thus, it was concluded by the authors that respiratory response to SO_2 was not strongly dependent on the clinical severity of asthma. However, the apparent lack of correlation between SO_2 response and asthma severity should be interpreted with caution, since the SO_2 response may have been attenuated by medication usage. Classification of asthma severity in this study was based on medication use to control asthma. Individuals who required regular medication to manage asthma were classified as “moderate/severe” asthmatics, while asthmatic subjects who did not use medication between episodes were classified as “mild” asthmatics. Three of the moderate/severe asthmatics were unable to withhold medication usage prior to most exposures. Trenga et al. (1999) observed that 25 out of 47 adult asthmatics experienced a drop in FEV_1 versus baseline of between 8 and 44% (mean = 17.2%) following a 10 min mouthpiece exposure to 0.5 ppm SO_2 during moderate exercise. However, severity of asthma, as defined by medication use, was not shown to be a predictor of sensitivity to SO_2. In a study of medication-dependent moderate asthmatics, Linn et al. (1990) found that normal treatment (typically regular use of a long-acting bronchodilator) did not prevent the airway responses to SO_2 and exercise. However, SO_2-induced bronchoconstriction was significantly reduced when normal medication was supplemented with administration of a short-acting beta agonist immediately preceding exposure.

Quick-relief and long-term-control asthma medications have been shown to provide varying degrees of protection against the bronchoconstrictive effect of SO_2 in mild and moderate asthmatics (see Annex Table D-1; (U.S. EPA, 1994c; Gong et al., 1996; 2001; Lazarus et al., 1997; Linn et al., 1988; 1990; Myers et al., 1986). While no therapy has been shown to completely eliminate the respiratory effects of SO_2 in asthmatics, some short- and long-acting asthma medications are capable of significantly reducing SO_2-induced bronchoconstriction (Gong et al., 1996; 2001; Koenig et al., 1987; Linn et al., 1990). However, asthma is often poorly controlled even among severe asthmatics due to inadequate drug therapy or poor compliance among those who are on regular medication (Rabe et al., 2004). Mild asthmatics, who constitute the majority of asthmatic individuals, are much less likely to use asthma

medication than asthmatics with more severe disease (O'Byrne, 2007; Rabe et al., 2004). It is therefore reasonable to conclude that all asthmatics, mild, moderate and severe, are at high risk of experiencing adverse respiratory effects of SO_2 exposure.

One of the key studies discussed in the 1994 Supplement to the Second Addendum was by Horstman et al. (1986). In this study, 27 asthmatic subjects were exposed to concentrations of SO_2 between 0 and 2 ppm SO_2 for 10 min on different days under exercising conditions ($\dot{V}_E$ = 42 L/min). The authors reported that for 22% of the subjects, the concentration of SO_2 needed to produce a doubling of sRaw compared to clean air exposure [$PC(SO_2)$] was < 0.5 ppm, with 2 subjects (7.4%) experiencing moderate decrements in lung function following exposure to concentrations of SO_2 at or below 0.3 ppm (see Figure 3-1). For approximately 15% of the subjects, the $PC(SO_2)$ was > 2 ppm, with approximately 35% of asthmatic subjects experiencing a doubling in sRaw versus clean air at ≤ 0.6-ppm SO_2.

SO_2-induced decrements in lung function (increased sRaw and decreased FEV_1) have frequently been associated with increases in respiratory symptoms among asthmatics (Balmes et al., 1987; Gong et al., 1995; Linn et al., 1983b; 1987; 1988; 1990). Linn et al. (1987) exposed 40 mild and moderate asthmatics during 10 min periods of exercise to 0, 0.2, 0.4, and 0.6 ppm SO_2. The effect of SO_2 on lung function and respiratory symptoms was assessed immediately following exposure, and the individual-specific results have been made available to the U.S. EPA by the study authors (Smith, 1994). Following exposure to 0.6 ppm SO_2 and after adjusting for effects of exercise in clean air, 21 of the 40 subjects demonstrated moderate or greater decrements in lung function, defined as a ≥15% decrease in FEV_1, a ≥100% increase in sRaw, or both. Of these 21 responders, 14 (67%) also experienced mild to severe respiratory symptoms (6 mild, 6 moderate, and 2 severe). In the same study, 14 asthmatics experienced moderate or greater decrements in lung function at 0.4 ppm SO_2, 5 of whom (36%) also experienced mild to moderate respiratory symptoms (2 mild, 3 moderate). Five asthmatics experienced moderate or greater decrements in lung function at the lowest SO_2 concentration tested (0.2 ppm), with 1 of the 5 (20%) also experiencing mild respiratory symptoms.



Source: Horstman et al. (1986).

Figure 3-1. Distribution of individual airway sensitivity to SO_2. Each data point represents the value of $PC(SO_2)$ for an individual subject. $PC(SO_2)$ is defined as the provocative concentration of SO_2 causing a doubling of sRaw compared to clean air exposure.

It has been proposed that, as in asthmatics, individuals with COPD may also be more susceptible to SO_2-induced respiratory health effects. However, this group has not been extensively studied in human clinical studies. Among a group of older adults with physician-diagnosed COPD, Linn et al. (1985a) reported no significant effect on lung function following 15 min exposures to SO_2 at concentrations of 0.4 and 0.8 ppm. While it was concluded that older adults with COPD appear to be less sensitive to SO_2 when compared with younger adult asthmatics, the authors suggested that the lack of response may have been due in part to the very low levels of exercise used in the study ($\dot{V}_E$ = 18 L/min), which would result in a lower dose of SO_2 reaching the lower airway. In contrast to studies with asthmatics, most of the subjects in this study regularly used bronchodilators and were permitted their use up to 4 h prior to the study.

3.1.3.3. Airway Inflammation

A very limited number of human clinical studies have investigated the role of airway inflammation in the asthmatic response following peak exposure to SO_2. Gong et al. (2001) observed an SO_2-induced increase in sputum eosinophil counts in exercising asthmatics 2 h after a 10 min exposure to 0.75 ppm SO_2. The results of this study provide some evidence that SO_2 may elicit an inflammatory response in the airways of asthmatics which extends beyond the short time period typically associated with SO_2 effects.

3.1.3.4. Mixtures and Interactive Effects

The interaction of SO_2 with other common air pollutants or the sequential exposure of SO_2 after prior exposure to another pollutant can potentially modify SO_2-induced respiratory effects. However, only a few human clinical studies have looked at the interactive effects of coexisting ambient air pollutants. In a human clinical study designed to simulate an ambient "acid summer haze," Linn et al. (1997) exposed healthy and asthmatic children (9–12 years of age) for 4 h with intermittent exercise to a mixture of SO_2 (0.1 ppm), H_2SO_4 (100 μg/m^3), and O_3 (0.1 ppm). Compared with exposure to filtered air, exposure to the air pollution mixture did not result in statistically significant changes in lung function or respiratory symptoms.

In a human clinical study of asthmatic adolescents (12- to 16-years-old), Koenig et al. (1983) evaluated changes in FEV_1 following a 10-min mouthpiece exposure during moderate exercise to 1 mg/m^3 NaCl alone and in combination with 0.5 and 1.0 ppm SO_2. Statistically significant decreases of 15 and 23% were reported in FEV_1 following exposure to 1 mg/m^3 NaCl in combination with 0.5 and 1.0 ppm SO_2, respectively. No significant changes in FEV_1 were observed between pre- and post-exposure to 1 mg/m^3 NaCl without SO_2. The effect observed in this study may be the result of the presence of hygroscopic particles that can carry SO_2 deeper into the lung.

Koenig et al. (1990) also examined the effect of 15-min exposures to 0.1 ppm SO_2 via mouthpiece in adolescent asthmatics engaged in moderate levels of exercise. Immediately preceding this exposure, subjects were exposed for 45 min to 0.12 ppm O_3 during intermittent moderate exercise. Subjects also underwent two additional exposure sequences with the same exercise regimen: 15-min exposure to 0.1 ppm SO_2 following a 45-min exposure to clean air, and 15-min exposure to 0.12 ppm O_3 following a 45-min exposure to 0.12 ppm O_3. The authors found that the change in FEV_1 relative to baseline was significantly different following the O_3-SO_2 exposure (8% decrease) when compared to the change following the air-SO_2 or O_3-O_3 exposures (decreases of 3% and 2%, respectively). In a more recent study using a mouthpiece exposure system, Trenga et al. (2001) reported that among adult asthmatics, exposure to O_3 (0.12 ppm for 45 min) resulted in a slight increase in lung function responses to SO_2 at a concentration of 0.25 ppm (6.5% decrease in FEV_1 with pre-exposure to O_3, compared with a 3.4% decrease in FEV_1 with pre-exposure to filtered air). Hazucha and Bates (1975) demonstrated a synergistic effect of concurrent exposure to SO_2 (0.37 ppm) and O_3 (0.37 ppm) on lung function in healthy asthmatics; however, no such effect was observed in a similar study conducted by Bedi et al. (1979).

Jörres and Magnussen (1990) and Rubinstein et al. (1990) investigated the effects of a prior NO_2 exposure on SO_2-induced bronchoconstriction in asthmatic adults. While Jörres and Magnussen suggested that prior exposure to NO_2 increased the responsiveness to SO_2, Rubinstein et al. did not find that NO_2 exacerbated the effects of SO_2. Linn et al. (1980) reported no difference in lung function or respiratory symptoms among a group of exercising asthmatics exposed to both clean air and a combination of NO_2 (0.5 ppm) and SO_2 (0.3 ppm).

3.1.3.5. Summary of Evidence on the Effect of Peak Exposure on Respiratory Health

Collectively, evidence from earlier studies considered in the previous review, along with a limited number of new human clinical studies, consistently indicates that with elevated ventilation rates a large percentage of asthmatic individuals (up to 60%) experience moderate or greater decrements in lung function, frequently accompanied by respiratory symptoms, following peak exposures to SO_2 at concentrations of 0.4-0.6 ppm (Balmes et al., 1987; Gong et al., 1995; Horstman et al., 1986; Linn et al., 1983b; 1987; 1988; 1990). SO_2-induced decrements in lung function have also been observed at lower SO_2 concentrations (0.2-0.3 ppm) in a smaller fraction (~5-30%) of asthmatic subjects (Bethel et al., 1985; Linn et al., 1987; 1988; 1990; Sheppard et al., 1981). At these concentrations, SO_2-induced decrements in lung are less likely to be accompanied by respiratory symptoms (Linn et al., 1983b; 1987; 1988; 1990; Roger et al., 1985). These findings are consistent with the current understanding of the potential modes of action for respiratory health as described in Section 3.1.2. Among asthmatics, both the magnitude of SO_2-induced decrements in lung function and the percent of individuals affected have consistently been shown to increase with increasing exposure to SO_2 concentrations between 0.2 and 1.0 ppm. This is summarized in Table 3-1 along with supporting evidence of SO_2-induced increases in respiratory symptoms at various exposure concentrations. The table includes data from all studies where individual data are presented or have been made available by the authors (Smith, 1994). This information represents the response to SO_2 among groups of relatively healthy asthmatics and cannot necessarily be extrapolated to the most sensitive asthmatics in the population who are likely more susceptible to the respiratory effects of exposure to SO_2.

Although the vast majority of human clinical studies involving controlled exposure to SO_2 have been conducted in adult asthmatics, there is a relatively strong body of evidence to suggest that adolescents may experience many of the same respiratory effects at similar SO_2 exposure concentrations (Koenig et al., 1981, 1983; 1987; 1988; 1990; 1992). It should be noted, however, that in all of these studies involving adolescents, SO_2 was administered via inhalation through a mouthpiece rather than an exposure chamber. This exposure technique bypasses nasal absorption of SO_2, likely resulting in a relative increase of pulmonary SO_2 uptake (see Section 2.7.1) (Linn et al., 1983a).

Table 3-1. Percentage of asthmatic adults in controlled human exposures experiencing SO_2 induced decrements in lung function.

SO_2 Conc (ppm)	Exposure Duration	No. Subj	Ventilation (L/min)	Cumulative Percentage of Responders (Number of Subjects)[1] Lung Func	sRaw ≥ 100% ↑ / FEV1 ≥ 15% ↓	sRaw ≥ 200% ↑ / FEV1 ≥ 20% ↓	sRaw ≥ 300% ↑ / FEV1 ≥ 30% ↓	Study	Respiratory Symptoms: Supporting Studies
0.2	10 min	40	~40	sRaw	5% (2)	0	0	Linn et al. (1987)[2]	
	10 min	40	~40	FEV_1	13% (5)	5% (2)	3% (1)	Linn et al. (1987)	
0.25	5 min	19	~50-60	sRaw	32% (6)	16% (3)	0	Bethel et al. (1985)	Limited evidence of SO_2-induced increases in respiratory symptoms in some asthmatics: Linn et al. (1983b; 1984; 1987; 1988; 1990), Schachter et al. (1984)
	5 min	9	~80-90	sRaw	22% (2)	0	0	Bethel et al. (1985)	
	10 min	28	~40	sRaw	4% (1)	0	0	Roger et al. (1985)	
0.3	10 min	20	~50	sRaw	10% (2)	5% (1)	5% (1)	Linn et al. (1988)[3]	
	10 min	21	~50	sRaw	33% (7)	10% (2)	0	Linn et al. (1990)[3]	
	10 min	20	~50	FEV_1	15% (3)	0	0	Linn et al. (1988)	
	10 min	21	~50	FEV_1	24% (5)	14% (3)	10% (2)	Linn et al. (1990)	
0.4	10 min	40	~40	sRaw	23% (9)	8% (3)	3% (1)	Linn et al. (1987)	Stronger evidence with some statistically significant increases in respiratory symptoms: Balmes et al. (1987)[5], Gong et al. (1995), Linn et al. (1983b; 1987), Roger et al. (1985)
	10 min	40	~40	FEV_1	30% (12)	23% (9)	13% (5)	Linn et al. (1987)	
0.5	5 min	10	~50-60	sRaw	60% (6)	40% (4)	20% (2)	Bethel et al. (1983)	
	10 min	28	~40	sRaw	18% (5)	4% (1)	4% (1)	Roger et al. (1985)	
	10 min	45	~30	sRaw	36% (16)	16% (7)	13% (6)	Magnussen et al. (1990)[5]	
0.6	10 min	40	~40	sRaw	35% (14)	28% (11)	18% (7)	Linn et al. (1987)	Clear and consistent increases in SO_2-induced respiratory symptoms: Linn et al. (1983b; 1984; 1987; 1988; 1990), Gong et al. (1995), Horstman et al. (1988)
	10 min	20	~50	sRaw	60% (12)	35% (7)	10% (2)	Linn et al. (1988)	
	10 min	21	~50	sRaw	62% (13)	29% (6)	14% (3)	Linn et al. (1990)	
	10 min	40	~40	FEV_1	53% (21)	48% (19)	20% (8)	Linn et al. (1987)	
	10 min	20	~50	FEV_1	55% (11)	55% (11)	5% (1)	Linn et al. (1988)	
	10 min	21	~50	FEV_1	43% (9)	33% (7)	14% (3)	Linn et al. (1990)	
1.0	10 min	28	~40	sRaw	50% (14)	25% (7)	14% (4)	Roger et al. (1985)[4]	
	10 min	10	~40	sRaw	60% (6)	20% (2)	0	Kehrl et al. (1987)	

[1]Data presented from all references from which individual data were available. Percentage of individuals who experienced greater than or equal to a 100, 200, or 300% increase in specific airway resistance (sRaw), or a 15, 20, or 30% decrease in FEV_1. Lung function decrements are adjusted for effects of exercise in clean air (calculated as the difference between the percent change relative to baseline with exercise/SO_2 and the percent change relative to baseline with exercise/clean air). Quality control of data was performed separately by two EPA staff scientists.

[2]Responses of mild and moderate asthmatics reported in Linn et al. (1987) have been combined. Data reported only for the first 10 min period of exercise in the first round of exposures.

[3]Analysis includes data from only mild (Linn et al., 1988) and moderate (Linn et al., 1990) asthmatics who were not receiving supplemental medication.

[4]One subject was not exposed to 1.0 ppm due to excessive wheezing and chest tightness experienced at 0.5 ppm. For this subject, the values used for 0.5 ppm were also used for 1.0 ppm under the assumption that the response at 1.0 ppm would be equal to or greater than the response at 0.5 ppm.

[5]Indicates studies in which exposures were conducted using a mouthpiece rather than a chamber.

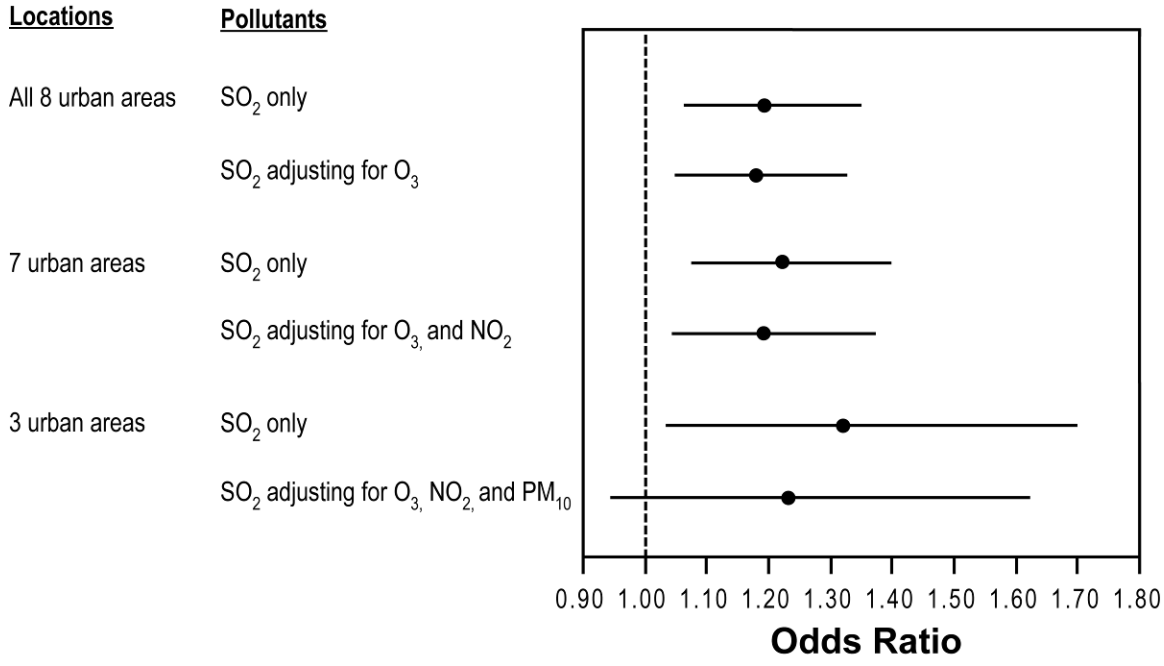
3.1.4. Respiratory Effects Associated with Short-Term (≥ 1 h) Exposure

3.1.4.1. Respiratory Symptoms

Epidemiologic studies have examined the association between ambient SO_2 concentrations and respiratory symptoms in both adults and children. In air pollution field studies, respiratory symptoms are usually assessed using questionnaire forms (or "daily diaries") completed by study subjects. Questions address the daily experience of coughing, wheezing, shortness of breath (or difficulty breathing), production of phlegm, and others.

Children

Epidemiologic studies on respiratory symptoms published since the last review are summarized in Annex Table F-1; key studies are discussed in detail below.



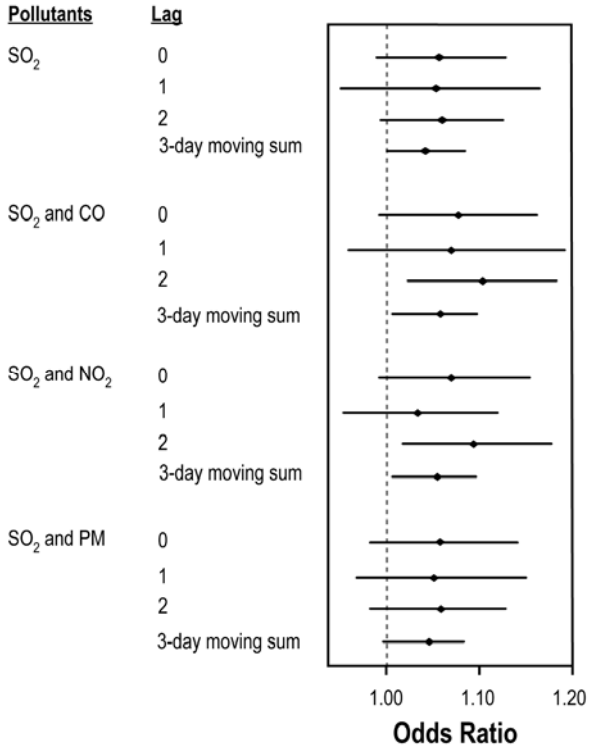
Source: Mortimer et al. (2002).

Figure 3-2. Odds ratios (95% CI) for incidence of morning asthma symptoms of 846 asthmatic children from the National Cooperative Inner-City Asthma Study. Effects associated with a 20 ppb increase in 3-h avg SO_2 with a lag of 1-2 day moving average are presented. SO_2 effect estimates from single- and multipollutant models are shown.

The strongest epidemiologic evidence for an association between respiratory symptoms and exposure to ambient SO_2 comes from two large U.S. multicity studies (Mortimer et al., 2002; Schildcrout et al., 2006). Mortimer et al. examined 846 asthmatic children from eight U.S. urban areas in the National Cooperative Inner-City Asthma Study (NCICAS) for summertime air pollution-related respiratory

symptoms. Median 3-h avg SO_2 (8 to 11 a.m.) levels ranged from 17 ppb in Detroit, MI to 37 ppb in East Harlem, NY. Morning symptoms were found to be most strongly associated with an avg of a 1- to 2-day lag of SO_2 concentrations. In multipollutant models with O_3 and NO_2 (measured in seven cities), the SO_2 association remained robust (see Figure 3-2). When PM_{10} was also included in the multipollutant models, the SO_2 effect estimate decreased only slightly; however, it became nonsignificant, possibly due to reduced statistical power (only three of eight cities were included in the analysis adjusting for PM_{10}) or collinearity resulting from adjustment of multiple pollutants (in addition to PM_{10}, O_3 and NO_2 were also adjusted for in this model).

In the Childhood Asthma Management Program (CAMP) study, the association between ambient air pollution and asthma exacerbations in children (n = 990) from eight North American cities was investigated (Schildcrout et al., 2006). SO_2 measurements were available in seven of the eight cities. The median 24-h avg SO_2 concentrations ranged from 2.2 ppb (interquartile range [IQR]: 1.7, 3.1) in San Diego, CA to 7.4 ppb (IQR: 5.3, 10.7) in St. Louis, MO. Results for the associations between asthma symptoms and all pollutants are shown in Figure 3-3. Analyses indicate that although SO_2 was positively related to increased risk of asthma symptoms at all lags, only the 3-day moving avg was statistically significant. No associations were observed between SO_2 and rescue inhaler use. Stronger associations were observed for CO and NO_2. The effect estimates appear to be slightly larger in joint-pollutant models with CO or NO_2, particularly at a 2-day lag, but did not change much when PM_{10} was jointly considered.



Source: Schildcrout et al. (2006).

Figure 3-3. Odds ratios (95% CI) for daily asthma symptoms of 990 asthmatic children from the Childhood Asthma Management Program Study. Effects associated with a 10 ppb increase in within-subject concentrations of 24-h avg SO_2 are presented. Data collected from November 1993 to September 1995 were used. Results from single- and joint-pollutant models are shown.

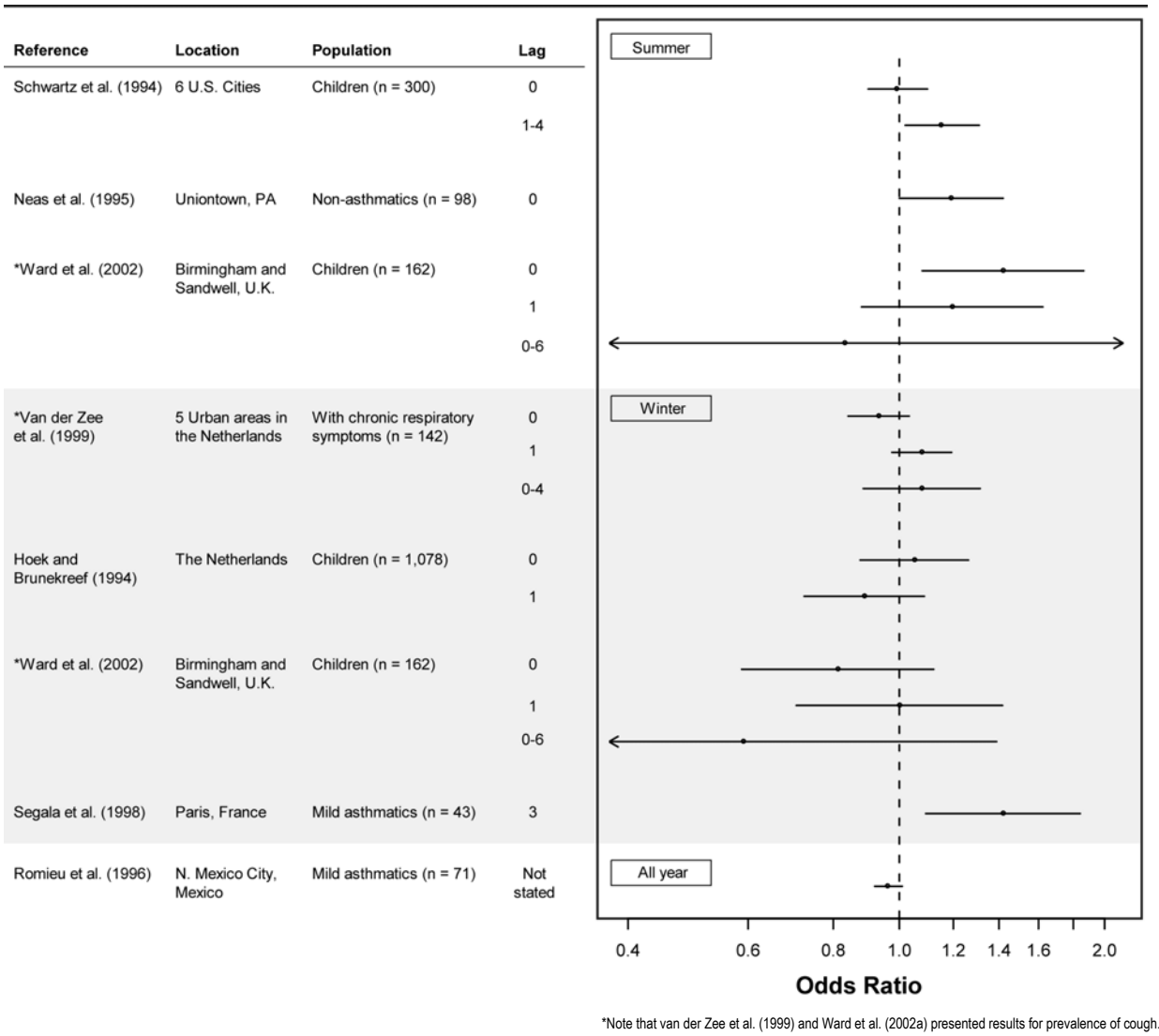
A longitudinal study of 1,844 schoolchildren during the summer from the Harvard Six Cities Study suggested that the association between SO_2 and respiratory symptoms could be confounded by PM_{10} (Schwartz et al., 1994). The median 24-h avg SO_2 concentration during this period was 4.1 ppb (10th–90th percentile: 0.8, 17.9; max 81.9). SO_2 concentrations were found to be associated with cough incidence and lower respiratory tract symptoms. Of the pollutants examined, PM_{10} had the strongest associations with respiratory symptoms. In two-pollutant models, the effect of PM_{10} was found to be robust to adjustment for other copollutants, while the effect of SO_2 was substantially reduced after adjustment for PM_{10}. Because the PM_{10} concentrations were correlated strongly to SO_2-derived sulfate particles ($r = 0.80$), the diminution of the SO_2 effect estimate may indicate that for PM_{10} dominated by fine sulfate particles, PM_{10} has a slightly stronger association than SO_2. This study further investigated the concentration-response function and observed a nonlinear relationship between SO_2 concentrations and respiratory symptoms. Though an increasing trend was observed at concentrations as low as 10 ppb, no statistically significant increase in the incidence of lower respiratory tract symptoms was seen until concentration exceeded a 24-h avg SO_2 of 22 ppb.

In the Pollution Effects on Asthmatic Children in Europe (PEACE) study, a multicenter study of 14 cities across Europe, the effects of acute exposure to various pollutants including SO_2 on the respiratory health of children with chronic respiratory symptoms ($n = 2,010$) was examined during the winter of 1993–1994 (Roemer et al., 1998). Mean 24-h avg SO_2 concentrations ranged from 1 ppb in the urban area of Umeå, Sweden, to 43 ppb in the urban area of Prague, Czech Republic. No associations were observed between SO_2 and daily prevalence of respiratory symptoms or bronchodilator use at any of the single- and multiday lags considered. In addition, no associations were observed for any of the other pollutants examined. It should be noted that during the study period, there were only two major air pollution episodes, at the beginning and end of the study period. In the epidemiologic model, the control for time trend was accomplished through the use of linear and quadratic terms. Given the timing of the air pollution episodes, the quadratic trend term would have removed most of the air pollution effect.

Other studies that participated in the PEACE study and analyzed results for longer periods of time have observed statistically significant associations between SO_2 and respiratory symptoms in children. Van der Zee et al. (1999) looked at the association between respiratory symptoms and SO_2 in 7- to 11-year-old children ($n = 633$) with and without chronic respiratory symptoms in the Netherlands. Significant associations with lower respiratory tract symptoms and increased bronchodilator use were observed for SO_2, as well as PM_{10}, BS, and sulfate, in symptomatic children living in urban areas ($n = 142$). In a two-pollutant model with PM_{10}, the results were robust for bronchodilator use, but slightly reduced for lower respiratory tract symptoms. A subgroup analysis of this cohort was conducted by Boezen et al. (1999). They examined 7- to 11-year-old children ($n = 459$) in the Netherlands and tested them for AHR and atopy. It was hypothesized that children with AHR, as measured using a methacholine (MCh) challenge, and atopy, indicated by raised serum total IgE (> 60 kU/L, the median value), may be susceptible to the effects of air pollution. One of the strengths of this study was the use of AHR and serum IgE concentration to indicate susceptibility; these measurements would be less prone to error than self-reported chronic respiratory symptoms. A total of 121 children were found to have AHR and relatively high serum total IgE; 67 had AHR and relatively low serum total IgE, 104 had no AHR but had a relatively high serum total IgE concentration, and 167 were found to have neither AHR nor relatively high serum total IgE. For the subset of children with relatively low serum total IgE with or without AHR, no associations were observed between SO_2 and any respiratory symptoms. However, for children with relatively high serum total IgE either with or without AHR, the prevalence of lower respiratory tract symptoms increased with increasing SO_2 concentrations. For children with AHR and relatively high serum total IgE, the OR for the prevalence of lower respiratory tract symptoms was 1.70 (95% CI: 1.26, 2.29) with a 5-day moving avg for every 10 ppb increase in SO_2. For children without AHR but with relatively high serum total IgE, the OR was 1.82 (95% CI: 1.33, 2.50) with a 5-day moving avg.

Additional studies have examined the relationship between respiratory symptoms and ambient SO_2 concentrations and generally found positive associations, including two U.S. studies (Delfino et al., 2003a; Neas et al., 1995) and several European studies (Hoek and Brunekreef, 1995; Peters et al., 1996a;

Roemer et al., 1993; Segala et al., 1998; Timonen and Pekkanen, 1997). However, some did not find a consistent association between respiratory symptoms and SO_2 concentrations (Hoek and Brunekreef, 1993; Romieu et al., 1996). None of these studies examined possible confounding of the SO_2 effect by copollutants.

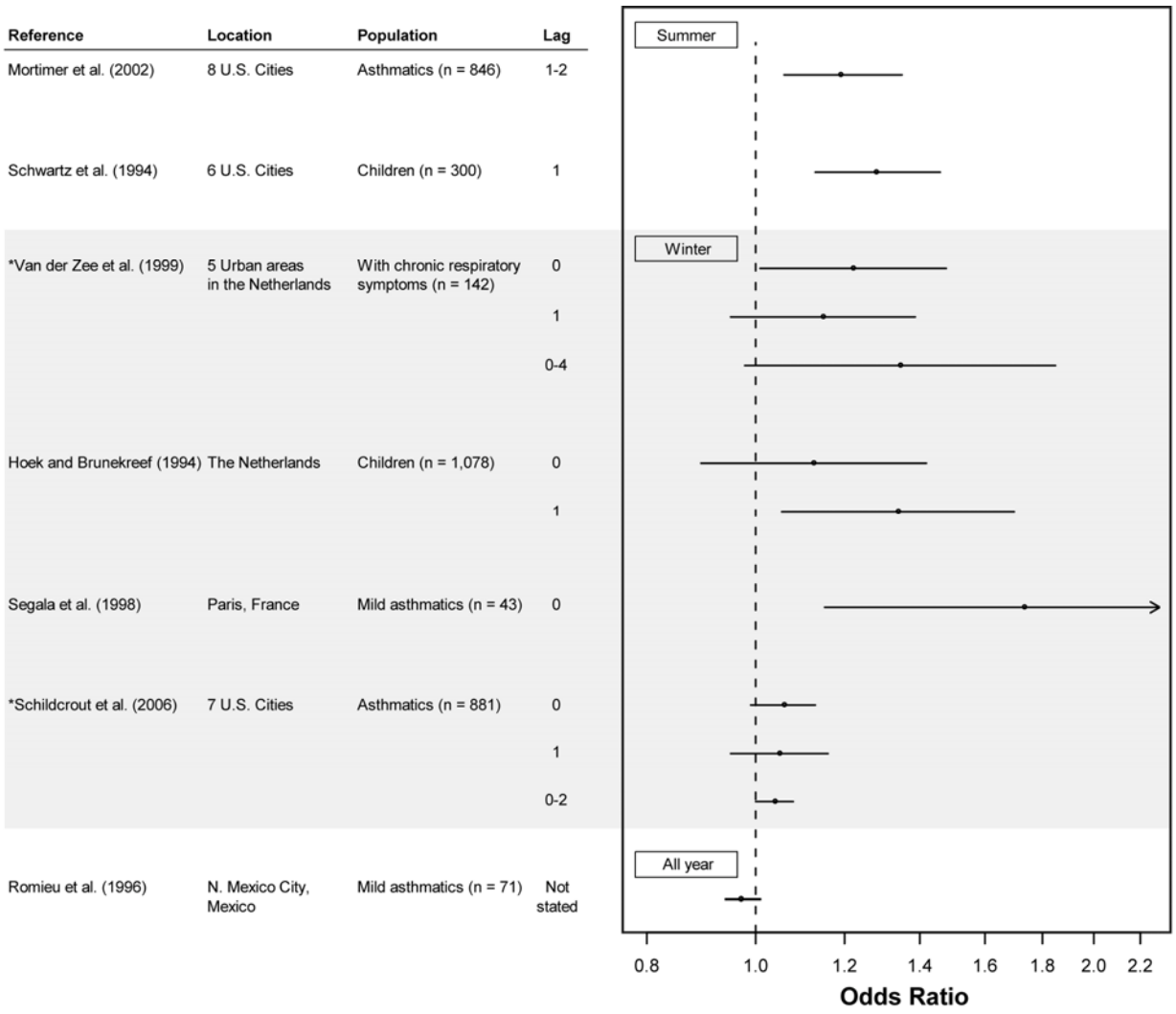


*Note that van der Zee et al. (1999) and Ward et al. (2002a) presented results for prevalence of cough.

Figure 3-4. Odds ratios (95% CI) for incidence of cough among children, grouped by season. For single-day lag models, current day and/or previous day SO_2 effects are shown, except for Ségala et al. (1998b), which only presented results for a 3-day lag. Multiday lag models represent the effect of the mean concentration from the range of days noted. Risk estimates are standardized per 10 ppb increase in 24-h avg SO_2 level.

Figure 3-4 and Figure 3-5 present the odds ratios for SO_2-related cough, and lower respiratory tract or asthma symptoms, respectively, among children from epidemiologic studies published since the last NAAQS review. All studies that reported quantitative results with relevant data are included in the figure. The results for cough were somewhat variable with wide confidence intervals, as shown in Figure 3-4.

The studies conducted in the summer generally indicate increased risk of cough from exposure to SO_2. A more consistent effect of SO_2 is observed on lower respiratory tract or asthma symptoms (Figure 3-5). Although there is some variability in the individual effect estimates, the majority of the odds ratios appear to be greater than one. As was the case with cough, stronger associations with lower respiratory tract or asthma symptoms were observed in the summer, as opposed to the winter. There was some variability among the different lags of exposure; however, effects were generally observed with current day or previous day exposure and, in some cases, with a distributed lag of 2 to 3 days.



*Note that van der Zee et al. (1999) and Schildcrout et al. (2006) presented results for prevalence of lower respiratory tract or asthma symptoms.

Figure 3-5. Odds ratios (95% CI) for the incidence of lower respiratory tract or asthma symptoms among children, grouped by season. Risk estimates are standardized per 10 ppb increase in 24-h avg SO_2 level. For single-day lag models, current day and/or previous day SO_2 effects are shown. Multiday lag models represent the effect of the moving average from the range of days noted.

Overall, recent epidemiologic studies provided evidence for an association between ambient SO_2 exposures and increased respiratory symptoms in children, particularly those with asthma or chronic respiratory symptoms. Recent U.S. multicity studies observed significant associations between SO_2 and respiratory symptoms at a median range of 17 to 37 ppb (75th percentile: ~25 to 50) across cities for 3-h avg SO_2 (NCICAS, Mortimer et al., 2002) and 2.2 to 7.4 ppb (90th percentile: 4.4 to 14.2) for 24-h avg SO_2 (CAMP, Schildcrout et al., 2006). However, an earlier study that examined the concentration-response function found that a statistically significant increase in the incidence of lower respiratory tract symptoms was not observed until concentrations exceeded a 24-h avg SO_2 of 22 ppb, though an increasing trend was observed at concentrations as low as 10 ppb (Harvard Six Cities Study, Schwartz et al., 1994). In the limited number of studies that examined potential confounding by copollutants through multipollutant models, the SO_2 effect was generally found to be robust after adjusting for PM and other copollutants. More details of the literature published since the last review are found in Annex Table F-1.

Adults

Compared to the number of studies conducted with children, fewer epidemiologic studies were performed that examined the effect of ambient SO_2 exposure on respiratory symptoms in adults. Most of these studies focused on potentially susceptible populations, i.e., those with asthma or COPD. One of the larger studies was conducted by van der Zee et al. (2000) in 50- to 70-year-old adults, with (n = 266) and without (n = 223) chronic respiratory symptoms in the Netherlands. In adults both with and without chronic respiratory symptoms, no consistent associations were observed between SO_2 levels and respiratory symptoms or medication use. A subgroup analysis of this cohort examining SO_2-related respiratory symptoms in individuals with AHR and atopy was conducted by Boezen et al. (2005). The subgroup of individuals with elevated serum total IgE, both with (n = 48) and without (n = 112) AHR, were found to be more susceptible to air pollutants when contrasted with those who did not have elevated serum total IgE (n = 167). Significant associations were observed between previous-day 24-h avg SO_2 concentrations and the prevalence of upper respiratory tract symptoms in those with elevated serum total IgE. Stratified analyses by gender indicated that, among those with AHR and elevated IgE, only males (n = 25) were at a higher risk for respiratory symptoms. The OR for these males was 3.54 (95% CI: 1.79, 7.07) increase in 24-h avg SO_2 for a 5-day moving avg, compared with 1.05 (95% CI: 0.59, 1.91) for the females.

Studies by Desqueyroux et al. (2002a; 2002b) examined the association between air pollution and respiratory symptoms in other potentially susceptible populations, i.e., those with severe asthma (n = 60, mean age 55 years) and COPD (n = 39, mean age 67 years), in Paris, France. The mean 24-h avg SO_2 concentration was 3 ppb (range: 1, 10) in the summer and 7 ppb (range: 1, 31) in the winter. No associations were observed between SO_2 concentrations and the incidence of asthma attacks or episodes of symptom exacerbation in severe asthmatics or individuals with COPD. Among the pollutants considered, O_3 was found to have the strongest effect in these studies.

Several other European studies did observe an association between ambient SO_2 concentrations and respiratory symptoms in adults with asthma or chronic bronchitis (Higgins et al., 1995; Neukirch et al., 1998; Peters et al., 1996a). Only one of these studies examined possible confounding of the association by copollutants. Higgins et al. (1995) examined the effect of summertime air pollutant exposure on respiratory symptoms in 62 adults with either asthma, COPD, or both. The max 24-h avg SO_2 level was 45 ppb. An association was observed between SO_2 and symptoms of wheeze, and it remained robust after adjustment for O_3 and NO_2. The effects of PM were not examined in this study.

Results from the epidemiologic studies examining the association between SO_2 and respiratory symptoms in adults were generally mixed, with some showing positive associations and others finding no relationship at current ambient levels. There was limited epidemiologic evidence which suggested that atopic adults may be at increased risk for SO_2-induced respiratory symptoms. The overall epidemiologic evidence that 24-h avg SO_2 exposures at or near ambient concentrations has an effect on adults is inconclusive. However, as discussed in Section 3.1.3.1, human clinical studies have observed an effect of peak exposures to SO_2 on respiratory symptoms, particularly among SO_2-sensitive asthmatics, with 10 min

exposures to SO_2 concentrations as low as 0.2-0.6 ppm under exercise conditions. These effects in clinical studies are at levels that have sometimes been measured in ambient air for similarly short-time durations.

3.1.4.2. Lung Function

The 1982 AQCD reported bronchoconstriction, indicated by increased pulmonary resistance, as the most sensitive indicator of lung function effects of acute SO_2 exposure, based on the observations of increased pulmonary resistance in guinea pigs that were acutely exposed to 0.16 ppm SO_2. Since then, only a few animal toxicological studies have measured lung function at or near ambient levels of SO_2. These recent studies, and those using higher concentrations of SO_2, are summarized in Annex Table E-1. Increased pulmonary resistance and decreased dynamic compliance were observed in conscious guinea pigs exposed to 1 ppm SO_2 for 1 h (Amdur et al., 1983). Effects were seen immediately after exposure and were not present 1 h post-exposure. No changes in tidal volume, minute volume or breathing frequency were found. These same investigators also exposed guinea pigs to 1 ppm SO_2 for 3 h/day for 6 days (Conner et al., 1985). No changes were observed in pulmonary function or respiratory parameters, i.e., diffusing capacity for CO, functional reserve capacity, vital capacity, total lung capacity, respiratory frequency, tidal volume, pulmonary resistance or pulmonary compliance. In another study, Barthelemy et al. (1988) demonstrated a 16% increase in airway resistance following a 45-min exposure of anesthetized rabbits to 0.5 ppm SO_2 via an endotracheal tube. This latter exposure is more relevant to oronasal than nasal breathing.

Children

Most epidemiologic studies discussed in the previous section on respiratory symptoms also examined lung function. In these studies self-administered PEF meters were primarily used to assess lung function. PEF follows a circadian rhythm, with the highest values found during the afternoon and lowest values during the night and early morning (Borsboom et al., 1999). Therefore, these studies generally analyzed PEF data stratified by time of day. The epidemiologic studies on lung function are summarized in Annex Table F-1.

Mortimer et al. (2002) examined 846 asthmatic children from eight U.S. urban areas in the NCICAS for changes in PEF related to air pollution. The mean 3-h avg SO_2 was 22 ppb across the eight cities during the study period of June through August, 1993. No associations were observed between SO_2 concentrations and morning or evening PEF. Of all the pollutants examined, including PM_{10}, O_3, and NO_2, only O_3 was associated with changes in morning PEF.

In another U.S. study (Neas et al. 1995), 83 children from Uniontown, PA reported twice-daily PEF measurements during the summer of 1990. The mean daytime 12-h avg SO_2 concentration was 14.5 ppb (max 44.9). No associations were observed between daytime 12-h avg SO_2 concentrations and mean deviation in evening PEF, even after concentrations were weighted by the proportion of hours spent outdoors during the prior 12-h. Statistically significant associations were observed for O_3, total sulfate particles, and particle-strong acidity.

A study by van der Zee et al. (1999) observed associations between ambient SO_2 concentrations and daily PEF measurements in 7- to 11-year-old children (n = 142) with chronic respiratory symptoms living in urban areas of the Netherlands. The OR for a > 10% decrement in evening PEF per 10 ppb increase in 24-h avg SO_2 was 1.20 (95% CI: 0.97, 1.47) with same-day exposure. A greater effect was observed at a 2-day lag, OR = 1.40 (95% CI: 1.18, 1.67), and this effect remained robust in a two-pollutant model with PM_{10}, OR = 1.34 (95% CI: 1.08, 1.64).

Multipollutant analyses also were conducted in a study by Chen et al. (1999), which examined the effects of short-term exposure to air pollution on the pulmonary function of 895 children, ages 8 to 13 years, in three communities in Taiwan. The daytime 1-h max SO_2 the day before spirometry ranged from 0 to 72.4 ppb. In a single-pollutant model, 1-h max SO_2 concentration at a 2-day lag was significantly

associated with FVC, -50.80 mL (95% CI: -97.06, -4.54), or a 2.6% decline, per 40 ppb 1-h max SO_2. However, in multipollutant models, authors noted that only O_3 remained significantly associated with FVC and FEV_1. Effect estimates for SO_2 in multipollutant models were not provided.

While additional studies have observed associations between ambient SO_2 concentrations and changes in lung function in children (e.g., Hoek and Brunekreef, 1993; Peters et al., 1996a; Roemer et al., 1993; Segala et al., 1998; Timonen and Pekkanen, 1997), several other studies did not find a significant association between SO_2 and lung function parameters (e.g., Delfino et al., 2003a; Peacock et al., 2003; Romieu et al., 1996). In addition, within studies that did observe an association, the correlations between SO_2 and other pollutants, particularly PM indices, were high [for example, r = 0.8-0.9 with TSP] (Peters et al., 1996a) making it difficult to separate the contributions of individual pollutants.

In conclusion, while some epidemiologic studies observed a positive association between short-term SO_2 exposure and lung function in children, several others, including a large U.S. multicity study, did not observe such an association. The limited evaluation of potential confounding by copollutants also indicated mixed results. Overall, the evidence is insufficient to conclude that short-term exposure to ambient SO_2 has an independent effect on lung function in children.

Adults

Only a limited number of epidemiologic studies have been conducted examining the association between ambient SO_2 concentrations and lung function in adults, as in the case of respiratory symptoms. In a cross-sectional survey, Xu et al. (1991) investigated the effects of indoor and outdoor air pollutants on the respiratory health of 1,140 adults (aged 40 to 69 years) living in residential, industrial, and suburban areas of Beijing, China. The annual mean concentrations of SO_2 in residential, industrial, and suburban areas from 1981 to 1985 were 49 ppb, 22 ppb, and 7 ppb, respectively. Log-transformed SO_2 and TSP were significantly associated with reductions in FEV_1 and FVC. The authors cautioned that since SO_2 and TSP concentrations were strongly correlated, the effect of SO_2 could not be separated.

Van der Zee et al. (2000) observed an association between SO_2 and morning PEF in 50- to 70-year-old adults (n = 138) with chronic respiratory symptoms living in urban areas of the Netherlands. No associations were observed with evening PEF. The OR for a > 20% decrement in PEF was 1.21 (95% CI: 0.76, 1.92) per 10 ppb increase in 24-h avg SO_2 with same-day exposure and 1.56 (95% CI: 1.02, 2.39) at a 1-day lag. No associations were observed for a > 10% decrement in PEF. The authors hypothesized that while SO_2 level did not have much effect on PEF in most subjects, a small subgroup of individuals experienced fairly large PEF decrements when SO_2 levels were high. No multipollutant analyses were conducted.

Higgins et al. (1995) examined the association between pulmonary function and air pollution in 75 adults with either asthma, COPD, or both. Exposure to SO_2 was associated with increased variation in PEF, but not with mean or minimum PEF. The SO_2 effects on PEF variation were robust to adjustment for O_3 and NO_2. Effects of PM were not considered. Neukirch et al. (1998) also observed associations between lung function and SO_2 concentrations in a study of asthmatic adults in Paris, France; however, significant associations were found for all pollutants examined, including BS, PM_{13}, and NO_2. Other epidemiologic studies observed only weak relationships between ambient SO_2 concentrations and lung function in adults (Peters et al., 1996a; Taggart et al., 1996).

Evidence from human clinical studies clearly indicates that asthmatic individuals experience moderate or greater decrements in lung function, as well as increased respiratory symptoms, following peak exposure (5-10 min) to SO_2 (Balmes et al., 1987; Gong et al., 1995; Horstman et al., 1986; Linn et al., 1983b; 1987). These effects were seen at peak concentrations as low as 0.2-0.6 ppm. In a human clinical study by Tunnicliffe et al. (2003) that evaluated the effect of 1-h exposures to 0.2 ppm SO_2 in resting healthy and asthmatic subjects, no significant changes were observed in lung function as measured by FEV_1, FVC, and maximal midexpiratory flow (MMEF). However, these results are not unexpected given that subjects were exposed while at rest.

In summary, the epidemiologic studies examining adults do not provide strong evidence for an association between short-term exposure to ambient SO_2 and lung function. While some studies did observe associations between SO_2 exposure and decrements in lung function parameters, the strong correlation between SO_2 and various copollutants in most studies, and the lack of evidence evaluating potential confounding by copollutants, limit interpretation of independent effects of SO_2 on lung function.

3.1.4.3. Airway Inflammation

The animal toxicological studies on airway inflammation are summarized in Annex Table E-2. In one study, guinea pigs were exposed to 1 ppm SO_2 for 3 h/day for 1-5 days and bronchoalveolar lavage was performed (Conner et al., 1989). No change in numbers of total cells or neutrophils in lavage fluid was observed over this time period. However, in two models of allergic sensitization, SO_2 exposure increased airway inflammation. In one study Park et al. (2001a), guinea pigs were exposed to 0.1 ppm SO_2 for 5 h/day for 5 days and sensitized with 0.1% ovalbumin aerosols for 45 min on days 3-5. One week later, animals were subjected to bronchial challenge with 1.0% ovalbumin and bronchoalveolar lavage and histopathologic examination were performed 24 h later. Results demonstrated increased numbers of eosinophils in lavage fluid, and an infiltration of inflammatory cells, bronchiolar epithelial cell damage and plugging of the airway lumen with mucus and cells in the bronchial tissues of animals treated with both SO_2 and ovalbumin, but not in animals treated with ovalbumin or SO_2 alone. In a second study, rats which were sensitized and challenged with ovalbumin and exposed to 2 ppm SO_2 for 1 h/day for 7 days had an increased number of inflammatory cells in bronchoalveolar lavage fluid and an enhanced histopathological response compared with those treated with ovalbumin or SO_2 alone (Li et al., 2007). Similarly, ICAM-1, a protein involved in regulating inflammation, and MUC5AC, a mucin protein, were upregulated in lungs and trachea to a greater extent in rats treated with ovalbumin and SO_2 than those treated with ovalbumin or SO_2 alone. Further experiments are required to determine whether exposure to near ambient SO_2 also enhance inflammatory responses in non-allergic and allergic rats.

In a human clinical study, Tunnicliffe et al. (2003) measured levels of exhaled NO (eNO) in asthmatic and healthy adult subjects, before and after 1-h exposure to 0.2 ppm SO_2 under resting conditions. While eNO concentrations were higher in the asthmatic than in healthy subjects, no significant difference was observed between pre- and postexposure in either group.

One epidemiologic study by Adamkiewicz et al. (2004) examined eNO as a biological marker for inflammation in 29 older adults (median age 70.7 years) in Steubenville, OH. The mean 24-h avg SO_2 concentration was 12.5 ppb (IQR 11.5). The authors reported that, while significant and robust associations were observed between increased daily levels of fine PM ($PM_{2.5}$) and increased eNO, no associations were observed with any of the other pollutants examined, including SO_2, NO_2, and O_3.

Overall, the very limited human clinical and epidemiologic evidence is insufficient to conclude that exposure to SO_2 at current ambient concentrations is associated with inflammation in the airway. However, toxicological studies indicated that repeated exposures to SO_2, at concentrations as low as 0.1 ppm in guinea pigs, may exacerbate inflammatory responses in allergic animals.

3.1.4.4. Airway Hyperresponsiveness and Allergic Sensitization

The toxicological studies describing SO_2-induced effects on airway responsiveness and allergic sensitization in guinea pigs, rabbits, dogs, and sheep are summarized in Annex Table E-3. In one study, Amdur et al. (1988) exposed guinea pigs for 1 h to 1 ppm SO_2 and measured airway responsiveness to acetylcholine 2 h later. No AHR was observed. In a second study, Douglas et al., (1994) found no AHR following a histamine challenge 24 h after exposure of rabbits to 5 ppm SO_2 for 2 h. In a third study, exposure of sheep for 4 h to 5 ppm SO_2 failed to result in AHR following carbachol (Abraham et al., 1981). In a fourth study, a 5-min exposure to 30 ppm but not to 10 ppm SO_2 resulted in AHR in dogs

challenged with methacholine (Lewis and Kirchner, 1984). Collectively, these results show that a single exposure to SO_2 at a concentration of 10 ppm or less failed to induce AHR following challenge in 4 different animal models.

However, two other studies demonstrated increased airway responsiveness in guinea pigs exposed repeatedly to SO_2 and allergen. Riedel et al. (1988) studied the effect of SO_2 exposure on local bronchial sensitization to inhaled antigen. Guinea pigs were exposed by inhalation to 0.1, 4.3 and 16.6 ppm SO_2 for 8 h/d for 5 days. During the last 3 days, SO_2 exposure was followed by exposure to nebulized ovalbumin for 45 min. Following bronchial provocation with inhaled ovalbumin (0.1%) one week later, airway obstruction was measured by whole body plethysmography. In addition, specific antibodies against ovalbumin were measured in serum and bronchaolveolar fluids. Results show significantly higher bronchial obstruction in animals exposed to SO_2 (at all concentration levels) with ovalbumin compared with animals exposed only to ovalbumin. In addition, significant increases in anti-ovalbumin IgG antibodies were detected in bronchoalveolar lavage fluid of animals exposed to 0.1, 4.3 and 16.6 ppm SO_2 and in serum from animals exposed to 4.3 and 16.6 ppm SO_2 compared with controls exposed only to ovalbumin. These results demonstrate that repeated exposure to SO_2 can enhance allergic sensitization in the guinea pig at a concentration as low as 0.1 ppm. In a second study, guinea pigs were exposed to 0.1 ppm SO_2 for 5 h/day for 5 days and sensitized with 0.1% ovalbumin aerosols for 45 min on days 3 to 5 (Park et al., 2001a). One week later, animals were subjected to bronchial challenge with 1.0% ovalbumin and lung function was evaluated 24 h later by whole body plethysmography. Results demonstrated a significant increase in enhanced pause (P_{enh}), a measure of airway obstruction, in animals exposed to SO_2 with ovalbumin but not in animals treated with ovalbumin or SO_2 alone. These experiments also indicate that near ambient levels of SO_2 may play a role in exacerbating allergic responses in the guinea pig.

In a human clinical study evaluating SO_2-induced AHR to an inhaled allergen (house dust mite), Devalia et al. (1994) found that neither SO_2 (0.2 ppm) nor NO_2 (0.4 ppm) enhanced airway response to the allergen in asthmatic individuals. However, following concurrent exposure (6 h) to SO_2 and NO_2 while at rest, subjects did exhibit an increased response to the inhaled allergen. In a subsequent study, Rusznak et al. (1996) confirmed these findings and observed that the combination of SO_2 and NO_2 enhanced airway response to house dust mite antigen up to 48 hours post-exposure.

A limited number of epidemiologic studies also examined the association between SO_2 and AHR. These studies are summarized in Annex Table F-1. Søyseth et al. (1995a) investigated the effect of short-term exposure to SO_2 and fluoride on the number of capillary blood eosinophils, and the prevalence of AHR in schoolchildren, ages 7 to 13 yr, (n = 620) from two regions in Norway, a valley containing an SO_2-emitting aluminum smelter (Ardal) and a similar but nonindustrialized valley (Laerdal). The median 24-h avg SO_2 concentration was 8 ppb (10th–90th percentile: 1, 33) in the exposed area and 1 ppb (10th–90th percentile: 0, 4) in the nonindustrialized valley. The mean number of eosinophils was significantly greater in children living near the aluminum smelter compared to the nonindustrialized area. However, within children in the exposed area, a negative concentration-response relationship was observed between mean eosinophils and previous-day 24-h avg SO_2. The observed association between SO_2 and eosinophils was limited to atopic children. In children living in the exposed area, a statistically significant positive association was observed between prevalence of AHR and previous-day 24-h avg SO_2 concentrations. Similar associations were observed for fluoride. The authors hypothesized that recent exposure to SO_2 may have induced changes in the airway leading to AHR, in addition to recruitment of eosinophils to the airways in atopic subjects. Exposure to PM was not assessed in this study.

A study by Taggart et al. (1996) examined the effect of summertime air pollution levels in northwestern England on AHR in nonsmoking, asthmatic subjects (n = 38) aged 18 to 70 years who were determined to be MCh reactors. Subjects were tested multiple times, for a total of 109 evaluable challenge tests, with a range of two to four tests per subject. The max 24-h avg SO_2 concentration during the study period was 40 ppb. This study reported that 24-h avg SO_2 levels were marginally associated with a decreased dose of MCh required for a 20% drop in the postsaline FEV_1 ($PD20FEV_1$).

In summary, the animal toxicological evidence suggests that repeated exposures to SO_2 at concentrations as low as 0.1 ppm in guinea pigs can exacerbate AHR following allergic sensitization. Two

recent human clinical studies have demonstrated an increase in airway response to an inhaled allergen in asthmatic subjects following exposures to a combination of 0.2-ppm SO_2 and 0.4-ppm NO_2. These findings are consistent with the very limited epidemiologic evidence that suggests that exposure to SO_2 may lead to AHR in atopic children and asthmatic adults.

3.1.4.5. Respiratory Illness-Related Absences

An additional concern has been the potential for SO_2 exposure to enhance susceptibility to, or the severity of illness resulting from respiratory infections, especially in children. School absenteeism is used as an indicator of morbidity in children caused by acute conditions. Respiratory conditions are the most frequent cause, particularly influenza and the common childhood infectious diseases. Studies discussed in this section are summarized in Annex Table F-1. Park et al. (2002) examined the association between air pollution and school absenteeism in 1,264 first- to sixth-grade students attending school in Seoul, Korea. The study period extended from March 1996 to December 1999, with a mean 24-h avg SO_2 concentration of 9.19 ppb (SD 4.61). Note that analyses were performed using Poisson Generalized Additive Model (GAM) with default convergence criteria. Same-day SO_2 concentrations were positively associated with illness-related absences (16% excess risk [95% CI: 13, 22] per 10 ppb increase in 24-h avg SO_2), but inversely associated with non-illness–related absences (9% decrease [95% CI: 2, 15]). PM_{10} and O_3 concentrations also were positively associated with illness-related absences. In two-pollutant models containing SO_2 and either PM_{10} or O_3, the SO_2 estimates were robust.

A study by Pönka (1990) observed results that were consistent with those from the Park et al. (2002) study. Pönka found that absenteeism due to febrile illnesses among children in day care centers and schools, and in adults was significantly higher on days of higher SO_2 concentrations (> 8.1 ppb weekly mean of 1-h avg), compared to days of lower SO_2 concentrations in Helsinki, Finland. In addition, on days of higher SO_2 concentrations, the mean weekly number of cases of upper respiratory tract infections and tonsillitis reported from health centers increased. Temperature, but not NO_2, was also found to be associated with febrile illnesses and respiratory tract infections. From these epidemiologic studies, it is unknown whether SO_2 increases susceptibility to infection or whether its presence exacerbates morbidity following infection.

Pino et al. (2004) examined the association between air pollution and respiratory illnesses in a cohort of 504 infants recruited at 4 months of age from primary health care units in southeastern Santiago, Chile. The infants were followed through the first year of life. The mean 24-h avg SO_2 concentration was 11.6 ppb (5th–95th percentile: 3.0, 29.0). The most frequent diagnosis during follow-up was wheezing bronchitis. No associations were observed between current-day or previous-day SO_2 and wheezing bronchitis, but with a 7-day lag, a 21% (95% CI: 8, 39) excess risk in wheezing bronchitis was observed per 10 ppb increase in 24-h avg SO_2. However, it should be noted that stronger associations were observed with $PM_{2.5}$, which was well-correlated with SO_2 ($r = 0.73$). These epidemiologic studies are summarized in Annex Table F-1.

To summarize, very few studies have examined the association between ambient SO_2 concentrations and absences from school or work as a result of respiratory illnesses. The limited evidence indicates a possible association between exposure to SO_2 concentrations and increased respiratory illnesses, particularly among young children; however, this association was also seen with PM, which was correlated with SO_2.

3.1.4.6. Emergency Department Visits and Hospitalizations for Respiratory Diseases

Total respiratory causes for ED visits and hospital admissions typically include asthma, bronchitis and emphysema (collectively referred to as COPD), upper and lower respiratory tract infections, pneumonia, and other minor categories. Temporal associations between ED visits or hospital admissions

for respiratory diseases and the ambient concentrations of SO_2 have been the subject of more than fifty peer-reviewed research publications since 1994. In addition to considerable statistical and analytical refinements, recent studies have examined responses of morbidity in different age groups, the effect of seasons on ED and hospital usage, and multipollutant models to characterize the effects of copollutant mixtures. The epidemiologic studies of ED visits and hospital admissions for respiratory causes are summarized in Annex Table F-2.

All Respiratory Diseases

There are relatively few studies of ED visits for all respiratory causes in contrast to the quantity of studies that examine hospital admissions for all respiratory causes. Collectively, studies of ED visits and hospitalizations provide evidence to support an association between ambient SO_2 levels and ED visits and hospitalizations for all respiratory causes. When analyses were restricted by age, the results among children (0-14 years) and older adults (65+ years) were mainly positive, though not all statistically significant. The studies that examined the association of these outcomes and SO_2 levels among adults (15-64 years) reported a mix of positive and negative results. When all age groups were combined, the results of ED and hospitalization studies were mainly positive; however, the excess risk estimates were generally smaller compared to the children and older adults groups (see additional discussion in Section 4.2.3). It is possible that the effects observed in the combined age groups were driven by increases in the very young or older adult subpopulations. SO_2-related relative risks from the hospitalization and ED studies, separated by analyses among all ages and age-specific analyses, are shown in Figure 3-6. All studies that reported quantitative data are included in the figure (studies using GAM with default convergence criteria are not included). Figure 3-6, as well as Figure 3-7 are presented to assess the general consistency of the findings. Overall, the effect estimates in this figure range from a -5% to 20% excess risk in ED visits or hospital admissions for respiratory causes per 10 ppb increase in 24-h avg SO_2, with the large majority of studies suggesting an increase in risk.

Wilson et al. (2005) examined ED visits for all respiratory causes in Portland, ME from 1996–2000 and in Manchester, NH from 1998–2000. The mean 1-h max SO_2 concentration in Portland was 11.1 ppb (SD 9.1), and was higher during the winter months (mean 17.1 ppb [SD 12.0]) and lower in the summer (mean 9.1 ppb [SD 8.0]). In Manchester, the mean 1-h max SO_2 concentration was 16.5 ppb (SD 14.7 ppb), and also was higher in the winter months (mean 25.7 ppb [SD 15.8]) than in the summer months (mean 10.6 ppb [SD 15.1]). Though the authors reported the 1-h max SO_2 concentrations, they used the 24-h avg SO_2 concentrations in their analyses. When all ages where included in analyses, Wilson et al. (2005) found positive associations between ED visits and SO_2, with a 7% (95% CI: 3.0, 12) and 1% (95% CI: -3.0, 5.0) excess risk per 10 ppb increase in 24-h avg SO_2 at a 0-d lag in Portland, ME and Manchester, NH, respectively.

Peel et al. (2005) investigated ED visits for all respiratory causes in Atlanta, GA from 1993–2000. This study included 484,830 ED visits. The mean 1-h max SO_2 concentration was 16.5 ppb (SD 17.1). The researchers found a weak positive relationship between ED visits and SO_2, though the increased risk was not statistically significant (1.6% [95% CI: −0.6, 3.8] excess risk per 40 ppb increase in 1-h max SO_2). Tolbert et al. (2007) recently reanalyzed these data with four additional years of data and found similar results (0.8% [95% CI: -0.7, 2.3]). An analysis by Dab et al. (1996) examined the association between SO_2 and hospital admissions for all respiratory causes in Paris, France, using both the 24-h avg and 1-h max. It should be noted that these researchers observed similar effect estimates for both exposure metrics; however, only the estimate using 24-h avg was statistically significant (1.1% [95% CI: 0.1, 2.0] excess risk per 10 ppb increase in 24-h avg SO_2 versus 1.9% [95% CI: −1.3, 5.0]) per 40 ppb increase in 1-h max SO_2).

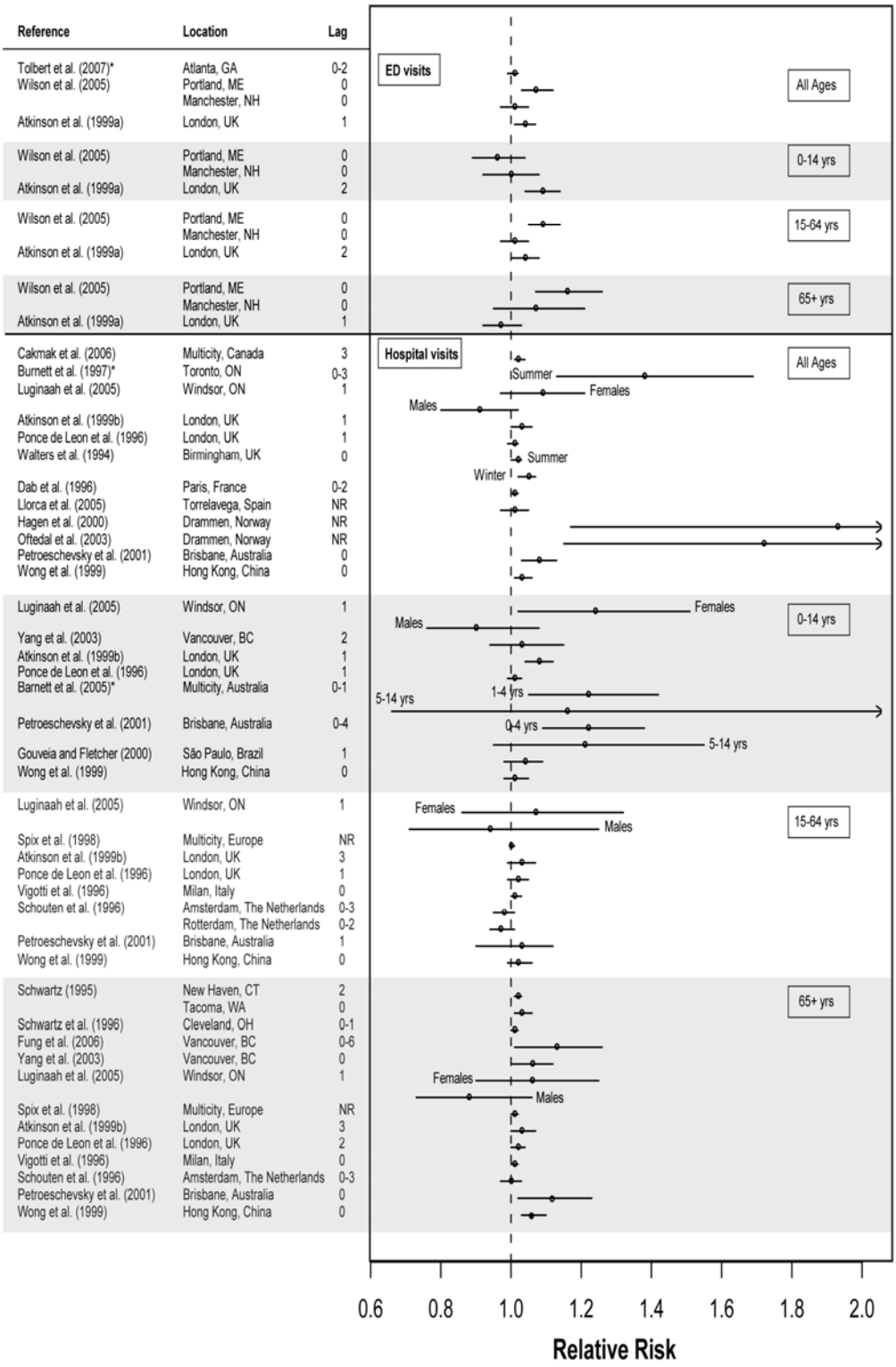


Figure 3-6. Relative risks (95% CI) of SO_2-associated emergency department visits and hospitalizations for all respiratory causes among all ages and separated by age group. Risk estimates are standardized per 10 ppb increase in 24-h avg SO_2 concentrations or 40 ppb increase in 1-h max SO_2 (*).

When analyses were stratified to include only children (0-14 years), evidence of a modest association between SO_2 and ED visits or hospitalizations for all respiratory causes in children was reported in several Australian (Barnett et al., 2005; Petroeschevsky et al., 2001) and European (Anderson et al., 2001 [using GAM default convergence criteria]; Atkinson et al., 1999a; 1999b) studies. Excess risks ranging from 3% to 22% per 10 ppb increase in 24-h avg SO_2 were reported by these studies. In a multicity study spanning Australia and New Zealand, Barnett et al. (2005) compared hospital admission data collected from 1998–2001 with ambient SO_2 concentrations, where the mean 24-h avg SO_2 concentration ranged from 0.9 to 4.8 ppb. The authors found a 22% (95% CI: 5, 42) excess risk per 10 ppb increment in 24-h avg SO_2 among children (1-4 years) in these cities. Petroeschevsky et al. (2001) found similar results for the 0-4 age group in their Brisbane, Australia study (22.4% increase [95% CI: 8.7, 37.7]). However, some additional U.S. (Wilson et al., 2005), European (Fusco et al., 2001 [using GAM default convergence criteria]; Ponce de Leon et al., 1996), and Latin American (Braga et al., 1999; 2001) studies did not find statistically significant associations between ambient SO_2 concentrations and hospitalizations for all respiratory causes among children.

Wilson et al. (2005) found a positive association between ED visits and SO_2, with a 16% (95% CI: 7.0, 22.0) excess risk per 10 ppb increase in 24-h avg SO_2 at a 0-d lag in Portland, and a 7% (95% CI: -5.0, 21.0) in Manchester, NH when only older adults (65+ years) were considered. In another two-city study, Schwartz (1995) compared 13,740 hospital admission among older adults in New Haven, CT and Tacoma, WA from 1988–1990 with ambient SO_2 concentrations. The mean 24-h avg SO_2 concentration was 29.8 ppb (90^{th} percentile: 159) in New Haven and 16.8 ppb (90^{th} percentile: 74) in Tacoma. Schwartz found positive associations between hospitalizations and SO_2, with a 2% (95% CI: 1.0, 3.0) excess risk at a 2-d lag in New Haven and 3% (95% CI: 1.0, 6.0) excess risk at a 0-d lag in Tacoma per 10 ppb increase in 24-h avg SO_2. In two-pollutant models, the SO_2 effect estimate from New Haven, but not Tacoma, was found to be robust to adjustment for PM_{10}. Here, the term robust is used to indicate that there was little change in the magnitude of the central estimate, though statistical significance may have been lost. In Vancouver, BC, both Fung et al. (2006) and Yang et al. (2003b) also found positive associations between hospitalizations among older adults and SO_2. In a multipollutant model including coefficient of haze (CoH), NO_2, O_3, and CO, the SO_2 effect estimate diminished slightly (Yang et al., 2003b).

Additional evidence of a positive association between ED visits or hospitalizations for all respiratory causes among older adults and SO_2 comes from several European (Spix et al., 1998; Sunyer et al., 2003a; Vigotti et al., 1996) and Australian (Petroeschevsky et al., 2001) studies. Excess risks ranging from 1% to 12% per 10 ppb increase in 24-h avg SO_2 were reported by these studies. Petroeschevsky et al. (2001) examined 33,710 hospital admissions in Brisbane, Australia from 1987–1994. The mean 24-h avg SO_2 concentration was 4.1 ppb, and was highest in the winter months (4.8 ppb) and lowest in the spring (3.7 ppb). Petroeschevsky et al. found a 12% (95% CI: 2.0, 23.0) excess risk per 10 ppb increase in 24-h avg SO_2 at 0-d lag. Additional European studies did not find statistically significant associations between ambient SO_2 concentrations and ED visits or hospitalizations for all respiratory causes among older adults (Anderson et al., 2001 [using GAM with default convergence criteria]; Atkinson et al., 1999a; 1999b; Ponce de Leon et al., 1996; Schouten et al., 1996).

In summary, studies generally observed small, positive associations between ambient SO_2 concentrations and ED visits and hospitalizations, particularly among children and older adults (65+ years). The positive evidence from these studies is supported by the results of panel, human clinical, and limited toxicological studies that also found a positive relationship between SO_2 levels and adverse respiratory outcomes.

Asthma

Studies of ED visits and hospitalizations provide evidence to support an association between ambient SO_2 levels and ED visits and hospitalizations for asthma. The results from the hospitalization and ED studies, separated by analyses among all ages and age-specific analyses, are shown in Figure 3-7. Overall, central effect estimates in the figure range from a -10% to 40% excess risk in ED visits and

hospitalizations for asthma per 10 ppb increase in 24-h avg SO_2. Most of the effect estimates are positive (suggesting an association with SO_2 and ED visits and hospitalizations for asthma), though few are statistically significant at the 95% confidence level.

When all ages were included in the analyses, Wilson et al. (2005) found a positive association between ED visits and SO_2, with an 11% (95% CI: 2, 20) excess risk per 10 ppb increase in 24-h avg SO_2 at a 0-d lag in Portland, ME and a positive, though not statistically significant association in Manchester, NH (6% increase [95% CI: -4, 17]). Ito et al. (2007b) found a 36% (95% CI: 22.2, 51.2) excess risk in asthma ED visits per 10 ppb increase in 24-h avg SO_2 during warm months in New York City. This effect was robust to the inclusion of $PM_{2.5}$ in the model, though this association was diminished once NO_2 was included in the model. Another study conducted in New York City (NY DOH, 2006) found a 10% (95% CI: 5, 15) excess risk in asthma hospital admissions per 10 ppb increase in 24-h avg SO_2 for Bronx residents, but a null association for the residents of Manhattan (-1% [95% CI: -11, 11]). A study conducted in Atlanta (Peel et al., 2005) found a null relationship between asthma ED visits and 1-h max SO_2 (0.2% increase [95% CI: -3.2, 3.4]). A study by Jaffe et al. (2003) examined the association between SO_2 and ED visits for asthma in three cities in Ohio – Cincinnati, Cleveland, and Columbus – in asthmatics aged 5 to 34 years. The mean 24-h avg SO_2 concentrations were 14 ppb (range: 1–50) in Cincinnati, 15 ppb (range: 1-64) in Cleveland, and 4 ppb (range: 0–22) in Columbus. A positive association was observed in the multicity analysis, with a 6.1% (95% CI: 0.5, 11.5) excess risk in asthma visits observed per 10 ppb increase in 24-h avg SO_2. In the city-stratified analyses, significant associations were observed only for Cincinnati (17.0% [95% CI: 4.6, 30.8]).

When analyses were stratified to include children (0-14 years) only, Wilson et al. (2005) found positive, but not statistically significant associations between ED visits and SO_2 in Portland, ME (5% [95% CI: -12, 25]) and Manchester, NH (20% [95% CI: -3, 49]). Similarly, Lin et al. (2003b) observed a positive association between hospitalizations for asthma and SO_2 among girls (30% [95% CI: 6, 60]), and a negative association for boys (-10% [95% CI: -23.4, 5.8] Toronto, ON; mean 24-h avg SO_2 of 5.36 ppb [SD 5.90]). Stronger evidence comes from a study of childhood asthma hospitalizations conducted in Bronx County, New York (Lin et al., 2004e). In this study, the authors conducted a case-control study of children aged 0-14 years and examined the association of daily ambient SO_2 concentrations (categorized into quartiles of both avg and max levels) and cases admitted to the hospital for asthma or controls who were admitted for reasons other than asthma. The mean 24-h avg SO_2 was below 17 ppb for both cases and controls across all lag days examined. The authors found that cases were exposed to higher 24-h avg SO_2 than controls. When the highest exposure quartile was compared with the lowest, the ORs were strongest when a 3-day lag was employed (OR 2.16 [95% CI: 1.77, 2.65] for 24-h avg SO_2; OR 1.86 [95% CI: 1.52, 2.27] for 1-h max SO_2). The results were positive and statistically significant for all lag days examined. These results suggest a consistent positive association between SO_2 exposure and hospitalizations for childhood asthma.

Additional evidence of a positive association between ED visits or hospitalizations for asthma among children and SO_2 comes from several European (Anderson et al., 1998; Atkinson et al., 1999a; 1999b; Hajat et al., 1999; Sunyer et al., 1997; 2003a [using GAM with default convergence criteria]; Thompson et al., 2001) and Asian (Park et al., 2002 [using GAM with default convergence criteria]) studies. Excess risks ranging from 2% to 10% per 10 ppb increase in 24-h avg SO_2 were reported by these studies. Several of these studies observed that the SO_2 effect estimate was robust to adjustment for BS and NO_2 (Anderson et al., 1998; Sunyer et al., 1997), but one study observed that the SO_2 effect diminished considerably with adjustment for PM_{10} and benzene (Thompson et al., 2001). Atkinson et al. (1999a) compared 165,032 respiratory hospital admissions in London from 1992–1994 with ambient SO_2 levels (mean 24-h avg of 7.2 ppb [SD 4.7]). They found a 10% (95% CI: 4.0, 16.0) excess risk per 10 ppb increase in 24-h avg SO_2 at 1-d lag for children aged 0-14 years. Additional European (Fusco et al., 2001 [using GAM with default convergence criteria]), Australian (Barnett et al., 2005; Petroeschevsky et al., 2001), Asian (Ko et al., 2007b; Lee et al., 2006a) and Latin American (Gouveia and Fletcher, 2000) studies did not find statistically significant associations between ambient SO_2 concentrations and hospitalizations for all respiratory causes among children.

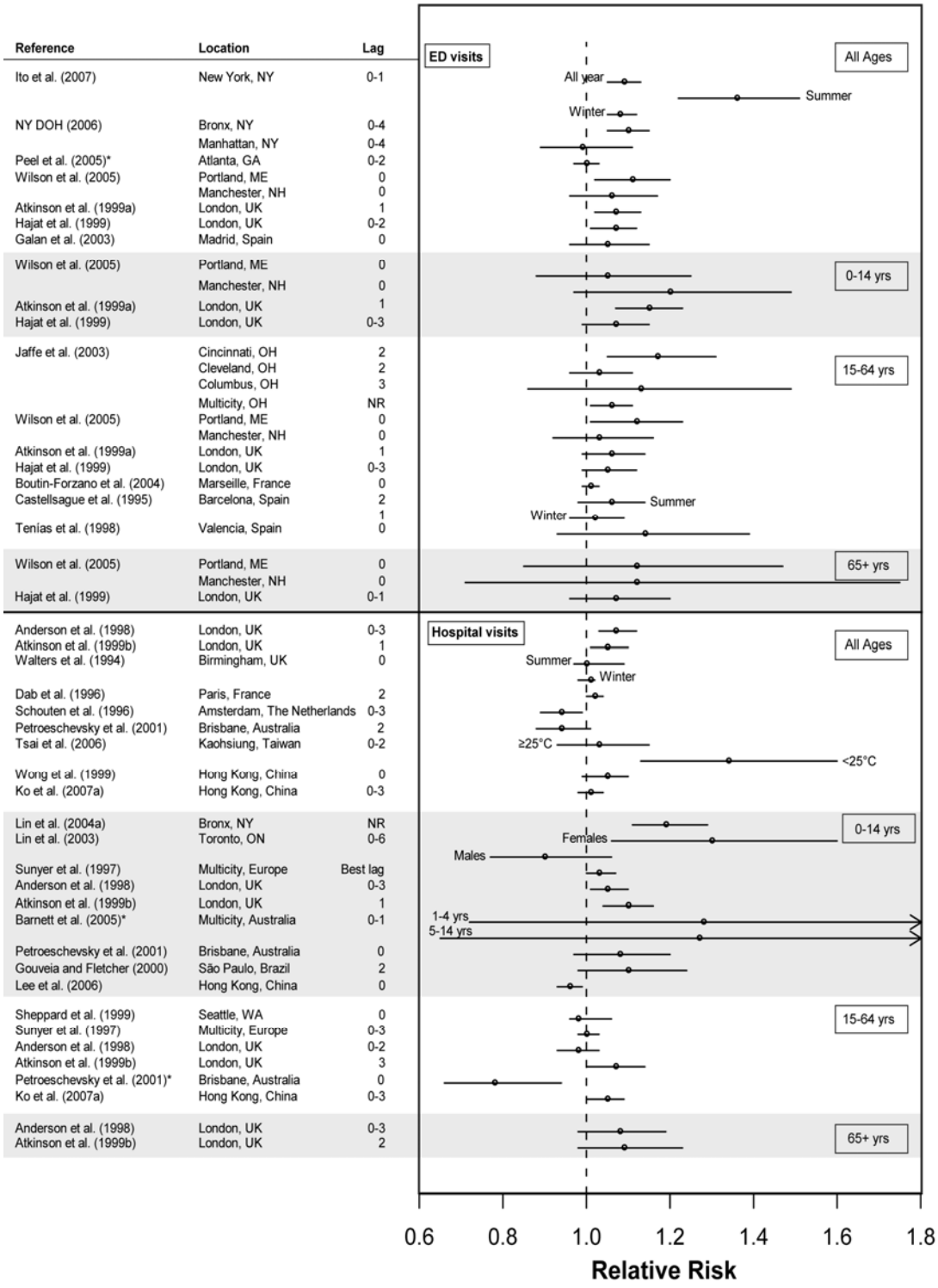


Figure 3-7. Relative risks (95% CI) of SO_2-associated emergency department visits and hospitalizations for asthma among all ages and age-specific groups. Risk estimates are standardized per 10 ppb increase in 24-h avg SO_2 concentrations or 40 ppb increase in 1-h max SO_2 (*).

In summary, small, positive associations were observed between ambient SO_2 concentrations and ED visits and asthma hospitalizations. Evidence from these studies is further supported by the results of panel and human clinical studies that have also found SO_2-related respiratory effects in asthmatics.

Chronic Obstructive Pulmonary Disease

There are relatively few studies that have examined the association of ED visits and hospitalizations for COPD and ambient SO_2 levels, and very little evidence that an association exists. A recent study (Ko et al., 2007a) found a significant association between hospital admissions for COPD (not including asthma) in Hong Kong (1.8% [95% CI: 0.3, 3.8]) excess risk per 10 ppb increase in 24-h avg SO_2 concentration). Three additional studies reported positive and statistically significant results for COPD and SO_2; all three studies included asthma in their diagnostic definition of COPD (Anderson et al., 2001; Moolgavkar, 2003a; Sunyer et al., 2003b). Anderson et al. (1999) reported a 12% (95% CI: 5.0, 20.0) excess risk per 10 ppb increase in 24-h avg SO_2 among children, while Moolgavkar (2003b) and Sunyer et al. (2003b) found 5% and 2% excess risks per 10 ppb increase in 24-h avg SO_2 among older adult populations, respectively. Other studies examining COPD did not find statistically significant results (Atkinson et al., 1999a; Burnett et al., 1999 [using GAM with default convergence criteria]; Michaud et al., 2004).

Overall, this limited and inconsistent evidence does not support a relationship between ED visits and hospitalizations for COPD and ambient SO_2 levels.

Respiratory Diseases Other than Asthma or COPD

Studies of ED visits or hospital admissions for other respiratory diseases looked at several other specific outcomes. There are limited studies with mixed results for upper respiratory tract infections (Burnett et al., 1999 [using GAM with default convergence criteria]; Hajat et al., 2002 [using GAM with default convergence criteria]; Lin et al., 2005; Peel et al., 2005), pneumonia (Barnett et al., 2005; Moolgavkar et al., 1997 [using GAM with default convergence criteria]; Peel et al., 2005), bronchitis (Barnett et al., 2005; Michaud et al., 2004), and allergic rhinitis (Hajat et al., 2002 [using GAM with default convergence criteria]; Villeneuve et al., 2006b). The limited evidence is suggestive of an association between SO_2 levels and ED visits or hospitalizations for lower respiratory tract diseases (Atkinson et al., 1999a; Farhat et al., 2005 [using GAM with default convergence criteria]; Hajat et al., 2002 [using GAM with default convergence criteria]; Lin et al., 1999; Martins et al., 2002 [using GAM with default convergence criteria]). All of the studies that characterized this relationship found a positive and statistically significant excess risk associated with increases in SO_2. Excess risks ranging from 3% to 33% per 10 ppb increase in 24-h avg SO_2 were reported by these studies.

In summary, only a few studies provide results for respiratory health outcomes other than asthma and COPD, and these results are mixed. This makes it difficult to draw conclusions about the effects of SO_2 on these diseases. Limited evidence is indicative of an association between ambient SO_2 levels and ED visits for lower respiratory tract diseases.

Summary of Evidence on Emergency Department Visits and Hospitalizations for Respiratory Diseases

Small, positive associations exist between ambient SO_2 concentrations and ED visits and hospitalizations for all respiratory causes, particularly among children and older adults (65+ years). Similar associations are found for asthma. The SO_2-related changes in ED visits or hospital admissions for respiratory causes ranged from -5% to 20% excess risk, with the large majority of studies suggesting an increase in risk. Mean 24-h avg SO_2 levels ranged from 1 to 30 ppb in these studies, with maximum values ranging from 12 to 75 ppb. No association was observed between SO_2 levels and ED visits and

hospitalizations for COPD. Given the limited number of studies with mixed results, it is difficult to draw conclusions about the effect of SO_2 on other respiratory diseases, though studies of lower respiratory tract diseases are somewhat indicative of an association.

The potential influence of copollutants has not been systematically considered in the epidemiologic literature. A limited subset of the studies examined potential confounding by copollutants using multipollutant regression models. Figure 3-8 presents SO_2 excess risk estimates with and without adjustment for various copollutants. PM and NO_2 are the main foci, since these pollutants have been found to be highly-correlated with SO_2 in epidemiologic studies and have known respiratory health effects. Multipollutant regression analyses indicated that although copollutant adjustment had varying degrees of influence on the SO_2 effect estimates, the effect of SO_2 on respiratory health outcomes appeared to be generally robust and independent of the effects of gaseous copollutants, including NO_2 (Anderson et al., 1998; Lin et al., 2004c; Sunyer et al., 1997), and O_3 (Anderson et al., 1998; Hajat et al., 1999; Tsai et al., 2006; Yang et al., 2003b; 2005). The evidence for PM_{10} was less consistent, with three studies finding that positive SO_2 effect estimates became negative, though not statistically significant, with the inclusion of PM_{10} in the model (Galan et al., 2003; Schwartz, 1995 [in New Haven, CT]; Tsai et al., 2006 [in Tacoma, WA]). Several other studies found the effects estimates for SO_2 to be generally robust to the inclusion of PM_{10} in the model (Burnett et al., 1997b; Hagen et al., 2000; Hajat et al., 1999 [using GAM with default convergence criteria]; Schwartz, 1995 [in New Haven, CT]). The studies that examined $PM_{2.5}$ and $PM_{10-2.5}$ in copollutant models found that the SO_2 estimates were generally robust to the adjustment for PM of these size fractions (Burnett et al., 1997b; Ito et al., 2007; Lin et al., 2003b; NY DOH, 2006).

The results of several studies (Anderson et al., 1998; Hajat et al., 1999; Schouten et al., 1996; Spix et al., 1998; Wong et al., 1999a) have demonstrated a greater increase in ED visits and hospitalizations for respiratory illnesses during the summer months, despite the fact that the avg concentrations for SO_2 in some of the areas studied were greatest in winter. In contrast, some studies found the associations between ED visits and hospital admissions and respiratory disease with similar increases in SO_2 to be greater in winter than summer (Vigotti et al., 1996; Walters et al., 1994). Other studies were unable to discern a seasonal difference in ED visits and hospitalizations for respiratory causes (Castellsague et al., 1995; Tenias et al., 1998; Wong et al., 2002c [using GAM with default convergence criteria]). These effects were not consistent across age groups. Warmer months were more likely to show evidence of an association with adverse respiratory outcomes in children, while older adults appeared more likely to be affected during the cooler months. These seasonal associations remain somewhat uncertain and require additional investigation.

In conclusion, a large number of epidemiologic studies provide evidence of an association between ambient SO_2 concentrations and ED visits and hospitalizations for all respiratory causes, in particular among children and older adults (65+ years), and for asthma. The findings are generally robust when additional copollutants are included in the model. These associations are supported by panel studies that observed SO_2-related increases in asthma and other respiratory symptoms in children, and human clinical and animal toxicological studies that found a positive relationship between SO_2 exposure and various respiratory outcomes.

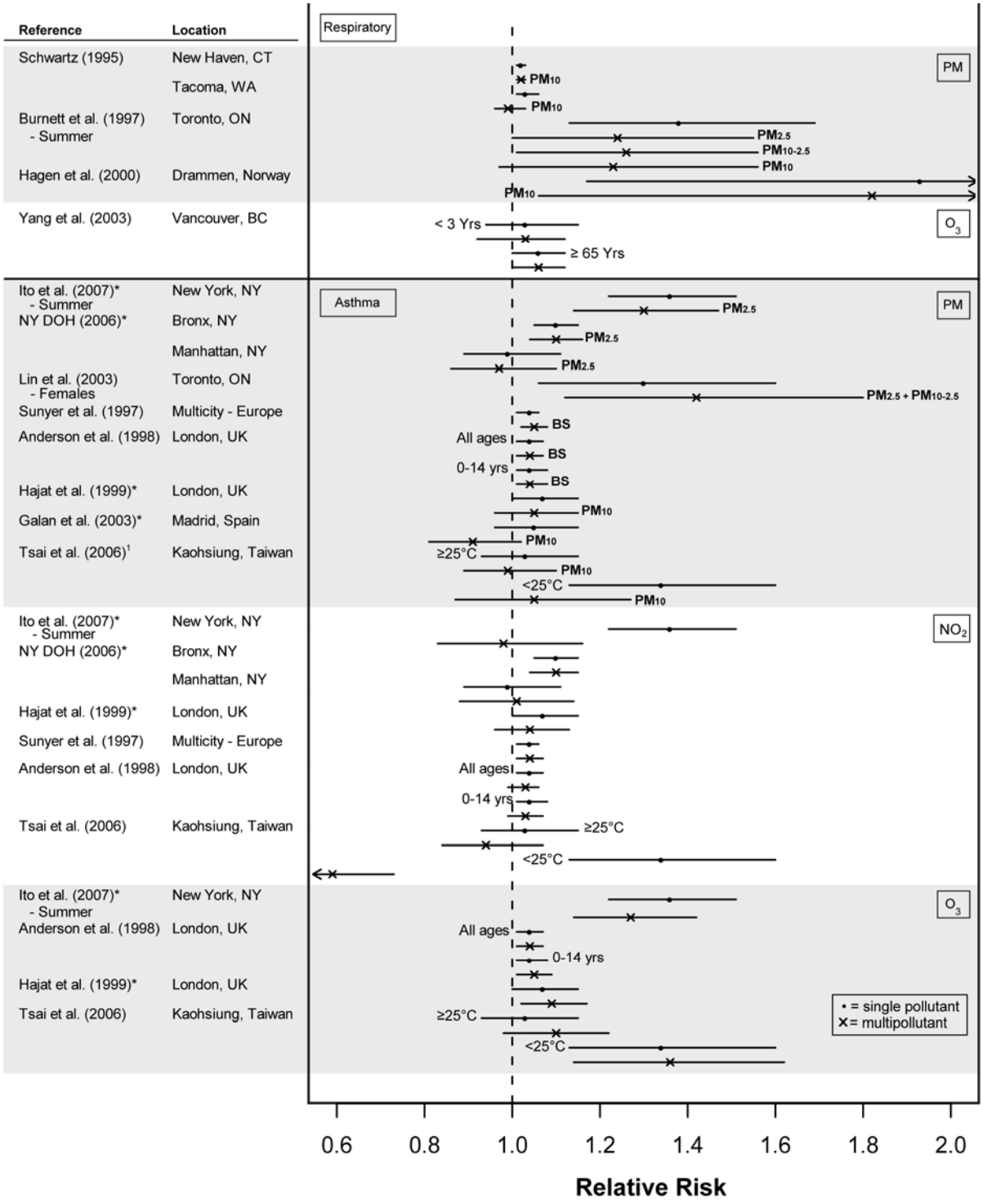


Figure 3-8. Relative risks (95% CI) of SO_2-associated emergency department visits (*) and hospitalizations for all respiratory causes and asthma, with and without copollutant adjustment. Risk estimates are standardized per 10 ppb increase in 24-h avg SO_2 concentrations or 40 ppb increase in 1-h max SO_2.

3.1.4.7. SO_2-PM Interactions and Other Mixture Effects

As discussed earlier, SO_2 is a component of complex air pollution mixtures that vary geographically and temporally (e.g., by hour, week, and season). The 1982 AQCD addressed the question of possible effects of PM on the response to SO_2. It was noted that sorption of SO_2 onto liquid or solid particles, which may act as carriers, tended to increase its potency in animal toxicological experiments. However, the mechanism for the effect was not known. Since then, additional animal studies have demonstrated respiratory responses following inhalation of SO_2 which was adsorbed onto metal oxide or carbon particles. These studies are summarized in Annex Table E-4 and both confirm and extend earlier findings. In all of the recent studies, the resulting particles were submicron in size; they would be expected to deposit in the lower respiratory tract. Acute and subacute exposures to SO_2 and PM resulted in additive or more-than-additive effects on pulmonary resistance (Amdur et al., 1983; Chen et al., 1991), diffusing capacity for CO (Amdur et al., 1988), AHR following an acetylcholine challenge (Amdur et al., 1988; Chen et al., 1992), and decreased host defense responses (Clarke et al., 2000; Jakab et al., 1996). Many of these studies reported transformation of SO_2 to sulfite, sulfate, sulfur trioxide and H_2SO_4 depending on conditions of temperature and relative humidity (Amdur et al., 1983; 1988; Chen et al., 1991; Clarke et al., 2000; Jakab et al., 1996). Respiratory responses observed in these experiments were in some cases attributed to the formation of particular sulfur-containing species. For example, repeated exposure to 20 $\mu g/m^3$ carbon black-associated sulfate resulted in impaired host defenses (Clarke et al., 2000). However, the relevance of these animal toxicological studies has been called into question because concentrations of both PM (1 mg/m^3 and higher) and SO_2 (1 ppm and higher) utilized in these studies are much higher than ambient levels. Furthermore, the SO_2-adsorbed PM utilized in some of these studies is not representative of ambient PM. For example, some of the laboratory-generated aerosols contained sulfite but atmospheric chemistry studies do not indicate significant amounts of sulfite ion in atmospheric PM. In summary, animal toxicological studies conducted since the last review suggest that SO_2 effects may be potentiated by coexposure to PM but the relevance of these results to ambient exposures is not clear.

The 1982 AQCD also described an informative study of complex air pollutants which was conducted in dogs (Stara et al., 1980). In dogs that were exposed to $SO_2 + H_2SO_4$, with or without irradiated or non-irradiated auto exhaust concentrations relevant to urban exposures, functional lung changes were observed at 61 months of exposure and at 2 years after exposures ended. Morphological and biochemical changes were observed at 2.5-3 years after exposure. Additional animal studies have been conducted since the 1982 AQCD which involved binary mixtures, laboratory-generated complex mixtures (e.g., simulation of regional air pollution), or actual ambient air mixtures. Annex Tables E-5 through E-7 summarize results from short-term studies on possible toxicity relationships between SO_2 and O_3, SO_2 and sulfates, as well as the effects of complex air pollution mixtures in healthy animals and disease models. Possible interactions between SO_2 and cold air were also examined (Annex Table E-8). Generally, most studies with ambient or laboratory-generated complex mixtures did not include a SO_2-only exposure group, making it difficult to determine the contribution of SO_X. No definitive conclusions can be made from these studies.

3.1.4.8. Summary of Evidence on the Effect of Short-Term (≥ 1 h) Exposure on Respiratory Health

Numerous epidemiologic studies have observed associations between short-term (≥ 1-h, generally 24-h avg) exposure to SO_2 and respiratory health effects, ranging from respiratory symptoms to ED visits and hospital admissions for respiratory causes. The associations between ambient SO_2 concentrations and several respiratory outcomes were generally consistent, with the large majority of studies showing positive associations, and multicity studies, as well as several single-city studies, indicating statistically significant findings. The effects on lung inflammation and AHR related to short-term exposure to SO_2 at

levels as low as 0.1 ppm found in animal toxicological studies provide a degree of coherence and biological plausibility for the observed epidemiologic associations. In addition, the causal respiratory effects of peak exposures (5-10 min) of SO_2 at levels as low as 0.2 ppm found in the human clinical studies of asthmatics (see Section 3.1.3.) provide further evidence of biological plausibility for the effects associated with short-term exposure to SO_2.

Two recent multicity studies (Mortimer et al., 2002; Schildcrout et al., 2006) and several other studies (Delfino et al., 2003a; Neas et al., 1995; van der Zee et al., 1999) have found an association between short-term ambient SO_2 concentrations and respiratory symptoms in children. In the limited number of studies that assessed potential confounding by copollutants using multipollutant models, the SO_2 effect on respiratory symptoms was generally found to be robust to adjustment for copollutants. These findings indicate an association between short-term exposure to ambient SO_2 exposure and respiratory symptoms in children, particularly those with asthma. Several recent studies (Desqueyroux et al., 2002a; 2002b; van der Zee et al., 2000) found no association between ambient SO_2 levels and respiratory symptoms in adults, though there was limited epidemiologic evidence which suggested that atopic adults as well as children may be at increased risk for SO_2-induced respiratory symptoms (Boezen et al., 1999; 2005).

Epidemiologic studies do not provide strong evidence for an association between short-term ambient SO_2 exposure and lung function in either children (Delfino et al., 2003a; Mortimer et al., 2002; Roemer et al., 1998) or adults (e.g., Peters et al., 1996a; Taggart et al., 1996). Several other studies reported positive results; however, the generally mixed findings, as well as the relative lack of evidence available to evaluate potential confounding by copollutants, limits the causal interpretation of ambient SO_2 on lung function.

Only one epidemiologic study (Adamkiewicz et al., 2004) evaluated inflammation, as indexed by eNO, and found no association with SO_2 exposure. Animal toxicological studies found that repeated exposure to SO_2 leads to increased airway inflammation in two models involving animals which were sensitized to an antigen (Li et al., 2007; Park et al., 2001a). Studies of other ambient pollutants indicate that influx of macrophages and other inflammatory cells, with the related release of cytokines, is a common response to injury.

Effects of short-term exposure to SO_2 on AHR have been observed. In two animal toxicological studies, repeated exposure to 0.1 ppm SO_2 led to AHR in guinea pigs sensitized to an antigen (Park et al., 2001a; Riedel et al., 1988). Human clinical studies by Devalia et al. (1994) and Rusznak et al. (1996) demonstrated enhanced airway responses to an inhaled allergen in asthmatic subjects following exposure to a combination of SO_2 (0.2 ppm) and NO_2 (0.4 ppm). This effect was not observed following exposure to either SO_2 or NO_2 alone. These findings of increased airway resistance are in concordance with the limited epidemiologic study results that showed SO_2-induced increases in AHR among atopic children and asthmatic adults (Soyseth et al., 1995a; Taggart et al., 1996).

Epidemiologic studies provide evidence for an association between ambient SO_2 levels and ED visits and hospitalizations for all respiratory diseases in two susceptible populations: children (Dab et al., 1996; Petroeschevsky et al., 2001; Walters et al., 1994) and older adults (65+ years) (Fung et al., 2006; Schwartz, 1995; Spix et al., 1998; Wong et al., 1999a). Evidence for an association between ambient SO_2 levels and these outcomes in non-elderly adults was weaker. A modest association between ambient SO_2 and ED visits and hospitalizations for asthma was also observed. SO_2 effect estimates were generally robust to the inclusion of copollutants, including PM, O_3, CO and NO_2, indicating that the observed effects of SO_2 on respiratory endpoints is independent of the effects of other ambient air pollutants.

In summary, recent epidemiologic studies, supported by a limited number of animal toxicological studies conducted at near ambient concentrations, indicate an association between short-term ($\geq$ 1-h, generally 24-h avg) exposure to SO_2 and several measures of respiratory health, including respiratory symptoms, inflammation, airway hyperreponsiveness, and ED visits and hospitalizations for respiratory causes. The epidemiologic evidence further observed that the SO_2-related respiratory effects were more pronounced in asthmatic children and older adults (65+ years).

3.1.5. Evidence of the Effects of SO_2 on Respiratory Morbidity from Intervention Studies

Many epidemiologic studies have examined the association of short-term SO_2 concentrations and various respiratory morbidity outcomes. These studies collectively suggest that increased ambient SO_2 concentrations are associated with increased risk of respiratory outcomes, ranging from respiratory symptoms to ED visits and hospitalizations. Further contributing to the evidence base are intervention studies that reported decreases in respiratory morbidity following improvements in air quality, particularly reductions in SO_2 concentrations.

In Hong Kong, a sudden change in regulation in July 1990 required all power plants and road vehicles to use fuel oil with a sulfur content of ≤ 0.5% by weight. These regulations were enforced quickly, and provided opportunities to observe changes in morbidity before and after the intervention. Peters et al. (1996b) followed 3,521 children (mean age 9.5 years) residing in two districts with good and poor air quality before the intervention from 1989 to 1991. The intervention resulted in large reductions in SO_2 (up to 80% in polluted district), along with a modest reduction in sulfate (38% in polluted district). Only a small change in TSP levels was observed after the intervention (15% decline in polluted district). In 1989 and 1990, an excess risk of respiratory symptoms was observed in the polluted district. After the intervention, there was a greater decline in reported symptoms of cough, sore throat, phlegm, and wheezing in the polluted compared with the unpolluted district. For example, the OR for cough, comparing the polluted to the unpolluted district, was 1.22 (95% CI: 1.05, 1.42) in 1989 and 1990, and decreased to 0.92 (95% CI: 0.73, 1.15) in 1991.

A study by Keles et al. (1999) evaluated the prevalence of chronic rhinitis among high school students before and after installation of a natural gas network for domestic heating and industrial works, in a polluted area of Istanbul, Turkey. Concentrations of CO, NO_2, and hydrocarbons were relatively low compared to SO_2 and TSP in this area. After the intervention, the annual mean TSP concentration declined by 23% from 89.7 $\mu g/m^3$ to 68.8 $\mu g/m^3$. An even greater decline (46%) was observed for SO_2, from an annual mean of 70.8 ppb to 38.2 ppb. The prevalence of rhinitis decreased significantly from 62.5% to 51% of the student population ($p < 0.05$) following the installation of the natural gas network. Symptoms of rhinitis were associated with air pollution levels, but not with any of the other factors considered, including sex, household crowding, heating source, and smoking status. Although the effects from TSP could not be separated from SO_2 effects, this study demonstrated that reductions in both pollutants (with greater declines in SO_2) resulted in significant reductions in the prevalence of chronic rhinitis in a highly polluted area.

Another study in Germany observed that reductions in air pollutant levels were associated with improvement in reported respiratory symptoms. Heinrich et al. (2002) examined the influence of reduced air pollution levels on respiratory symptoms in children aged 5 to 14 years (n = 7,632). Questionnaires were collected from the children during 1992–1993, 1995–1996, and 1998–1999 in three study areas. During the study period, SO_2 concentrations decreased by more than 90% and TSP concentrations decreased by approximately 60%. Concentrations of nucleation-mode particles (10-30 nm) increased during this time period. For most respiratory outcomes, the prevalence continued to decline in each of the three surveys. The temporal changes followed similar trends in all three study areas. Stronger effects between SO_2 and prevalence of respiratory symptoms were observed among children without indoor exposures. For those without indoor exposures, ORs of 1.21 (95% CI: 1.11, 1.32) were observed for prevalence of bronchitis and 1.11 (95% CI: 1.02, 1.22) for frequent colds per 5-ppb increase in the annual mean of SO_2. Frye et al. (2003) reported changes in lung function parameters associated with declines in SO_2 concentrations in 2,493 children during this period as well. The researchers observed a 0.6% (95% CI: 0.1, 1.2) increase in FVC and a 0.4% (95% CI: -0.1, 0.9) increase in FEV_1 per 5-ppb decrease in the annual mean of SO_2. They concluded that the decreasing prevalence of respiratory symptoms and the increase in lung function following decreases in air pollution levels might indicate the reversibility of adverse health effects in children.

In summary, these studies observed that improvements in air quality, in particular large decreases in SO_2 concentrations, were associated with improvements in respiratory symptoms and lung function. However, the decreased respiratory morbidity following large reductions in ambient SO_2 concentrations does not preclude the possibility that other constituents of the pollution mixture that share the same source as SO_2 are also responsible for adverse effects. In the German and Turkey studies, both SO_2 and TSP concentrations decreased dramatically. Although PM_{10} levels before and after the intervention were stable in Hong Kong, large reductions in ambient nickel and vanadium were observed concomitantly with reductions of sulfur after the intervention (Hedley et al., 2006). Animal toxicological studies conducted at higher concentrations ($\geq$ 1 mg/m^3 PM and $\leq$ 1 ppm SO_2) suggest that SO_2 effects may be potentiated by coexposure to PM, but the relevance of these results to ambient exposures is not clear. The improvements in respiratory health may be jointly attributable to declines in both SO_2 and PM. Considered collectively with the larger body of evidence from epidemiologic, human clinical, and animal toxicological studies, these intervention studies are supportive of SO_2-related effects on respiratory morbidity.

3.1.6. Summary of Evidence of the Effect of Short-Term SO_2 Exposure on Respiratory Health

Evaluation of the health evidence led to the conclusion that there is *a causal relationship between respiratory morbidity and short-term exposure to* SO_2. This conclusion is supported by the consistency, coherence, and plausibility of findings observed in human clinical studies with 5-10 min exposures, epidemiologic studies using largely 24-h avg exposures, and animal toxicological studies using exposures of minutes to hours.

The strongest evidence for this causal relationship comes from human clinical studies reporting respiratory symptoms and decreased lung function following peak exposures of 5-10 min duration to SO_2. These effects have been observed consistently across studies involving exercising mild to moderate asthmatics. Statistically significant decrements in lung function accompanied by respiratory symptoms including wheeze and chest tightness have been clearly demonstrated following exposure to 0.4-0.6 ppm SO_2. Although studies have not reported statistically significant respiratory effects following exposure to 0.2-0.3 ppm SO_2, some asthmatic subjects (5-30%) have been shown to experience moderate to large decrements in lung function at these exposure concentrations.

A larger body of evidence supporting this determination of causality comes from numerous epidemiologic studies reporting associations with respiratory symptoms, ED visits, and hospital admissions with short-term SO_2 exposures, generally of 24-h avg. Important new multicity studies and several other studies have found an association between 24-h avg ambient SO_2 concentrations and respiratory symptoms in children, particularly those with asthma. Furthermore, limited epidemiologic evidence indicates that atopic children and adults may be at increased risk for SO_2-induced respiratory symptoms. Generally consistent and robust associations also were observed between ambient SO_2 concentrations and ED visits and hospitalizations for all respiratory causes, particularly among children and older adults (65+ years), and for asthma. Results of experiments in laboratory animals support these observations; studies in animals sensitized with antigen demonstrate that repeated exposure to near ambient SO_2 levels (as low as 0.1 ppm in guinea pigs) can exacerbate allergic responses including airway inflammation and AHR.

Mean 24-h avg SO_2 levels ranged from 1 to 30 ppb in the epidemiologic studies, with maximum values ranging from 12 to 75 ppb. In the human clinical studies, respiratory effects were observed in exercising asthmatics following 5-10 min exposure to SO_2 at levels as low as 0.2 ppm. 5-min SO_2 data acquired from a limited number of ambient monitoring sites across the U.S. during the years 1997 to 2006 indicated that 0.2% of the hourly maximum 5-min avg were at or above a concentration of 0.2 ppm. It is difficult to unequivocally relate the 24-h avg SO_2 concentrations typically assessed in epidemiologic studies with the peak exposures in the human clinical studies. The apparent gap between the SO_2

concentrations at which respiratory health effects are observed in the epidemiologic studies and the human clinical studies may be partially attributable to the differences in the study type (e.g., sample size, study subject selection, exposure conditions). Collectively, the findings from both human clinical and epidemiologic studies provide a strong basis for concluding a causal relationship between respiratory morbidity and short-term exposure to SO_2.

3.2. Systemic Morbidity Associated with Short-Term SO_2 Exposure

3.2.1. Summary of Findings from the Previous Review

The studies reviewed in the 1982 AQCD primarily investigated respiratory health outcomes. There were no key animal toxicological or human clinical studies available at the last review to address effects of SO_2 exposure on the cardiovascular system. The only report was a study in dogs exposed to air pollutant mixtures (SO_2 + H_2SO_4 with or without nonirradiated or irradiated auto exhaust) (Stara et al., 1980). No changes were observed in cardiovascular function at the end of 3 years of exposure and 3 years after exposure. No epidemiologic studies linking exposure to SO_2 with cardiovascular physiological endpoints or ED visits or hospital admissions for cardiovascular causes were examined in the last review. Furthermore, no studies of SO_2 effects on other organ systems were addressed in the 1982 AQCD.

3.2.2. Cardiovascular Effects Associated with Short-Term Exposure

The biological basis for SO_2-related cardiovascular health effects may lie in the stimulation of chemosensitive receptors found in the respiratory tract which respond to irritants like SO_2. Vagally-mediated responses may affect the cardiovascular system by inducing bradycardia and either hypotension or hypertension, as discussed in Section 3.1.2. Alternatively oxidation reactions mediated by the SO_2 metabolites sulfite and bisulfite which have been absorbed into the systemic circulation may potentially alter cardiovascular function. In general, vagally-mediated responses have been observed at lower concentrations of SO_2 than oxidative injury.

Since 1982, several animal toxicological studies have addressed the effects of SO_2 on cardiovascular endpoints. These are summarized below and in Annex Table E-9. In addition, there is one noteworthy study examining the hematological effects of short-term SO_2 exposure (Annex Table E-10). Acute exposure of rats to 0.87 ppm SO_2 for 24 h resulted in increased hematocrit, sulfhemoglobin and osmotic fragility as well as decreased whole blood and packed cell viscosities (Baskurt, 1988). These results indicate a systemic effect of inhaled SO_2 and are consistent with an oxidative injury to red blood cells. Only one study since 1982 measured systemic levels of sulfite or bisulfite following SO_2 inhalation (Gunnison et al., 1987; Annex Table E-11). Further studies are required to confirm that inhalation exposures of SO_2 at or near ambient levels increase blood sulfite and bisulfite levels sufficiently for oxidative injury to blood cells or other tissues.

Recent epidemiologic studies have examined the association between air pollution and cardiovascular effects, including increased heart rate (HR), reduced heart rate variability (HRV), incidence of ventricular arrhythmias, changes in blood pressure, incidence of myocardial infarctions (MI), and ED visits and hospitalizations due to cardiovascular causes. The results of these cardiovascular studies are summarized in Annex Tables F-3 and F-4.

3.2.2.1. Heart Rate and Heart Rate Variability

Heart rate variability (HRV) is generally determined by analyses of time (e.g., standard deviation of normal R-R intervals [SDNN]) and frequency domains (e.g., low frequency [LF] / high frequency [HF] ratio by power spectral analysis, reflecting autonomic balance) measured during 24 h of electrocardiography (ECG). Brook et al. (2004) stated that HRV, resting heart rate, and blood pressure are modulated by a balance between the two determinants of autonomic tone (the sympathetic and parasympathetic nervous systems). An imbalance of cardiac autonomic control may predispose susceptible people to greater risk of ventricular arrhythmias and mortality from cardiovascular causes (Brook et al., 2004; Liao et al., 2004).

A limited number of human clinical studies examined the effect of SO_2 on HRV. During a controlled exposure of 12 healthy subjects and 12 subjects with asthma to 0.2 ppm SO_2 for 1 h under resting conditions, Tunnicliffe et al. (2001) reported that HF power, LF power, and total power were higher with SO_2 exposures compared to air exposure in the healthy subjects, but that these indices were reduced during SO_2 exposure in the subjects with asthma. The LF/HF ratios were unchanged in both groups. The authors postulated two autonomic pathways for SO_2-mediated bronchoconstriction. In healthy subjects, the dominant pathway was proposed to be the rapidly adapting receptor/C-fiber route, which results in activation of a central nervous system reflex with an increase in vagal tone. In the asthmatic subjects, proximal airway narrowing was proposed as the dominant response, possibly through neurogenic inflammation. This likely causes a compensatory central nervous system-mediated reduction in vagal tone, resulting in bronchodilation of the distal airway. While there were no detectable changes in symptoms or lung function in either of the groups, this study provides some evidence that exposure to SO_2 may elicit systemic responses at these low levels (0.2 ppm).

In a similar study, Routledge et al. (2006) exposed patients with stable angina as well as healthy subjects to 50 $\mu g/m^3$ carbon particles and to 0.2 ppm SO_2, each alone and in combination, for 1 h under resting conditions. HRV, C-reactive protein, and coagulation markers were measured. The authors reported that for the healthy subjects, SO_2 exposure was associated with a decrease in HRV markers of cardiac vagal control 4 h after exposure. However, it should be noted that there was no apparent difference in the absolute value of the root mean square of successive RR interval differences (r-MSSD) at 4 h postexposure between the control, SO_2, carbon, and carbon/SO_2 groups. The significant difference reported in the change in r-MSSD from baseline to 4 h postexposure with SO_2 appears to be due to a higher baseline value of r-MSSD preceding the SO_2 exposure compared to the baseline value of r-MSSD preceding the air exposure. There were no changes in HRV among the patients with stable angina. The authors noted that this lack of response in the heart patients may be due to a drug treatment effect rather than decreased susceptibility; a large portion of the angina patients were taking beta blockers, which are known to increase indices of cardiac vagal control.

In an epidemiologic study, Liao et al. (2004) investigated short-term associations between ambient pollutants and cardiac autonomic control from the fourth cohort examination (1996 through 1998) of the population-based Atherosclerosis Risk in Communities (ARIC) study using a cross-sectional study design. Men and women aged 45 to 64 years (n = 6,784) from three U.S. study centers in North Carolina, Minnesota, and Mississippi were examined. Resting, supine, and 5-min beat-to-beat R-R interval data were collected. The mean 24-h avg SO_2 level measured 1 day prior to the HRV measurement was 4 ppb (SD 4). In addition to SO_2, the potential effects of PM_{10}, O_3, CO, and NO_2 were evaluated. Previous-day SO_2 concentrations were positively associated with HR and inversely associated with SDNN and LF power. Consistently more pronounced associations were suggested between SO_2 and HRV among persons with a history of coronary heart disease. Significant associations with HRV indices also were observed for PM_{10} and the other gaseous pollutants. When the regression coefficients for each individual pollutant model were compared, the effects of PM_{10} on HRV were considerably larger than the effects for the gaseous pollutants, including SO_2. No multipollutant analyses were conducted.

Gold et al. (2000; 2003) examined the effect of short-term changes in air pollution on HRV in a panel study of 21 older adults (aged 53 to 87 years) in Boston, MA. The study participants were observed

up to 12 times from June to September 1997. The mean 24-h avg SO_2 concentration was 3.2 ppb (range: 0, 12.6). The 24-h avg SO_2 concentration was associated with decreased HR in the first 5-min rest period, but not in the overall 25-min study protocol. The effect estimate for SO_2 slightly diminished but remained marginally significant in a two-pollutant model with $PM_{2.5}$. The inverse association between SO_2 and HR observed in this study are in contrast to the SO_2-related increases in HR observed by Liao et al. (2004) and Peters et al. (1999). No associations were observed between HRV and SO_2. The strongest associations with HRV were observed for $PM_{2.5}$ and O_3.

Another study of air pollutants and HRV was conducted in Boston, MA on 497 men from the Normative Aging Study (Park et al., 2005b). The best 4-consecutive-min interval from a 7-min sample was used for the HRV calculations. For the exposure variable, 4, 24, and 48 h moving averages matched on the time of the ECG measurement for each subject were considered. The mean 24-h avg SO_2 concentration was 4.9 ppb (range: 0.95, 24.7). Associations with measures of HRV were reported for $PM_{2.5}$ and O_3, but not with SO_2 for any of the averaging periods. In another study conducted in Boston, MA, Schwartz et al. (2005) found significant effects of increases in $PM_{2.5}$ on measures of HRV, while no associations with SO_2 were observed. Other studies examined the relationship of SO_2 with HRV (Chan et al., 2005; de Paula Santos et al., 2005; Holguin et al., 2003; Luttmann-Gibson et al., 2006). Most of these studies, with the exception of de Paula Santos et al., did not observe associations with SO_2.

In the limited number of epidemiologic studies that examined a possible effect of SO_2 on HRV, there were some positive findings; however, results reported from the human clinical studies were inconsistent. The overall evidence is insufficient to conclude that SO_2 has an effect on cardiac autonomic control.

3.2.2.2. Repolarization Changes

In addition to the role played by the autonomic nervous system in arrhythmogenic conditions, myocardial vulnerability and repolarization abnormalities are believed to be key factors contributing to the mechanism of such diseases.

Two in vitro studies (Nie and Meng, 2005, 2006) conducted with a 1:3 molar:molar mixture of the SO_2 derivatives bisulfite and sulfite demonstrated effects of a 10-µm bisulfite:sulfite mixture on sodium and L-type calcium currents (which included changes in inactivation and/or activation, recovery from inactivation, and inactivation/activation time constants) in ventricular myocytes. These in vitro observations suggested a potential role for L-type calcium current in cardiac injury following SO_2 exposure. Additional toxicological studies are necessary to evaluate repolarization changes at ambient levels of SO_2.

In an epidemiologic study, Henneberger et al. (2005) examined the association of repolarization parameters (QT duration, T-wave complexity, variability of T-wave complexity, and T-wave amplitude) with air pollutants in patients with preexisting coronary heart disease (n = 56, all males) in East Germany. The patients were examined repeatedly once every 2 weeks for 6 months, for a total of 12 ECG recordings. The mean 24-h avg SO_2 concentration was 2 ppb (range: 1, 4). Ambient SO_2 concentrations during the 24-h preceding the ECG were associated with the QT interval duration, but not with any other repolarization parameters. Stronger associations were observed between PM indices and QT interval duration, T-wave amplitude, and T-wave complexity.

Evidence from the limited number of in vitro toxicological studies indicates that L-type calcium current may have a role in cardiac injury following SO_2 exposure at higher than ambient concentrations. In the single epidemiologic study of SO_2 and repolarization changes, an association between SO_2 and one of several repolarization parameters examined (QT duration) was observed; however, stronger associations were reported for PM.

3.2.2.3. Cardiac Arrhythmias

One toxicological study examined the effects of PM, ultrafine carbon, and SO_2 on spontaneous arrhythmia frequency in 18-month-old rats (Nadziejko et al., 2004). The rats were exposed to 1 ppm SO_2 for 4 h. No significant change in the frequency of spontaneous arrhythmias was found with SO_2 and ultrafine carbon exposure. However, rats exposed to concentrated ambient PM had a significantly greater increase in the frequency of delayed beats than rats exposed to air.

In a panel study of 100 patients with implanted cardioverter defibrillators (ICDs) in Eastern Massachusetts, Peters et al. (2000a) tested the hypothesis that patients with ICDs would experience life-threatening arrhythmias after an air pollution episode. The mean 24-h avg SO_2 concentration measured at two sites in Boston during the study period was 7 ppb (5th–95th percentile: 1, 19). ICDs monitor ECG abnormalities, and treat ventricular fibrillation or ventricular tachycardias by administering shock therapy to restore the normal cardiac rhythm. The ICD device also stores information on each tachyarrhythmia and shock. There was no association between SO_2 and defibrillator discharges in the 33 subjects who had any defibrillator discharges during the follow-up period or in the 6 subjects who had at least 10 discharges. There was some evidence that NO_2 was associated with increased defibrillatory interventions in the subjects with any defibrillator discharges. Among the patients with at least 10 events, NO_2, CO, and $PM_{2.5}$ were found to be associated with defibrillator discharges.

In a follow-up study designed to confirm the findings of Peters et al. (2000a), Dockery et al. (2005) used a larger sample of ICD patients in Boston (n = 203) with a longer follow-up period. The median concentration of 48-h avg SO_2 averaged across multiple sites in Boston was 4.9 ppb (IQR 4.1). No significant associations were found between ventricular arrhythmic episode days and any of the air pollutants. However, when the analysis was stratified by recent arrhythmias (i.e., within 3 days), there was evidence of an excess risk of ventricular arrhythmia with SO_2, $PM_{2.5}$, black carbon, NO_2, and CO. Since $PM_{2.5}$, black carbon, NO_2, and CO were correlated with each other and with SO_2, the authors noted that differentiating the independent effects of the pollutants would be difficult. A case-crossover analysis of the same data by Rich et al. (2005) also observed associations with 48-h avg SO_2, but the SO_2 effect was not found to be robust to adjustment by $PM_{2.5}$. In a similar study conducted in St. Louis, MO, an excess risk was associated with SO_2 concentrations in the 24 h prior to an arrhythmia, but not with $PM_{2.5}$ and O_3 (Rich et al., 2006a). In this study, none of the other measured pollutants (PM, elemental carbon, O_3, CO, NO_2) were correlated with SO_2. The authors suggested that the different effects observed in St. Louis and Boston may be due to differences in the source or mix of air pollutants in these cities. Finally, findings from a time series study of tachyarrythmic events among 518 patients over a 10 year period in Atlanta do not indicate an association with SO_2, nor with the other pollutants studied including $PM_{2.5}$ and its components (Metzger et al., 2007).

Additional studies have examined the relationship of SO_2 with arrhythmias in Vancouver, and observed associations at very low ambient SO_2 concentrations (mean 24-h avg SO_2 of ~2.5 ppb with a max of 8.1 ppb). Vedal et al. (2004) stated that of all pollutants examined, the only one with somewhat consistent positive associations with arrhythmia events was SO_2. In season-stratified analyses, SO_2 was positively associated with arrhythmias in the winter, while in the summer the association was negative. On the other hand, in the Rich et al. (2004) study, positive associations were observed in the summer but not in the winter. The authors stated that it was difficult to interpret these findings.

Collectively, the epidemiologic evidence for an association between short-term exposure to SO_2 and arrhythmias is inconsistent. The limited toxicological evidence does not provide biological plausiblity for an effect.

3.2.2.4. Blood Pressure

Two animal toxicological studies examined the effect of SO_2 on blood pressure Hälinen et al. (2000a) examined blood pressure changes in guinea pigs which were hyperventilated to simulate exercise,

and exposed to 1, 2.5, and 5 ppm SO_2 in cold, dry air. After 10-min exposures to each SO_2 concentration, separated by 15-min exposures to clean, warm, humid air, a transient increase in blood pressure was observed during 5 ppm SO_2 exposure in cold, dry air. In a second study (Hälinen et al., 2000b), hyperventilated guinea pigs were exposed to cold, dry air alone or to 1 ppm SO_2 in cold, dry air for 60 min. The study reported similar increases in blood pressure and HR with exposure to cold, dry air or to SO_2 in cold, dry air. The increase in HR was gradual, while increases in blood pressure generally occurred during the first 10 to 20 min of exposure. Similar effects were observed with exposure to cold, dry air or to SO_2 in cold, dry air, suggesting that effects were associated with cold, dry air rather than with SO_2.

Ibald-Mulli et al. (2001) examined the association between blood pressure and SO_2 using survey data from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Project. Blood pressure measurements were taken from 2,607 men and women. The mean 24-h avg SO_2 concentration was 23 ppb (range: 5, 91). An increase in systolic blood pressure was associated with 24-h avg SO_2 and TSP. However, in a two-pollutant model with TSP, the effect of SO_2 on blood pressure was substantially reduced and became nonsignificant while the effect of TSP was robust.

In a study by de Paula Santos et al. (2005), changes in blood pressure in association with SO_2 were investigated in vehicular traffic controllers (n = 48) aged 31 to 55 years living in São Paulo, Brazil, where vehicles are the primary source of air pollution. The mean 24-h avg SO_2 level, measured at six different stations around the city, was 7 ppb (SD 3). Blood pressure was measured every 10 min when subjects were awake (6 a.m. to 11 p.m.) and every 20 min during sleep (11 p.m. to 6 a.m.). Results indicated that SO_2, as well as CO, were associated with increases in systolic and diastolic blood pressure. However, when a two-pollutant model was used to test the robustness of the associations, only the CO effect remained statistically significant.

Very few studies have examined the effects of short-term SO_2 exposure on blood pressure. Collectively, the limited toxicological and epidemiologic evidence that exposure to SO_2 has effects on blood pressure is inconclusive.

3.2.2.5. Blood Markers of Cardiovascular Risk

Folsom et al. (2001) demonstrated that elevated levels of fibrinogen, white blood cell count, factor VIII coagulant activity (factor VIII-C), and von Willebrand factor were associated with risk of cardiovascular disease. Schwartz (2001) investigated the association between various blood markers of cardiovascular risk and air pollution among subjects in the Third National Health and Nutrition Examination Survey (NHANES III) in the U.S. conducted between 1989 and 1994 across 44 counties. The NHANES III is a random sample of the U.S. population with oversampling for minorities (30% of NHANES sample) and the elderly (20% of the sample). The mean SO_2 concentration was 17.2 ppb (IQR 17) across the 25 counties where data were available. This study looked at fibrinogen levels, platelet counts, and white blood cell counts. After controlling for age, ethnicity, gender, body mass index, and smoking status and number of cigarettes per day, SO_2 was found to be positively associated with white blood cell counts. PM_{10} was associated with all blood markers. In two-pollutant models, PM_{10} remained a significant predictor of white blood cell counts after controlling for SO_2, but not vice versa.

A recent cross-sectional study (Liao et al., 2005) investigated the effects of air pollution on plasma hemostatic and inflammatory markers in the ARIC study (n = 10,208). The authors hypothesized that short-term exposure to air pollutants was associated with increased levels of inflammatory markers and lower levels of albumin, as serum albumin is inversely associated with inflammation. The mean 24-h avg SO_2 concentration was 5 ppb (SD 4). Significant curvilinear relationships were observed between SO_2 and factor VIII-C, white blood cell counts, and serum albumin. The authors noted that since no biological explanation could be offered for the "U"-shaped curve between SO_2 and factor VIII-C and the "inverse U"-shape between SO_2 and albumin, generalization of the association should be exercised with caution. No associations were observed between SO_2 and fibrinogen or von Willebrand factor.

In another large cross-sectional study of 7,205 office workers in London, Pekkanen et al. (2000) examined the association between plasma fibrinogen and ambient air pollutants. The mean 24-h avg SO_2 was 9 ppb (10th–90th percentile: 5, 19). Associations with fibrinogen were observed for all pollutants examined, either in all-year or summer-only analyses, except for SO_2 and O_3.

Taken together, results from the limited number of studies is insufficient to determine the effect of SO_2 on various blood markers of cardiovascular risk.

3.2.2.6. Acute Myocardial Infarction

The association between air pollution and the incidence of MI was examined in a small number of studies. As part of the Determinants of Myocardial Infarction Onset Study, Peters et al. (2001) examined 772 patients with MI living in greater Boston, MA. A case-crossover design was used to assess changes in the risk of acute MI after exposure to potential triggers. The mean 24-h avg SO_2 was 7 ppb (range: 1, 20) during the study period. Similarly, the mean 1-h avg SO_2 was 7 ppb (range: 0, 23). In an analysis that considered both the 2-h avg (between 60 and 180 min before the onset of symptoms) and 24-h avg (between 24 and 48 h before the onset) concentrations jointly, the study found no significant association between risk of MI and SO_2. Of all the pollutants considered, only $PM_{2.5}$ and PM_{10} were found to be associated with an excess risk of MI. In a study of 5,793 confirmed cases of acute MI in King County Washington, Sullivan et al. (2005) also used a case-crossover design to investigate the association of ambient levels of several air pollutants 1, 2, 4 and 24 h before the MI onset. No association with SO_2 (or with $PM_{2.5}$) was observed. The mean SO_2 level was 9 ppb (range: 0-39 ppb) at the time of the study.

In the MONICA Project, the effect of air pollution on acute MI was studied in Toulouse, France, using a case-crossover study design (Ruidavets et al., 2005b). The mean 24-h avg SO_2 level was 3 ppb (5th–95th percentile: 1, 5). A total of 399 cases of acute MI were recorded during the study period. O_3, but not SO_2, was found to be associated with the incidence of acute MI. Exposure to PM was not considered in this study.

Only a limited number of studies examined the association between ambient SO_2 concentrations and incidence of acute MI. These studies provide no evidence that exposure to SO_2 increases the risk of MI.

3.2.2.7. Emergency Department Visits and Hospitalizations for Cardiovascular Diseases

The current review includes more than 30 peer-reviewed studies that address the effect of SO_2 exposure on ED visits or hospitalizations for cardiovascular diseases. These studies are discussed briefly in this section and further summarized in Annex Table F-4.

All Cardiovascular Diseases

The disease grouping of all cardiovascular diseases typically includes all diseases of the circulatory system (e.g., heart diseases and cerebrovascular diseases, ICD9 Codes 390-459). A summary of the associations reported for ambient SO_2 concentrations with all cardiovascular diseases are presented in Figure 3-9.

In a study of 11 cities in Spain, an excess risk of 3.6% (95% CI: 0.6, 6.7) per 10 ppb increase in 24-h avg SO_2 at a 0-1 day lag was observed for all cardiovascular disease admissions (Ballester et al., 2006). The mean 24-h avg SO_2 level in the cities studied was 6.6 ppb. In addition, time-series data linking SO_2 with hospital admissions for cardiovascular diseases in three metropolitan areas in the U.S. (i.e., Cook, Maricopa, Los Angeles Counties) was conducted (Moolgavkar 2000; reanalysis 2003). Among older adults (65+ years) in Los Angeles County, a 13.7% (95% CI: 11.3, 16.1) excess risk in admissions

was observed per 10 ppb increase in 24-h avg SO_2 at lag 0 day, in the reanalysis using a Generalized Linear Model (GLM) and natural splines to adjust for temporal trends rather than GAM. The median 24-h avg SO_2 level for Los Angeles County was 2 ppb during the study period. Results for Maricopa and Cook counties were not presented in the reanalysis.

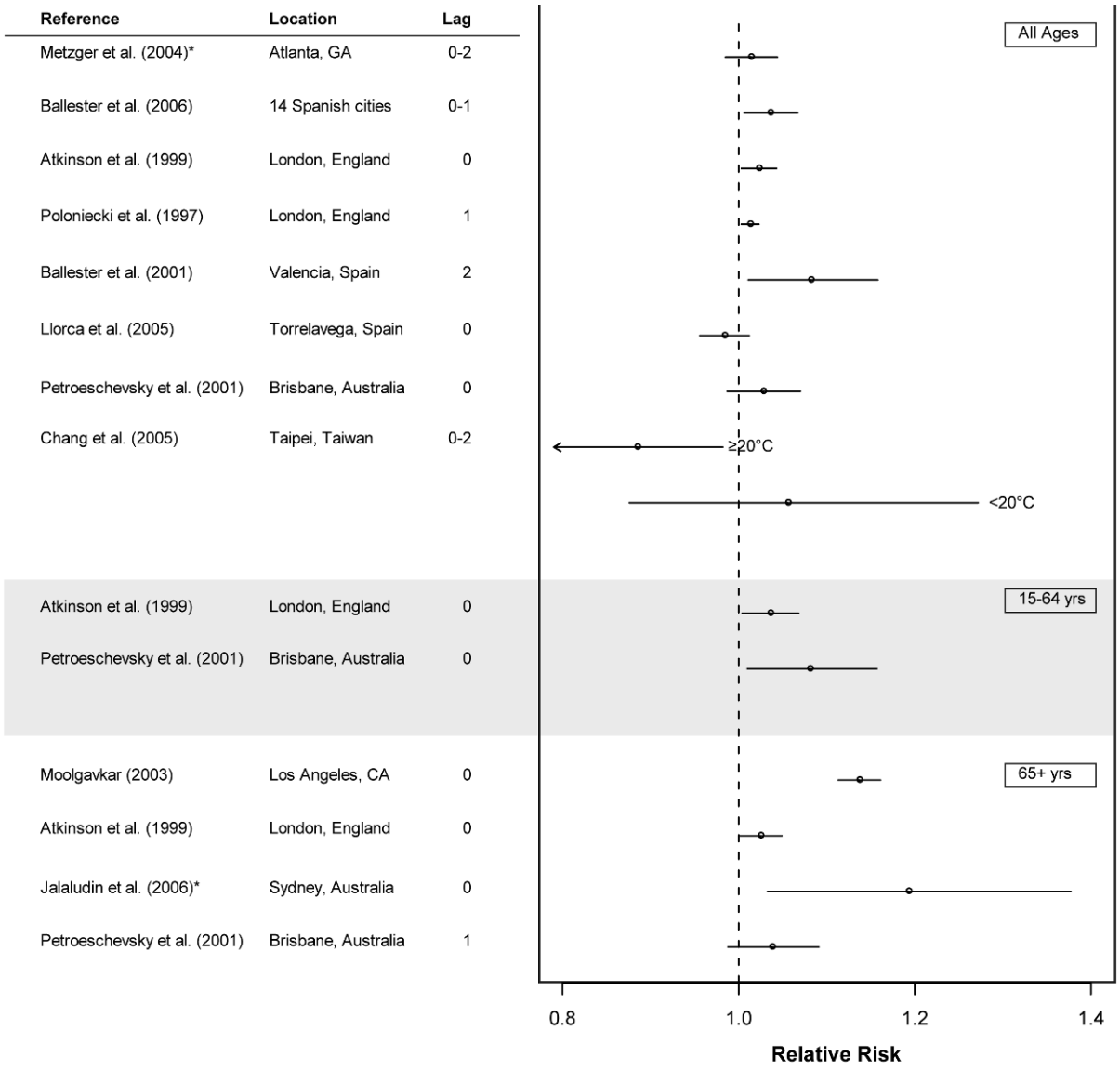


Figure 3-9. Relative risks (95% CI) of SO_2-associated emergency department visits (*) and hospitalizations for all cardiovascular causes, arranged by age group. Risk estimates are standardized per 10 ppb increase in 24-h avg SO_2 concentrations or 40 ppb increase in 1-h max SO_2.

In a large single city study Metzger et al. (2004) examined approximately 4.4 million hospital visits to 31 hospitals from 1993 to 2000 in Atlanta, GA and reported a 1.4% (95% CI: -1.5, 4.4) excess risk in ED visits for cardiovascular causes per 40-ppb increase in 1-h max SO_2. Peel et al. (2006) conducted

analyses using the same dataset to compare results obtained with a case-crossover design to the Metzer et al. (2007) results, which were obtained using a time series approach. Peel et al. (2006) and Metzger et al. (2004) report similar findings. The median 1-h max SO_2 level in Atlanta during the study period was 11 ppb (10th–90th percentile: 2–39). Results from several single-city studies in Europe, Australia, and Taiwan indicated positive associations with SO_2 (Atkinson et al., 1999a; Ballester et al., 2001; Jalaludin et al., 2006; Petroeschevsky et al., 2001; Poloniecki et al., 1997), though others observed negative associations (Chang et al., 2005; Llorca et al., 2005) (see Figure 3-9).

Specific Cardiovascular Diseases

Several studies examined the effect of ambient SO_2 on hospital admissions for cardiac disease (ICD9 Codes 390-429), ischemic heart disease (IHD, ICD9 Codes 410-414), dysrhythmia (ICD9 Code 427), congestive heart failure (CHF, ICD9 Code 428), MI (ICD9 Code 410) or cerebrovascular diseases (ICD9 Codes 430-438). In a study of the six cities of Metropolitan Toronto, Burnett et al. (1997b) reported an association between cardiac hospitalizations and ambient SO_2 (23.8% [95% CI: 5.5, 45.2]) excess risk per 40 ppb increase in 1-h max SO_2) that was robust to the inclusion of other gaseous pollutants in the model. PM was not identified as an independent risk factor for hospital admissions in this study. A European multicity study reported statistically significant positive associations with cardiac disease admissions (Ballester et al., 2006). However, adjustment for PM_{10} and CO in two-pollutant models diminished the association reported by Ballester et al. by approximately 50%. Findings for cardiac disease admissions reported in several additional single city studies conducted in the U.S., Canada, Australia and Europe were inconsistent (Fung et al., 2005b; Jalaludin et al., 2006; Llorca et al., 2005; Michaud et al., 2004).

Analyses restricted to diagnoses of IHD (Jalaludin et al., 2006; Lee et al., 2003b; Lin et al., 2003a; Metzger et al., 2004; Peel et al., 2007), CHF (Burnett et al., 1997c; Koken et al., 2003; Metzger et al., 2004; Morris et al., 1995; Peel et al., 2007; Wellenius et al., 2005a) dysrhythmia (Koken et al., 2003; Metzger et al., 2004; Peel et al., 2007), MI (Koken et al., 2003; Lin et al., 2003a), and angina pectoris (Hosseinpoor et al., 2005) were also conducted. Metzger et al. (2004) observed weak nonsignificant or negative associations of 1-h max SO_2 with IHD, CHF, and dysrhythmia. Using the same dataset, Peel et al. (2007) investigated effect modification of cardiovascular disease outcomes across comorbid disease status categories, including hypertension, diabetes, COPD, dysrhythmia, and CHF. Authors observed only weak nonsignificant or negative associations for IHD, CHF, and dysrhythmia with ambient 1-h max SO_2 level in any comorbid disease category. Both increases in admissions or ED visits (Jalaludin et al., 2006; Koken et al., 2003; Wellenius et al., 2005a) and weak or negative associations (Burnett et al., 1997; Hosseinpoor et al., 2005; Lee et al., 2003b; Lin et al., 2003a) were reported in other studies.

Studies of the effect of SO_2 on cerebrovascular admissions were also considered. Positive associations were reported for ischemic stroke (Villeneuve et al., 2006a; Wellenius et al., 2005a, 2005b). However, Wellenius et al. (2005b) reported stronger associations for NO_2 and CO than SO_2, and the association reported by Villenueve et al. (2006a) was diminished in two-pollutant models. No meaningful positive associations of ambient SO_2 with cerebrovascular diseases were observed in several other studies (Henrotin et al., 2007a; Jalaludin et al., 2006; Metzger et al., 2004; Peel et al., 2007; Tsai et al., 2003a).

Summary of Evidence on Emergency Department Visits and Hospitalizations from Cardiovascular Diseases

Several studies have observed positive associations between ambient SO_2 concentrations and ED visits or hospital admissions for cardiovascular diseases (e.g., all cardiovascular diseases, cardiac diseases, cerebrovascular diseases) particularly among individuals 65+ years of age, but results are not consistent across studies. The strongest evidence comes from a large multicity study conducted in Spain Ballester et al. (2006) that observed statistically significant positive associations between ambient SO_2

and cardiovascular disease admissions; however, the SO_2 effect was found to diminish by half with PM_{10} and CO adjustment. Only a limited number of studies assessed potential confounding by copollutants despite the moderate to strong correlation between SO_2 and various copollutants in most studies. While some studies indicated that the association of SO_2 with cardiovascular hospitalizations were generally robust to adjustment for BS and PM_{10} (Ballester et al., 2001; Fung et al., 2005b), several other studies, including that by Balleseter et al. (2006), observed that the effect of SO_2 on cardiovascular ED visits and hospitalizations may be confounded by copollutant exposures. Jalaludin et al. (2006) reported a 3% excess risk in cardiovascular disease hospital admissions per 0.75 ppb incremental change in 24-h avg SO_2 in single-pollutant models, which was reduced to null when CO was included. Chang et al. (2005) noted that the observed negative association of SO_2 with all cardiovascular disease hospitalizations was strengthened after adjusting for NO_2, PM_{10}, and CO in two-pollutant models. The authors attributed this finding to possible collinearity problems between SO_2 and copollutants. None of the epidemiologic studies examined effects of possible interactions among copollutants.

3.2.2.8. Summary of Evidence on the Effects of Short-Term SO_2 Exposure on Cardiovascular Health

Biologically plausible modes of action (e.g., vagally-mediated irritant responses and oxidative injury) that could explain short-term SO_2 effects on the cardiovascular system were summarized in a previous section of this chapter (Section 3.1.2). However, consideration of these modes of action in light of findings from additional animal toxicological, human clinical, and epidemiologic studies has led to the conclusion that the evidence as a whole is *inadequate to infer a causal relationship*.

Specifically, evidence from human clinical and epidemiologic studies of HRV in healthy persons as well as persons with asthma or cardiovascular disease was inconsistent and did not support an effect of SO_2 on the autonomic nervous system, despite some positive findings. In the single epidemiologic study of SO_2 and repolarization changes, an association with QT interval duration was observed. While in vitro studies suggested a potential role for L-type calcium current in cardiac injury, the relevance of these studies to ambient exposures is unknown. Epidemiologic evidence from studies of the effect of SO_2 on ICD-recorded arrhythmias was inconsistent. Furthermore, studies of blood pressure and blood markers of cardiovascular risk failed to provide consistent evidence to suggest a role for SO_2 in cardiovascular disease development. Finally, although some studies of hospital admissions and ED visits for cardiovascular diseases reported positive and statistically significant associations with SO_2, findings were inconsistent across this body of literature as a whole. Many researchers were unable to distinguish the effect of SO_2 from correlated copollutants while others reported a reduction in the SO_2 effect in two-pollutant models. The inconsistency of the evidence, lack of coherence across and within disciplines, as well as limitations inherent to the observational studies (e.g., inadequate control of copollutant exposures) contributed to this causal determination.

3.2.3. Other Effects Associated with Short-Term SO_2 Exposure

The short-term effects of SO_2 on other organ systems were not examined in the previous review. A review of animal toxicological studies published since the 1982 AQCD indicates a limited number of research inquiries addressing the systemic effects of short-term SO_2 exposure in various other organs. The most recent studies on these are summarized in Annex Tables E-12 through E-16.

Of note are three ex vivo acute exposure studies using SO_2 derivatives (sulfite and bisulfite) on hippocampal or dorsal root ganglion neurons isolated from Wistar rats (Du and Meng, 2004a, 2004b, 2006). Perturbations were observed in potassium-, sodium-, and calcium-gated channels at concentrations of 0.01-100 μM. These authors speculated that such effects might correlate with the neurotoxicity that has

been associated with SO_2 inhalation. However effects on the nervous system have generally been studied using chronic exposures ≥ 5 ppm SO_2. Effects observed at these levels are of questionable significance in evaluating the health effects at ambient levels. These studies are summarized in Annex Table E-12.

3.3. Mortality Associated with Short-Term SO_2 Exposure

3.3.1. Summary of Findings from the Previous Review

The studies available to review in the 1982 AQCD were mostly from historical data including London, England, and New York City air pollution episodes. Effects of SO_X (mainly SO_2) were investigated along with PM indices because they shared a common source, coal burning, and separating their associations with mortality was a challenge that many of the earlier episodic studies could not resolve. The SO_2 levels observed in these air pollution episodes were several orders of magnitude higher than the current avg levels observed in U.S. cities (e.g., in the 1962 New York City episode, SO_2 in Manhattan peaked at 400 to 500 ppb). Some of these London and New York City studies suggested that PM, not SO_2, was associated with observed mortality, but the 1982 AQCD could not resolve the relative roles of these two pollutants and suggested that the clearest mortality associations were seen when both pollutants were at high levels (24-h avg values of both BS and SO_2 exceeding 1000 $\mu g/m^3$ [~400 ppb for SO_2]) and less so at lower ranges although the review of the studies and reanalyses found no clear evidence of a threshold for SO_2.

The 1986 Second Addendum to the 1982 AQCD reviewed more reanalyses of the London data and analyses of New York City, Pittsburgh, and Athens data. While these reanalyses and some new analyses confirmed earlier findings (and suggested stronger evidence of BS effects than of the SO_2 effects), given the remaining uncertainties with exposure error and statistical modeling, there was not sufficient information to quantitatively determine concentration-response relationships at lower concentrations of either PM or SO_2.

A series of short-term mortality effects studies in the late 1980s and early 1990s (Dockery et al., 1992; Fairley, 1990; Pope, 1989; Pope et al., 1992; Schwartz and Dockery, 1992a, 1992b) showed associations between mortality and PM indices at relatively low levels. Since then, a large number of epidemiologic studies have investigated the adverse health effects of air pollution with hypotheses mainly focused on PM, and SO_2 was often analyzed as one of the potential confounders in these studies.

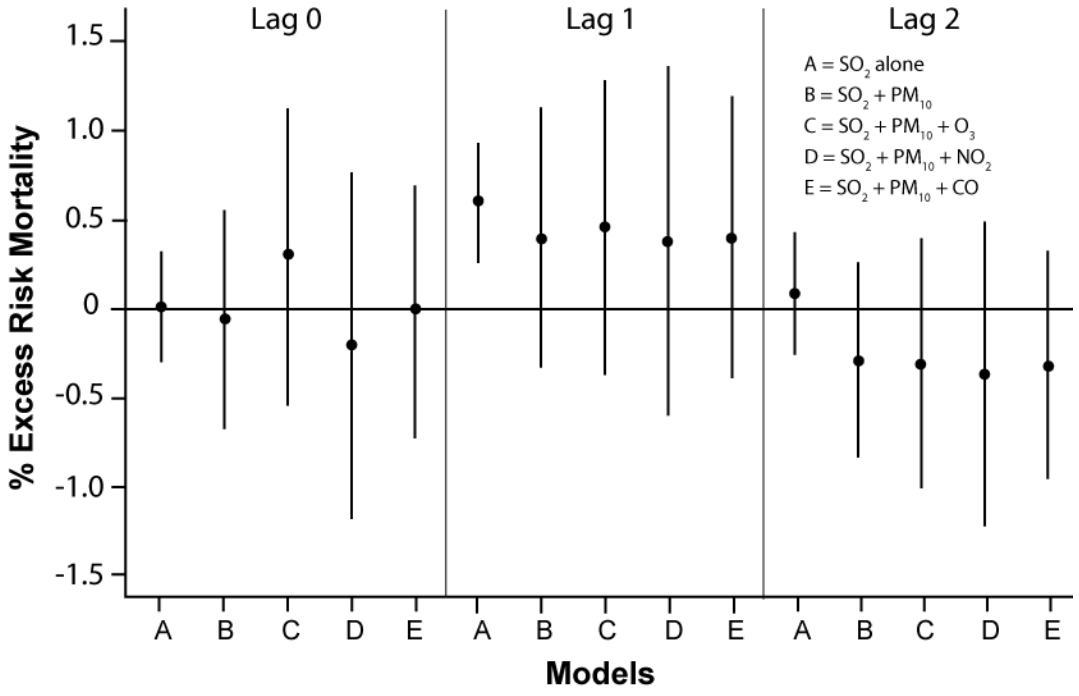
3.3.2. Mortality and Short-Term SO_2 Exposure in Multicity Studies and Meta-Analyses

In reviewing the range of SO_2 mortality effect estimates, multicity studies provide especially useful information because they analyze data from multiple cities using a consistent method, avoiding potential publication bias. There have been several multicity studies from the U.S., Canada, and Europe, some of which will be discussed in the sections below. Meta-analysis studies also provide useful information on describing heterogeneity of effect estimates across studies; however, in contrast to multicity studies, the observed heterogeneity may reflect the variation in analytical approaches across studies. In addition, the effect estimate from a meta-analysis may be subject to publication bias, unless the analysis specifically examines such bias and adjusts for it. These studies, as well as many other single-city studies, are summarized in Annex Table F-5.

3.3.2.1. Multicity Studies

National Morbidity, Mortality, and Air Pollution Study

The time-series analysis of the largest 90 U.S. cities (Samet et al., 2000a; reanalysis Dominici et al., 2003) in the National Morbidity, Mortality, and Air Pollution Study (NMMAPS) is by far the largest multicity study conducted to date to investigate the mortality effects of air pollution, but its primary focus was PM_{10}. It should also be noted that, according to the table of mean pollution levels in the original report (Samet et al., 2000a), SO_2 data were missing in 28 of 90 cities. Annual 24-h avg mean SO_2 levels ranged from 0.4 ppb (Riverside, CA) to 14.2 ppb (Pittsburgh, PA), with a mean of 5.9 ppb during the study period of 1987 to 1994. The analysis in the original report used GAM models with default convergence criteria. Dominici et al. (2003) reanalyzed the data using GAM with stringent convergence criteria as well as using GLM. It should be noted that this model's adjustment for weather effects employs more terms than other time-series studies in the literature, suggesting that the model adjusts for potential confounders more aggressively than the models in other studies.



Source: Dominici et al. (2003).

Figure 3-10. All cause mortality excess risk estimates for SO_2 from the National Morbidity, Mortality, and Air Pollution Study. Posterior means and 95% posterior intervals of national average estimates of SO_2 effects on all-cause mortality from non-external causes per 10 ppb increase in 24-h avg SO_2 at 0, 1, and 2-day lags within sets of the 62 cities with pollutant data available.

Figure 3-10 shows the all-cause mortality excess risk estimates for SO_2 from Dominici et al. (2003). The mortality excess risk estimate with a 1-day lag was 0.60% (95% CI: 0.26, 0.95) per 10 ppb increase in 24-h avg SO_2. PM_{10} and O_3 (in summer) appeared to be more strongly associated with

mortality compared to the other gaseous pollutants. The model with PM_{10} and NO_2 resulted in an appreciably reduced SO_2 excess risk estimate, 0.38% (95% CI: -0.62, 1.38) per 10 ppb increase in 24-h avg SO_2. These results suggest that the observed SO_2-mortality association could be confounded by PM_{10} and NO_2. The authors stated that the results did not indicate associations of SO_2, NO_2, and CO with all-cause mortality.

Canadian Multicity Studies

There have been three Canadian multicity studies conducted by the same group of investigators examining the association between mortality and short-term exposure to air pollutants (Burnett et al., 1998a; 2000; 2004). This section focuses on Burnett et al. (2004) as this study is the most extensive Canadian multicity study, both in terms of the length and coverage of cities. The discussion in this study focused on NO_2, because NO_2 was the best predictor of short-term mortality fluctuations among the pollutants. This was also the case in the Burnett et al. (1998a) study of the gaseous pollutants in 11 Canadian cities. The mean 24-h avg SO_2 levels across the 12 cities was 5.8 ppb, with city means ranging from 1 ppb in Winnipeg to 10 ppb in Halifax. The population-weighted avg was 5 ppb. The mean SO_2 levels in this study were similar to those in the NMMAPS (mean 24-h avg SO_2 levels across the 62 NMMAPS cities was 5.9 ppb).

All-cause (nonaccidental), cardiovascular, and respiratory mortality were analyzed in Burnett et al. (2004). For SO_2, $PM_{2.5}$, $PM_{10-2.5}$, PM_{10} (arithmetic addition of $PM_{2.5}$ and $PM_{10-2.5}$), CoH, and CO, the strongest mortality association was found at a 1-day lag, whereas for NO_2, it was the 3-day moving avg (i.e., avg of 0, 1, and 2-day lags), and for O_3, it was the 2-day moving avg. The daily 24-h avg values showed stronger associations than the daily 1-h max values for all the gaseous pollutants and CoH except for O_3. The SO_2 all-cause mortality excess risk estimate was 0.74% (95% CI: 0.29, 1.19) per 10 ppb increase in the 24-h avg SO_2 with a 1-day lag. After adjusting for NO_2, the SO_2 effect estimate was reduced to 0.42% (95% CI: 0.01, 0.84), while the NO_2 effect estimate was only slightly affected. In this analysis, no regression analysis using both SO_2 and PM was conducted. The Burnett et al. (2000) analysis observed that the simultaneous inclusion of SO_2 and $PM_{2.5}$ in the model reduced the SO_2 effect estimate by half, whereas the $PM_{2.5}$ estimate was only slightly reduced. Overall, these results suggest that SO_2 was not an important predictor of daily mortality in the Canadian cities and that its mortality associations could be confounded with NO_2 or PM.

Air Pollution and Health: A European Approach

Several Air Pollution and Health: a European Approach (APHEA) analyses have reported SO_2 mortality excess risk estimates. Katsouyanni et al. (2006) examined the association of PM_{10}, BS, and SO_2 with all-cause mortality in 12 European cities using the standard APHEA (GLM) approach. The same data set was reanalyzed to adjust for the seasonal cycles (Samoli et al., 2001; 2003). The reanalysis by Samoli et al. (2003) produced results that were similar to those in the original analysis by Katsouyanni et al. (2006). Since the original analysis presented more results, including multipollutant model results, discussion will focus on this analysis.

The study by Katsouyanni et al. (1997) includes seven western European cities (Athens, Barcelona, Cologne, London, Lyon, Milan, and Paris) and five central eastern European cities (Bratislava, Kracow, Lodz, Poznan, and Wroclaw). The data covered at least 5 consecutive years for each city within the years 1980 through 1992. The SO_2 levels in these cities were generally higher than in the U.S. or Canada, with the median 24-h avg SO_2 ranging from 5 ppb in Bratislava to 28 ppb in Kracow. Analysis was restricted to days when PM and SO_2 concentrations did not exceed 200 $\mu g/m^3$ (76 ppb for SO_2) to evaluate the effects of moderate to low exposures. The data were analyzed by each center separately following a standardized method, but the lag for the "best" model was allowed to vary in these cities from 0 to 3 days. The city-specific effect estimates were then examined in the second stage for source of heterogeneity using city-

specific variables such as mean pollution and weather variables, accuracy of the air pollution measurements, health of the population, smoking prevalence, and geographical differences.

The city-specific estimates were found to be heterogeneous and, among the explanatory variables, only the separation between western and central eastern European cities resulted in more homogeneous groups. The all-cause mortality excess risk estimates were 1.14% (95% CI: 0.88, 1.39), 1.99% (95% CI: 1.15, 2.83), and 0.46% (95% CI: -0.23, 1.15) for all the 12 cities combined, western cities, and central eastern cities, respectively, per 10 ppb increase in the 24-h avg SO_2 at variable single-day lags. Zmirou et al. (1998) analyzed cardiovascular and respiratory mortality in 10 of the 12 APHEA cities and observed that the cause-specific mortality excess risk estimates were higher than those for all-cause mortality. As in the analyses of all-cause mortality, SO_2 effect estimates for these cause specific deaths were higher in western European cities than in central eastern European cities.

Seasonal analyses indicated that the summer estimate was slightly higher than the winter estimate in the western cities, but the difference was not statistically significant. The results for the two-pollutant model with SO_2 and BS were presented for the western cities, with a similar extent (~30%) of reductions in the estimates of both pollutants (1.31% [95% CI: 0.40, 2.23] for SO_2). Furthermore, for western cities, they estimated effects for SO_2 for days with high or low BS levels and the corresponding BS effects for days with high or low SO_2 levels and found that the effects were similar in the stratified data. From these results, Katsuoyanni et al. (2006) suggested that the effects of the two pollutants were independent.

Overall, the APHEA studies provide some suggestive evidence that the effect of short-term exposure to SO_2 on mortality is independent of PM. This is somewhat in contrast to the U.S. and Canadian studies. The SO_2 levels were much higher in the European cities, but the type of PM constituents also might be different.

The Netherlands Study

In the Netherlands studies by Hoek et al. (2000; 2001; renalysis by Hoek, 2003) the association between air pollutants and mortality was examined in a large population (14.8 million for the entire country) over the period of 1986 through 1994. The Netherlands were not part of the APHEA analysis. The median 24-h avg SO_2 level in the Netherlands was 4 ppb (6 ppb for the four major cities). All the pollutants examined, including PM_{10}, BS, O_3, NO_2, SO_2, CO, sulfate, and nitrate, were associated with all-cause mortality, and for single-day models, a 1-day lag showed the strongest associations for all the pollutants. The following effect estimates are all from the GLM models with natural splines for smoothing functions. The SO_2 excess risk estimate in a single-pollutant model was 1.31% (95% CI: 0.69, 1.93) per 10 ppb increase in 24-h avg SO_2 at a 1-day lag and 1.78% (95% CI: 0.86, 2.70) at an avg of 0- to 6-day lag. Seasonal analyses showed slightly greater effect estimates during the summer compared to the winter. SO_2 was most highly correlated with BS ($r = 0.70$). The simultaneous inclusion of SO_2 and BS reduced the effect estimates for both pollutants (SO_2 effect estimate was 1.07% [95% CI: -0.27, 2.42] per 10 ppb increase with an avg of 0- to 6-day lag of 24-h avg SO_2). PM_{10} was less correlated with SO_2 ($r = 0.65$), and the simultaneous inclusion of these pollutants resulted in an increase in the SO_2 effect estimate. These results from the analysis of the Netherlands data suggested some indication of confounding between SO_2 and BS.

Cause specific analysis showed larger excess risk estimates for COPD (3.61% [95% CI: -0.29, 7.67] per 10 ppb increase in the avg of 0- through 6-day lags of 24-h avg SO_2) and pneumonia (6.56% [95% CI: 1.16, 12.24]) deaths compared to that from all causes, but because essentially all of the pollutants showed larger effect estimates for these sub-categories, it is difficult to interpret these estimates as effects of SO_2 alone. Similarly, the effect estimates for heart failure (7.1% [95% CI: 2.6, 11.7]) and thrombosis-related deaths (9.6% [95% CI: 3.1, 16.6]) were larger than that for total cardiovascular (2.7% [95% CI: 1.3, 4.1]) causes. Since the same pattern was seen for other pollutants as well, it is difficult to interpret these cause-specific effect estimates due to SO_2 alone or any one of the pollutants analyzed.

Other European Multicity Studies

Other European multicity studies were conducted in 8 Italian cities (Biggeri et al., 2005), 9 French cities (Le Tertre et al., 2002), and 13 Spanish cities (Ballester et al., 2002). The studies by Le Tertre et al. and Ballester et al. were conducted using GAM methods with the default convergence setting.

Biggeri et al. (2005) analyzed eight Italian cities (Turin, Milan, Verona, Ravenna, Bologna, Florence, Rome, and Palermo) for mortality and hospital admissions (mortality data were not available for Ravenna and Verona). The study period varied from city to city between 1990 and 1999. Only single-pollutant models were examined in this study. The SO_2 excess risk estimates were 4.14% (95% CI: 1.05, 7.33), 4.94% (95% CI: 0.41, 9.67), and 7.37% (95% CI: -3.58, 19.57) per 10 ppb increase with an avg of 0- and 1-day lag of 24-h avg SO_2 for all-cause, cardiovascular, and respiratory deaths, respectively. Since all the pollutants showed positive associations with these mortality categories and the correlations among the pollutants were not presented, it is not clear how much of the observed associations are shared or confounded. The mortality excess risk estimates were not heterogeneous across cities for all the gaseous pollutants. It should be noted that in Turin, Milan, and Rome, the mean SO_2 values declined by 50% from the first half to the second half of the study period, while the levels of other pollutants declined by smaller fractions. This also complicates the interpretation of SO_2 effect estimates in this study, which are much higher than those from the APHEA studies.

The Le Tertre et al. (2002) study of nine French cities examined BS, SO_2, NO_2, and O_3 by generally following the APHEA protocol, but using GAM with default convergence criteria and using the avg of lags 0 and 1 day for combined estimates. SO_2 data were not available in one of the nine cities (Toulouse). All four pollutants were positively associated with mortality outcomes. The study did not report descriptions of correlation among the pollutants or conduct multipollutant models, and therefore, it is difficult to assess the potential extent of confounding among these pollutants. The SO_2 effect estimates were homogeneous across cities, with the exception of Bordeaux, which was the only city that used strong acidity as a proxy for SO_2.

The Spanish Multicentre Study on Air Pollution and Mortality (EMECAM) examined the association of PM indices (i.e., PM_{10}, TSP, BS) and SO_2 with mortality in 13 cities (Ballester et al., 2002). These studies followed the APHEA protocol, but using GAM with default convergence criteria. The daily mean 24-h avg SO_2 concentrations ranged from 3 to 17 ppb. In the seven cities where 1-h max SO_2 data were also available, mean concentrations ranged from 21 to 43 ppb. The combined effect estimates for all-cause and respiratory mortality were statistically significant for both 24-h avg SO_2 and 1-h max SO_2. Controlling for PM indices substantially diminished the effect estimates for 24-h avg SO_2, but not for 1-h max SO_2. The authors reported that these results could indicate an independent impact of peak values of SO_2 more than an effect due to a longer exposure.

3.3.2.2. Meta-Analyses of Air Pollution-Related Mortality Studies

Meta-Analysis of All Criteria Pollutants

Stieb et al. (2002) reviewed time-series mortality studies published between 1985 and 2000, and conducted a meta-analysis to estimate combined effects for PM_{10}, CO, NO_2, O_3, and SO_2. Since many of the studies reviewed in that analysis used GAM with default convergence parameters, Stieb et al. (2003) updated the estimates by separating the GAM versus non-GAM studies. In addition, separate combined estimates were presented for single- and multipollutant models. There were more GAM estimates than non-GAM estimates for all the pollutants except for SO_2. For SO_2, there were 29 non-GAM estimates from single-pollutant models and 10 estimates from multipollutant models. The lags and multiday averaging used in these estimates varied. The combined estimate for all-cause mortality was 0.95% (95% CI: 0.64, 1.27) per 10 ppb increase in 24-h avg SO_2 from the single-pollutant models and 0.85% (95% CI: 0.32, 1.39) from the multipollutant models. Because these estimates are not from an identical set of

studies, the difference (or lack of a difference, as in this case) between the two estimates may not necessarily be due to the effect of adding a copollutant in the model. Note that the data extraction procedure of this meta-analysis for the multipollutant models was to include from each study the multipollutant model that resulted in the greatest reduction in effect estimates compared with that observed in single-pollutant models. It should also be noted that all the multicity studies whose combined estimates have been discussed in the previous section were published after this meta-analysis.

Health Effects Institute Review of Air Pollution Studies in Asia

The Health Effects Institute (HEI) conducted a comprehensive review of air pollution health effects studies in Asia (HEI, 2004) that summarized the results from mortality and hospital admission studies published in the peer-reviewed scientific literature from 1980 through 2003. Of the 138 papers the report identified, most were studies conducted in East Asia (mainland China, Taipei, Hong Kong, South Korea, and Japan). The levels of SO_2 in these Asian cities were generally higher than in U.S. or Canadian cities, with more than half of these studies reporting mean 24-h avg SO_2 levels of > 10 ppb. Based on a comparison of the reported mean SO_2 levels from the same cities in different time periods, it is clear that the SO_2 levels declined significantly in the 1990s. The meta-analysis used the most recent estimate for each city to reflect recent pollution levels. Based on the criteria of having at least one year of data, model adjustment for major time-varying confounders, and reporting effect estimates per unit increase in air pollution, the meta-analysis included 28 time-series studies (11 from South Korea, 6 from mainland China, 6 from Hong Kong, and 1 each from Taipei, India, Singapore, Thailand, and Japan). The lags selected to compute combined estimates were inevitably variable; a systematic approach was used to favor the a priori lag stated in the study, followed by the most significant lag, and then the largest effect estimate.

Among the health outcomes examined in the meta-analysis, all-cause mortality was addressed in the largest number of studies (13 studies) and SO_2 was the most frequently studied pollutant (11 studies). The report generally focused on the results of single-pollutant models, as there were too few studies with results of comparable multipollutant models to allow meaningful analysis. The SO_2 mortality effect estimates showed evidence of heterogeneity. The combined estimate for all-cause mortality was 1.49% (95% CI: 0.86, 2.13) per 10 ppb increase in 24-h avg SO_2. One of the limitations noted in the report was that some degree of publication bias was present in these studies.

3.3.3. Evidence of the Effect of SO_2 on Mortality from an Intervention Study

Many time-series studies provide estimates of excess risk of mortality, but a question remains as to the likelihood of a reduction in deaths when SO_2 levels are actually reduced. A sudden change in regulation in Hong Kong in July 1990 required the conversion to fuel oil with low sulfur content. The reduction in respiratory symptoms among children living in the polluted district in Hong Kong after the intervention was previously discussed in Section 3.1.5. Hedley et al. (2002) examined changes in mortality rates following the intervention. The SO_2 levels after the intervention declined about 50% (from about 17 ppb to 8 ppb), but the levels for PM_{10}, NO_2, and sulfate did not change and O_3 levels slightly increased. The seasonal mortality analysis results showed 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 death rate) in the following winter, then returned to the expected pattern three to five years after the intervention. Using Poisson regression of the monthly deaths, the avg annual trend in death rate significantly declined after the intervention for all causes (2.1%), respiratory causes (3.9%), and cardiovascular causes (2.0%), but not from other causes. These results seem to suggest that a reduction in SO_2 leads to an immediate reduction in deaths and a continuing decline in the annual trend in death rates.

Hedley et al. (2002) estimated that the expected average gain in life expectancy per year due to the lower SO_2 levels was 20 days for females and 41 days for males.

Interpreting these results is somewhat complicated by an upward trend in mortality across the intervention point, which the authors noted was 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 the 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, which can vary from year to year. 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 this study is the lack of a winter peak for respiratory and all-cause mortality during the year immediately following the intervention. Much could be made of this lack of a winter peak, but no discussion of the potential impact of (or a lack of) influenza epidemics is provided. These issues complicate the interpretation of the estimated decline in upward trend of mortality rate or the apparent lack of winter peak.

The decline in mortality following the intervention does not preclude the possibility that other constituents of the pollution mixture that share the same source as SO_2 are responsible for the adverse effects. Even though PM_{10} levels before and after the intervention were stable in Hong Kong, it is possible that constituents that do not explain a major fraction of PM may have declined. As also noted previously in Section 3.1.5, Hedley et al. (2006) noted large reductions in ambient nickel and vanadium concomitantly with reductions of sulfur after the intervention. SO_2 also may be serving as a modifier of the effect of respirable particles. Thus, while the Hong Kong data are supportive of SO_2-mortality effects, the possibility remains that mortality effects may be caused by constituents of SO_2-associated sources.

3.3.4. Summary of Evidence on the Effects of Short-Term SO_2 Exposure on Mortality

The epidemiologic evidence on the effect of short-term exposure to SO_2 on all-cause (nonaccidental) and cardiopulmonary mortality is *suggestive of a causal relationship* at ambient concentrations. The epidemiologic studies are generally consistent in reporting positive associations between SO_2 and mortality; however, there was a lack of robustness of the observed associations to adjustment for copollutants.

Figure 3-11 presents all-cause SO_2 mortality excess risk estimates from the multicity studies and meta-analyses. The mortality effect estimates from single-pollutant models range from 0.6% (NMMAPS) to 4.1% (Italian 8-cities study) per 10 ppb increase in 24-h avg SO_2 concentrations, but given the large confidence band in the Italian study, a more stable range may be 0.6 to 2%. It is noteworthy that the SO_2 effect estimates for the NMMAPS and Canadian 12-city studies are quite comparable (0.6 and 0.7%, respectively), considering the differences in the modeling approach. The heterogeneity of estimates in the multicity studies and meta-analyses may be due to several factors, including the differences in model specifications, averaging/lag time, SO_2 levels, and effect-modifying factors. Only the APHEA study examined possible sources of heterogeneity for SO_2-related mortality. They examined several potential effect modifiers such as the mean levels of pollution and weather variables, accuracy of the air pollution measurements, health of the population, smoking prevalence, and geographical differences. The only variable that could explain the heterogeneity of city-specific effect estimates was the geographic separation (western versus central eastern European cities) for both SO_2 and BS, but heterogeneity in the SO_2 effect estimates remained within the western cities.

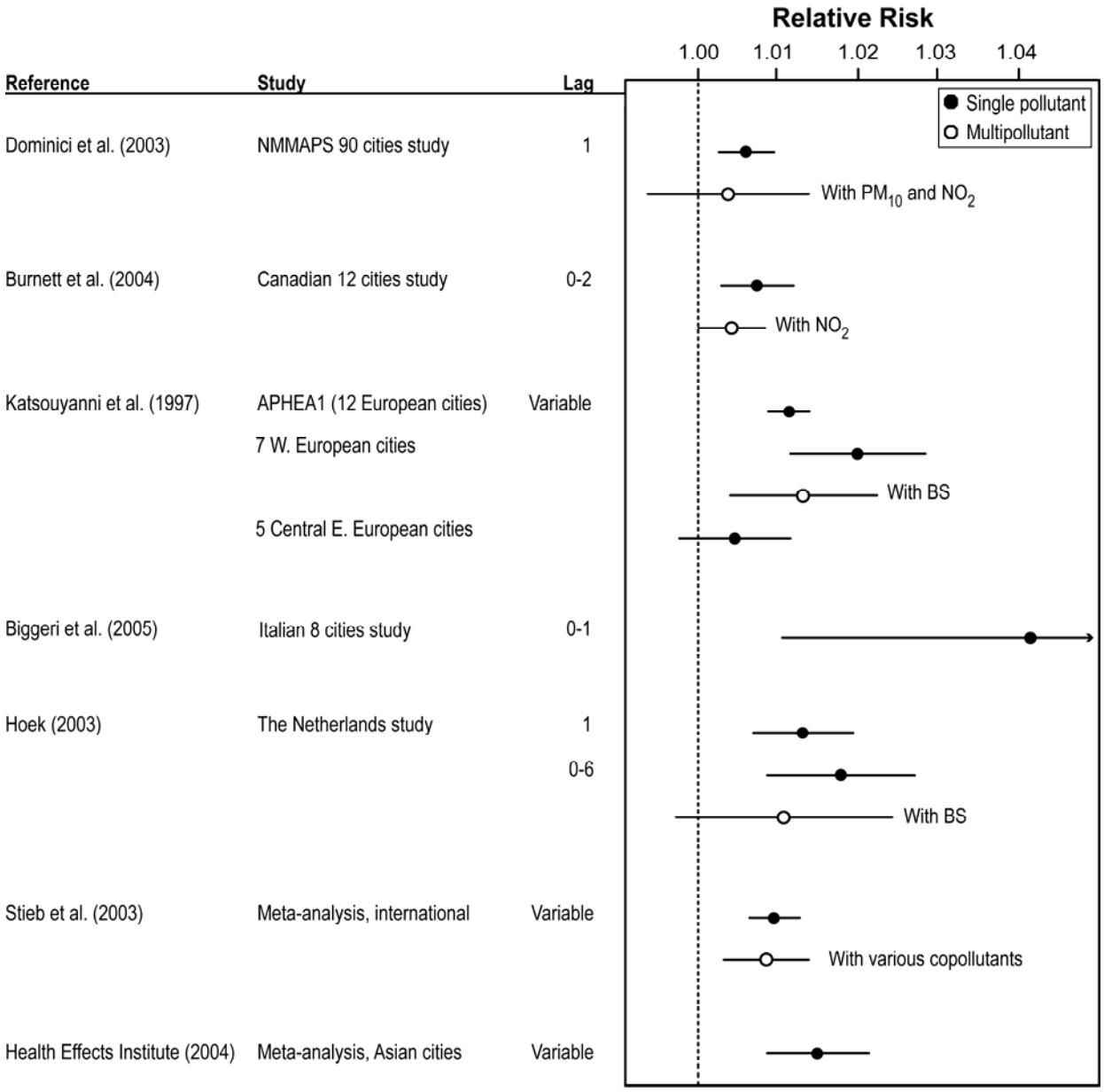
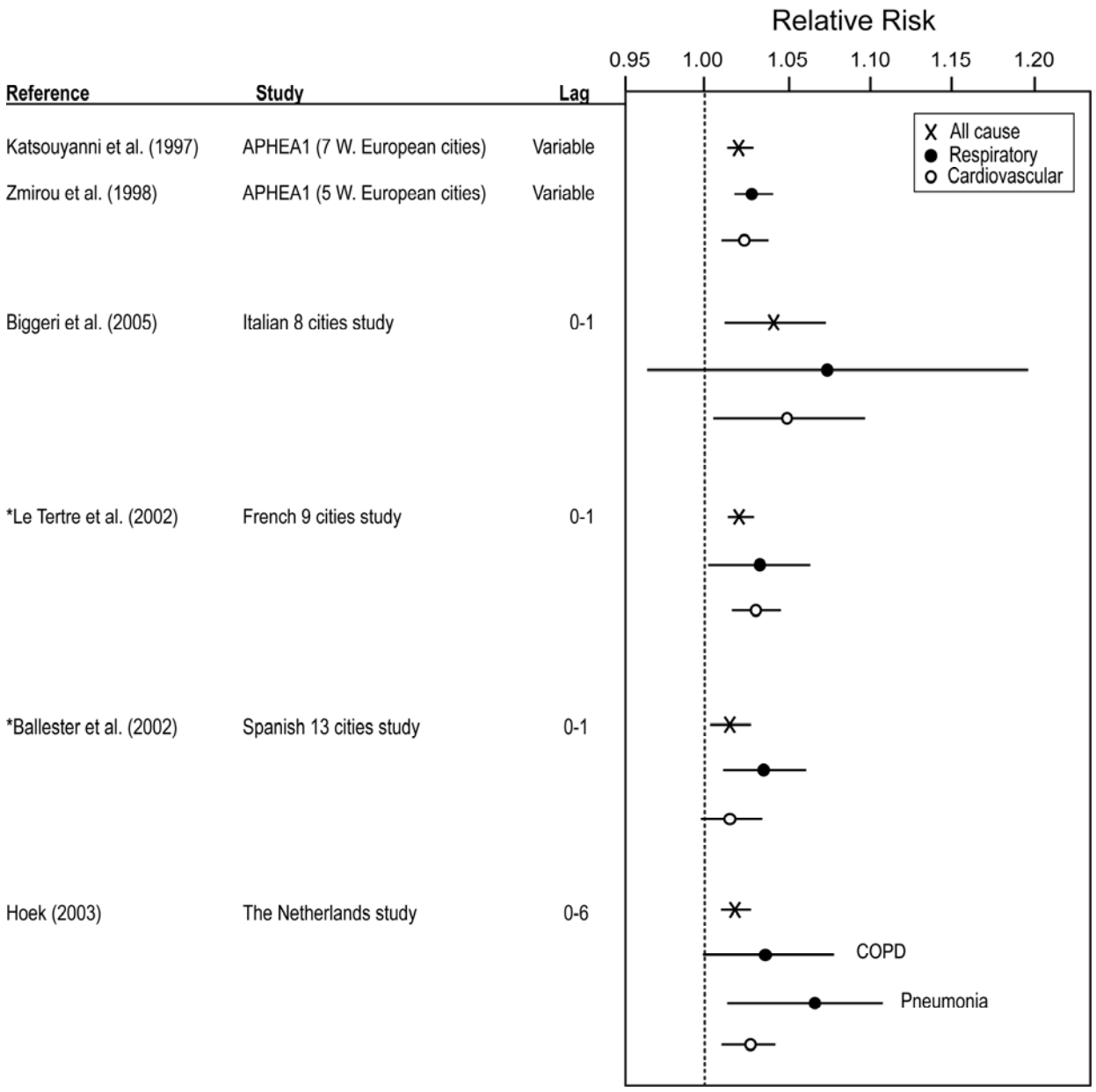


Figure 3-11. Relative risks (95% CI) of SO_2-associated all-cause (nonaccidental) mortality, with and without copollutant adjustment, from multicity and meta-analysis studies. Effect estimates are standardized per 10 ppb increase in 24-h avg SO_2 concentrations. For multipollutant models, results from the models that resulted in the greatest reduction in the SO_2 effects are shown. (NMMAPS = National Morbidity, Mortality, and Air Pollution Study; APHEA = Air Pollution and Health: a European Approach.)



*Note: Le Tertre et al. (2002) and Ballester et al. (2002) performed analyses using Poisson GAM with default convergence criteria.

Figure 3-12. Relative risks (95% CI) of SO_2-associated mortality for all (nonaccidental), respiratory, and cardiovascular causes from multicity studies. Effect estimates are standardized per 10 ppb increase in 24-h avg SO_2 concentrations. (APHEA = Air Pollution and Health: a European Approach.)

Several multicity studies provided effect estimates for broad cause-specific categories, typically respiratory and cardiovascular mortality. A summary of these effect estimates, along with the all-cause mortality estimates for comparison, are presented in Figure 3-12. These results from multicity studies suggest that the mortality effect estimates for cardiovascular and respiratory causes were generally larger than that for all-cause mortality, though in some cases the effects were not statistically significant, possibly because of reduced statistical power by which to examine cause-specific associations. In these

studies, the effect estimates for respiratory mortality were also found to be larger than the cardiovascular mortality effect estimates, suggesting a stronger association of SO_2 with respiratory mortality compared to cardiovascular mortality. This finding is consistent with the observed greater effects of SO_2 on respiratory morbidity compared to cardiovascular morbidity.

As shown previously in Figure 3-11, the mortality effect estimates from the multipollutant models in the multicity studies suggest some extent of confounding between SO_2 and PM and/or NO_2, as indicated by the instability of the effect estimates in multipollutant models. It should be noted, however, that interpretation of the single- versus multipollutant model results are complicated by potential interaction among copollutants and differing degrees of measurement error for correlated pollutants.

Very few studies specifically examined possible interactions among the copollutants. Katsouyanni et al. (2006) examined the effect estimates for SO_2 and BS in seven western European cities for subsets stratified by high and low levels of the other pollutant and found that the estimates were similar for days with low or high levels of the other pollutant. From these results, Katsouyanni et al. suggested that the effects of SO_2 and BS were independent.

In summary, recent epidemiologic studies have reported associations between mortality and SO_2, often at mean 24-h avg levels of < 10 ppb. The range of the excess risk estimates for SO_2 on all-cause mortality is 0.4 to 2% per 10 ppb increase in 24-h avg SO_2 in several multicity studies and meta-analyses. The effect estimates for more specific categories may be larger. The larger European study suggests that the observed heterogeneity in SO_2 effect estimates is at least in part regional. The intervention study from Hong Kong supports the idea that a reduction in SO_2 levels results in a reduction in deaths, but this does not preclude the possibility that the causal agent is not SO_2 but rather something else that is associated with SO_2 sources. Results from the multicity studies suggest that SO_2-mortality excess risk estimates may be confounded to some extent by copollutants, making a definitive distribution of effects among the pollutants difficult. However, the interpretation of multipollutant model results also requires caution because of possible interaction among the copollutants and influence of varying measurement error. Very limited information was available to determine possible interaction effects between SO_2 and PM or other copollutants. Overall, the evidence that SO_2 is causally related to mortality at current ambient levels is suggestive, but limited by potential confounding and lack of understanding regarding the interaction of SO_2 with copollutants in the epidemiologic data.

3.4. Morbidity Associated with Long-Term SO_2 Exposure

3.4.1. Summary of Findings from the Previous Review

The 1982 AQCD addressed some effects of long-term SO_2 exposure. It was reported that bronchoconstriction resulted from chronic exposure to 5.1 ppm SO_2 in dogs but not in monkeys. This increased pulmonary resistance was thought to occur as a result of morphological changes in the airway or hypersecretion of mucus leading to airway narrowing. However, there were no remarkable pulmonary pathological findings in monkeys and dogs in these studies. This could have been due to the conventional light microscopic examination applied, which could not detect alterations in surface membranes or subtle changes in cilia.

It was also noted that repeated exposures of rats ≥ 50 ppm SO_2 produced chronic bronchitis similar to that seen in humans although there was no evidence to suggest that bronchitis developed in humans at ambient levels of SO_2. Furthermore, nasal mucosal alterations were observed in mice exposed to 10 ppm SO_2 for 72 h by inhalation. Lack of data on morphological effects of SO_2 at near ambient concentrations was noted. In addition, some alterations in lung host defenses were discussed with chronic exposure to SO_2 at doses exceeding ambient concentrations.

In the 1982 AQCD, only a few epidemiologic studies provided sufficient quantitative evidence relating respiratory symptoms or pulmonary functions changes to long-term exposure to SO_2. Briefly, a study by Lunn et al. (1967) in Sheffield, England, provided the strongest evidence of an association between pulmonary function decrements and increased frequency of lower respiratory tract symptoms in 5- to 6-year-old children chronically exposed to ambient BS (annual level of 230 to 301 $\mu g/m^3$) and SO_2 levels (69 to 105 ppb). A follow-up study by Lunn et al. (1970) found no effect with much lower levels of BS (range: 48, 169 $\mu g/m^3$) and SO_2 (range: 36, 97 ppb); it was suggested that this might be due to insufficient power to detect small health effect changes.

The 1986 Second Addendum presented three additional studies that examined the effects of long-term exposure on respiratory health. A study by Ware et al. (1986) reported that respiratory symptoms were associated with annual avg TSP in the range of ~30 to 150 $\mu g/m^3$ in children (n = 8,380) from six U.S. studies. Only cough was found to be significantly associated with SO_2. Although the increase in symptoms did not appear concomitantly with any decrements in lung function, this may indicate different mechanisms of effect. Other studies by Chapman et al. (1995) and Dodge et al. (1985) also observed increased prevalence of cough among children and young adults living in areas of higher SO_2 concentrations; however, it was noted that the observed effects might have been due to intermittent high SO_2 peak concentrations.

In addition to respiratory effects from long-term exposure to SO_2, the potential carcinogenicity of SO_2 or other SO_X was also examined in the previous review. The 1982 AQCD concluded that little or no clear epidemiologic evidence substantiated the hypothesized links between SO_2 or other SO_X and cancer, though there was some animal toxicological evidence that led to the conclusion that SO_2 may be considered a suspect carcinogen/cocarcinogen. There was very limited consideration of the effects of long-term exposure to SO_2 on other organ systems.

Since the 1982 AQCD and the 1986 Second Addendum, a number of animal toxicological and epidemiologic studies have investigated the effect of long-term exposure to SO_2 on respiratory morbidity, including asthma, bronchitis and respiratory symptoms, lung function, morphological effects, and lung host defense. Additional studies have examined the effect of long-term SO_2 exposure on genotoxic and carcinogenic effects, cardiovascular effects, and prenatal and neonatal outcomes, which are also briefly discussed in this section.

3.4.2. Respiratory Effects Associated with Long-Term Exposure to SO_2

3.4.2.1. Asthma, Bronchitis, and Respiratory Symptoms

Several epidemiologic studies have examined the association between long-term exposure to SO_2 and other air pollutants on asthma, bronchitis, and a variety of respiratory symptoms. These studies are summarized in Annex Table F-6. In the Six Cities Study of Air Pollution and Health, cross-sectional associations between air pollutants and respiratory symptoms were examined in 5,422 white children aged 10 to 12 years old from Watertown, MA, St. Louis, MO, Portage, WI, Kingston-Harriman, TN, Steubenville, OH, and Topeka, KS (Dockery et al., 1989). Annual means of 24-h avg SO_2 concentrations ranged from 3.5 ppb in Topeka to 27.8 ppb in Steubenville. Except for O_3, the correlations among pairs of pollution measures varied between 0.53 and 0.98. No associations were observed between SO_2 and a variety of respiratory symptoms, including bronchitis, chronic cough, chest illness, persistent wheeze, and asthma. Stronger associations were observed for PM indices.

Dockery et al. (1996) examined the respiratory health effects of acid aerosols in 13,369 white children aged 8 to 12 years old from 24 communities in the U.S. and Canada between 1988 and 1991. The city-specific annual mean SO_2 concentration was 4.8 ppb, with a range of 0.2 to 12.9 ppb. With the exception of the gaseous acids, nitrous and nitric acid, none of the particulate or gaseous pollutants, including SO_2, were associated with increased asthma or any asthmatic symptoms. Stronger associations

with particulate pollutants were observed for bronchitis and bronchitic symptoms. For SO_2, the only significant association found was with chronic phlegm, with an OR of 1.19 (95% CI: 1.00, 1.40) per 5 ppb increase in SO_2.

Herbarth et al. (2001) performed a meta-analysis of three cross-sectional surveys conducted in East Germany investigating the relationship between lifetime exposure (from birth to completion of questionnaire survey) to SO_2 and TSP in children and the prevalence of chronic bronchitis. Using a logistic model that included variables on parental predisposition (mother or father with bronchitis) and environmental tobacco smoke exposure, the authors reported that the OR for bronchitis due to a lifetime exposure to SO_2 was 3.51 (95% CI: 2.56, 4.82) (the concentration change for which the OR was based was not presented). No associations were found between TSP and the prevalence of bronchitis in children.

As part of the international SAVIAH (Small-Area Variation in Air Pollution and Health) study, Pikhart et al. (2001) examined the respiratory health effects from long-term exposure to SO_2 in children (n = 6,959) from two central European cities with high pollution levels (Prague, Czech Republic, and Poznan, Poland). A novel technique was used to estimate the outdoor concentrations of SO_2 at a small-area level. Outdoor SO_2 was measured by passive samplers at 130 sites in the two cities during 2-week periods. Concentrations of SO_2 at each location in the study areas were estimated from these data by modeling using a geographic information system (GIS). The estimated mean exposure to outdoor SO_2 was 32 ppb (range: 25, 37) in Prague and 31 ppb (range: 17, 53) in Poznan. The prevalence of wheezing or whistling in the past 12 months was associated with SO_2 (OR of 1.08 [95% CI: 1.03, 1.13] per 5 ppb increase in SO_2). Moreover, the lifetime prevalence of wheezing or whistling (OR 1.03 [95% CI: 1.00, 1.07]) and lifetime prevalence of physician-diagnosed asthma (OR 1.09 [95% CI: 1.00, 1.19]) also were associated with SO_2 levels. In the SAVIAH study, the only other pollutant considered in relation to health outcomes was NO_2. An earlier publication by Pikhart et al. (2000) presented preliminary results of the Prague data and indicated that the observed associations between NO_2 and respiratory symptoms were generally similar to that of SO_2.

The International Study of Asthma and Allergies in Children (ISAAC) included thousands of children in several European countries and Taiwan (Hirsch et al., 1999; Hwang et al., 2005; Penard-Morand et al., 2005; Ramadour et al., 2000; Studnicka et al., 1997). Pénard-Morand et al. examined the effect of long-term exposures to air pollution and prevalence of exercise-induced bronchial reactivity (EIB), flexural dermatitis, asthma, allergic rhinitis, and atopic dermatitis in 9,615 children aged 9 to 11 years in six French communities. Using 3-year averaged concentrations of SO_2, the investigators reported that the prevalence of EIB reactivity, lifetime asthma, and allergic rhinitis were significantly associated with increases in SO_2 exposure. The estimated 3-year averaged concentration of SO_2 was 2 ppb in the low-exposure schools and 4 ppb in the high-exposure schools. In a single-pollutant model, the ORs were 2.37 (95% CI: 1.44, 3.77) for EIB and 1.58 (95% CI: 1.00, 2.46) for lifetime asthma per 5 ppb increase in SO_2. In this study, SO_2 was correlated with PM_{10} ($r = 0.76$) but not with O_3 ($r = -0.02$). Using a two-pollutant model that included PM_{10}, the associations of SO_2 with EIB and lifetime asthma were fairly robust (< 5% change).

In a German study of 5,421 children, the annual mean SO_2 concentration was associated with morning cough reported in the last 12 months, but not bronchitis (Hirsch et al., 1999). This study further observed that the association of SO_2 and other air pollutants with respiratory symptoms were stronger in nonatopic than in atopic children. The authors noted that these findings were in line with the hypothesis that these air pollutants induce nonspecific irritative rather than allergic inflammatory changes in the airway mucosa, as irritative effects would affect the clinical course in nonatopic children more strongly than in atopics whose symptoms are also determined by allergen exposure.

In contrast to the studies noted above, other studies using the ISAAC protocol did not observe an association between long-term exposure to SO_2 and respiratory symptoms. In France, Ramadour et al. (2000) performed an epidemiologic survey of 2,445 children aged 13 to 14 years living in communities with contrasting levels of air pollution to determine the relationship between long-term exposure to gaseous air pollutants and prevalence rate of rhinitis, asthma, and asthma symptoms. The avg SO_2 concentrations during the 2-month survey period ranged from 7 ppb to 22 ppb across the seven

communities. This study found no relationship between the mean levels of SO_2, NO_2, or O_3 and the above-mentioned symptoms. Another study of 843 children from eight nonurban communities in Austria did not observe consistent associations between SO_2 and prevalence of asthma and symptoms (Studnicka et al., 1997). Compared to the lowest SO_2 concentration category, the ORs in the higher SO_2 concentration categories (third and fourth quartiles) did not exceed one for any of the symptoms examined (wheeze, cough, bronchitis, and asthma).

A cohort study was conducted by Goss et al. (2004) to examine the effect of air pollutants on a potentially susceptible population, patients with cystic fibrosis. Study participants included 11,484 patients (mean age 18.4 years) enrolled in the Cystic Fibrosis Foundation National Patient Registry in 1999–2000. Exposure was assessed by linking air pollution values from ambient monitors with the patient's home ZIP code. During the study period, the mean SO_2 concentration was 4.9 ppb (SD 2.6, IQR: 2.7, 5.9). This study found no association between SO_2 and the odds of having two or more pulmonary exacerbations. One of the limitations addressed by the authors was the lack of information regarding tobacco use or environmental tobacco smoke, an important risk factor for pulmonary exacerbations.

Several studies examined the effects of long-term exposure to SO_2 on asthma, bronchitis, and respiratory symptoms. The studies reported positive associations in children; the notable exception was the Harvard Six Cities Study. However, there were inconsistencies in the results observed: some found effects on bronchitic but not asthmatic symptoms; others found the converse. A major limitation was that some subjects were asked to recall prevalence of symptoms in the last 12 months or in a lifetime; such long recall periods may have caused significant recall bias. Another concern is the high correlation of long-term avg SO_2 and copollutant concentrations, particularly PM, and the very limited evaluation of potential confounding in these studies. Overall, the epidemiologic studies do not provide sufficient evidence to conclude that long-term exposure to SO_2 has an effect on asthma, bronchitis, or respiratory symptoms.

3.4.2.2. Lung Function

Only a few new animal toxicological studies involving longer-term inhalation exposures to SO_2 were conducted since the last review. These studies are summarized here and in Annex Table E-1. Rabbits that were neonatally immunized to *Alternaria tenuis* and exposed to 5 ppm SO_2 for 13 weeks beginning in the neonatal period (Douglas et al., 1994) did not demonstrate alterations in lung resistance, dynamic compliance, trans-pulmonary pressure, tidal volume, respiration rate or minute volume. Similarly, no changes in physiological function were noted in dogs exposed to 15 ppm SO_2 for 2 h/day and 4-5 days/week for 5 months (Scanlon et al., 1987), although changes were noted at 50 ppm. However, Smith et al. (1989) found decreased residual volume and quasistatic compliance in rats at 4 months of exposure to 1 ppm SO_2 for 5 h/day and 5 days/week.

Only a limited number of epidemiologic studies examined the association between long-term exposure to SO_2 and changes in lung function. The Harvard Six Cities Study by Dockery et al. (1989) reported that no associations were observed between lung function and long-term exposure to air pollution, including SO_2, in a cohort of more than 5,000 children. An analysis of NHANES II data by Schwartz (1989), which included information on children and youths from 44 cities but was limited by a cross-sectional study design, also did not observe an association with SO_2, though inverse associations of FVC and FEV_1 with annual concentrations of TSP, NO_2 and O_3 were found. Additional studies conducted in Europe observed mixed results.

In a longitudinal cohort study of 1,150 children in nine communities in Austria, Frischer et al. (1999) examined the effect of long-term exposure to air pollutants on lung function. Lung function was measured in the spring and fall over a 3-year period from 1994 through 1996. Annual mean SO_2 concentrations ranged from 2 to 6 ppb across the nine communities. The authors reported no consistent associations between SO_2, PM_{10}, or NO_2 and lung function. For SO_2, a negative parameter estimate was observed during the summer, but a positive estimate was found during the winter period. Horak et al.

(2002a, 2002b) extended the study of Frischer et al. (1999) with an additional year of data. The mean SO_2 concentration was 6 ppb in the winter and 3 ppb in the summer. This study found a positive association between wintertime SO_2 concentrations and changes in FVC, which became null with PM_{10} in a two-pollutant model.

Jedrychowski et al. (1999) conducted a prospective cohort study of 1,001 preadolescent children from two areas of Krakow, Poland, that differed in ambient air pollutants. In the city center, which had higher air pollution, the mean annual level of SO_2 was 16.7 ppb (SD 12.5). In comparison, the mean annual SO_2 level in the control area was 12.1 ppb (SD 8.4). A similar difference in TSP levels was observed between the city center and control area. The adjusted ORs comparing the city center to the control area for the occurrence of slower lung function growth over a two-year period were 2.10 (95% CI: 1.27, 3.46) for FVC and 2.10 (95% CI: 1.27, 3.48) for FEV_1 in boys. The adjusted ORs for girls were 1.54 (95% CI: 0.89, 2.64) for FVC and 1.51 (95% CI: 0.90, 2.53) for FEV_1. However, as both TSP and SO_2 levels were higher in the city center, the observed effects on lung function growth cannot be specifically attributable to SO_2.

One notable study examined the potential effect of long-term exposure to air pollution on lung function in adults. The study by Ackermann-Liebrich et al. (1997) included 9,651 adults aged 18 to 60 years old residing in eight different areas in Switzerland (Study on Air Pollution and Lung Diseases in Adults [SAPALDIA]). They observed a 0.1% decrease in FEV_1 per 5 ppb increase in SO_2 for adults. Significant associations also were observed for PM_{10} and NO_2. The limited number of study areas and high intercorrelation between the pollutants made it difficult to assess the effect of an individual pollutant. The authors concluded that air pollution from fossil fuel combustion, which was the main source of air pollution for SO_2, NO_2, and PM_{10} in Switzerland, was associated with decrements in lung function parameters in this study.

Collectively, the results from the limited number of animal toxicological and epidemiologic studies on the effect of long-term exposure to ambient SO_2 on lung function is inconclusive.

3.4.2.3. Morphological Effects

Several animal toxicological studies of morphological effects resulting from subacute to chronic SO_2 exposures have been published since the 1982 AQCD. These studies are summarized in Annex Table E-17. No alveolar lesions (including electron microscopic evaluation) or changes in numbers of tracheal secretory cells were observed in guinea pigs exposed to 1 ppm SO_2 for 3 h/day for 6 days (Conner et al., 1985). No pulmonary or nasal lesions were observed in rats exposed to 5 ppm SO_2 for 2 h/day and 5 days/week for 4 weeks (Wolff et al., 1989). A weakness of the latter study is that histopathological methods were not reported. However, a third study reported histopathological changes in the respiratory system involving lesions in the bronchioles. Smith et al. (1989) exposed rats for 4 to 8 months to 1 ppm SO_2 for 5 h/day and 5 days/week and observed increased incidence of bronchiolar epithelial hyperplasia and a small increase (12%) in numbers of nonciliated epithelial cells in terminal respiratory bronchioles at 4 but not 8 months of exposure. A limitation of the study was the examination of a single concentration, which does not allow for concentration-response assessment or identification of a no-effect-level.

In summary, evidence from these animal toxicological studies is insufficient to conclude that long-term exposure to ambient SO_2 causes prolonged effects on lung morphology.

3.4.2.4. Lung Host Defense

The 1982 AQCD reported some detrimental effects of SO_2 on lung host defenses that generally occurred at concentrations exceeding ambient exposure concentrations. In rats exposed to 0.1 ppm SO_2 for ~2 to 3 weeks, clearance of labeled particles from the lung was accelerated at 10 and 23 days following exposure. In rats exposed to 1 ppm for ~2 to 3 weeks, clearance was accelerated at 10 days and

slowed down at 25 days. Tracheal mucus flow was decreased with a 1-year exposure of dogs to 1 ppm SO_2, but was unaffected by a 30-min exposure of donkeys to 25 ppm SO_2. Studies in mice suggested no effect on susceptibility to bacterial infection with exposure to SO_2 concentrations of ≤ 5 ppm for 3 months. Antiviral defenses were impaired in mice exposed to 7-10 ppm SO_2 for 7 days. No alterations in pulmonary immune system were reported with chronic exposure of mice to 2 ppm SO_2.

Several studies on lung host defense have been conducted since the last review and are summarized in Annex Table E18. Only one study published after the last review evaluated mucociliary clearance in rats after exposure to SO_2. In this subchronic study, no effect on clearance of radiolabeled particles from the lung was observed in rats exposed to 5 ppm SO_2 for 2 h/day for 4 weeks (Wolff et al., 1989). These findings are in contrast to the altered clearance reported in the 1982 AQCD. Three other recent studies were conducted evaluating the effects of 10 ppm SO_2 on immune responses. Impairment of host defense responses was seen following continuous exposure to SO_2 for 1-3 weeks (Azoulay-Dupuis et al., 1982), but not in response to a single 4 h exposure (Clarke et al., 2000; Jakab et al., 1996).

In summary, animal toxicological studies do not provide sufficient evidence to assess the effects of long-term exposure to ambient SO_2 on lung host defense.

3.4.2.5. Summary of Evidence on the Effects of Long-Term Exposure on Respiratory Health

The overall epidemiologic evidence on the respiratory effects of long-term exposure to SO_2 is *inadequate to infer a causal relationship*. Studies that examined the effects of long-term exposure to SO_2 on asthma, bronchitis, and respiratory symptoms observed positive associations in children. However, the variety of outcomes examined and the inconsistencies in the observed results make it difficult to assess the impact of long-term exposure of SO_2 on respiratory symptoms. In the limited number of studies examining the SO_2 associations with lung function, results were generally mixed. A major consideration in evaluating SO_2-related health effects in these epidemiologic studies of long-term exposure is the high correlation among the pollutant levels observed, particularly between long-term avg SO_2 and PM concentrations. The lack of evidence available to evaluate potential confounding by copollutants limits the ability to make a causal determination based on these studies.

A limited number of animal toxicological have examined the effect of long-term exposure to SO_2 on lung function. Results from these studies do not provide strong biological plausibility for effects of long-term ambient exposure to SO_2 on respiratory morbidity. These studies observed no effects on physiological lung function at SO_2 concentrations ≤ 5 ppm in rabbits and dogs; however, one study found decreased residual volume and quasistatic compliance at 1 ppm SO_2 in rats. In addition, no morphological changes were found in guinea pigs exposed subacutely to 1 ppm SO_2, or in rats exposed subchronically to 5 ppm SO_2. While mild, bronchiolar epithelial hyperplasia was observed in rats exposed to 1 ppm for 4 months, this change was not apparent at 8 months. Furthermore, animal toxicological studies provide no evidence for decrements in lung host defense at or near ambient levels of SO_2.

Overall, the available evidence from the generally limited number of epidemiologic and animal toxicological studies is inadequate to infer that respiratory effects occur from long-term exposure to SO_2 at ambient concentrations.

3.4.3. Carcinogenic Effects Associated with Long-Term Exposure

The 1982 AQCD concluded that little or no clear epidemiologic evidence substantiated the hypothesized links between SO_2 or other SO_X and cancer. From the toxicological studies, it was noted that while there were some indications of carcinogenicity for both SO_2 and SO_2 + benzo[*a*]pyrene (B[*a*]P),

complex exposure regimens, problematic dose determinations, and/or inadequately reported experimental details led to the conclusion that SO_2 could only be considered a suspect carcinogen/cocarcinogen.

Since the last review, numerous studies have examined the genotoxic effects of SO_2. These are summarized in Annex Table E-19. SO_2 and its metabolite sulfite were found not to be mutagenic or to induce DNA damage in vitro (Pool-Zobel et al., 1990; Pool et al., 1988b). However, inhalation studies demonstrated increased mouse bone marrow micronucleated polychromatic erythrocytes and DNA damage in cells isolated from various organs when mice were exposed for 4-6 h/day for 7 days to 5-30 ppm SO_2 (Meng et al., 2002; 2005b; Ruan et al., 2003). These in vivo studies suggest that inhaled SO_2 may have systemic effects at high concentrations, but they are of questionable significance in evaluating the effects of SO_2 at ambient levels.

The carcinogenic potential of SO_2 was examined in animal toxicological studies which are summarized in Annex Table E-11. Gunnison et al. (1988) conducted a two-part study in which rats were exposed either for 21 weeks (6 h/day, 5 days/week) by inhalation to 0, 10, or 30 ppm SO_2, or for 21 weeks to two tungsten-supplemented, molybdenum-deficient diets. This latter regimen induced a condition of sulfite oxidase deficiency, resulting in elevated systemic levels of sulfite:bisulfite relative to control values (e.g., in plasma, from 0 to 44 μM; and in tracheal tissue, from 33 to 69 or 550 nmol/g wet weight). Beginning with week 4, some groups from each regimen received weekly tracheal installations of 1-mg B[*a*]P for 15 weeks. Overall results indicated that squamous cell carcinoma was not induced, or in the B[*a*]P groups coinduced or promoted, by SO_2 inhalation or elevated systemic sulfite:bisulfite. Researchers found a very high incidence of animals with tumors in the groups exposed to only B[*a*]P (128 of144 animals). As a result, carcinogenicity or cocarcinogenicity of SO_2 or sulfite:bisulfite could only have been detected as a shortening of tumor induction time or an increase in rate of tumor appearance, and neither was observed. As noted by the authors, these findings do not support the conclusion that SO_2 exposure enhances the carcinogenicity of B[*a*]P . It was proposed that SO_2 exposure, by elevating systemic sulfite:bisulfite, would generate glutathione-*S*-sulfonates, which in turn could inhibit glutathione *S*-transferase (GST) and reduce intracellular GSH and, thus, interfere with a major detoxication pathway for B[*a*]P. See Annex Table E-20 for discussion (Menzel et al. 1986).

Two similar studies were published that investigated the ability of 10 to 11 months of exposure (16 h/day) to 4 ppm SO_2, 6 ppm NO_2, or their combination to affect the carcinogenicity of either urban suspended PM (SPM) (Ito et al., 1997) or diesel exhaust particle (DEP) extract-coated carbon particles (Ohyama et al., 1999). The former study found that, while exposure to SPM extract-coated carbon particles significantly increased pulmonary endocrine cell (PEC) hyperplasia, coexposure to SO_2, NO_2, or their combination was without additional affect. Also, irrespective of gas coexposure, SPM extract-coated carbon particles demonstrated a few PEC papillomas versus control frequencies of zero.

Using Syrian golden hamsters, Heinrich et al. (1989) investigated whether coexposure to 10 ppm SO_2 and 5 ppm NO_2 for 6 to 8 months (5 days/week, 19 hours/day) could enhance tumorigenesis induced by a single subcutaneous injection of diethylnitrosamine (DEN) during week 2. The combined gas exposure did not affect body weight gain and only minimally shortened survival times. Compared to the DEN groups, serial sacrifices of gas-exposed animals demonstrated progressively increasing numbers of tracheal mucosal cells and aberrant tracheal cell cilia. In the lung, effects related to gas mixtures were largely limited to a progressive type of alveolar lesion that involved the lining of bronchiolar epithelium and the appearance of pigment-containing AM and to a mild, diffuse thickening of the alveolar septa. Exposure to the combined gases by itself did not induce tumors of the upper respiratory tract, nor did it enhance the induction of such tumors by DEN.

In addition to the animal toxicological studies that examined the genotoxic and carcinogenic potential of SO_2, a limited number of recent epidemiologic studies have investigated the relationship between long-term exposure to SO_2 and lung cancer incidence and mortality. These studies are summarized in Annex Table F-7. Nyberg et al. (2000) conducted a case-control study of men aged 40 to 75 years with (n = 1,042) and without (n = 2,364) lung cancer in Stockholm County, Sweden. They mapped residence addresses to a GIS database to assign individual exposures to SO_2 from defined emission sources (mainly local oil-fueled residential heating). Available SO_2 measurement data were used

to calibrate the model. In this study, SO_2 was considered an indicator of air pollution from residential heating. Exposure to NO_2, considered to be a marker of traffic pollution, also was evaluated in this study. The 90th percentile 30-year avg SO_2 level was 30 ppb. After adjusting for potential confounders (e.g., smoking, occupational exposures), long-term avg heating-related SO_2 exposure was not associated with an increase in risk of lung cancer incidence. A weak association for the 30-year avg traffic-related NO_2 exposure was observed.

Very similar results were reported in a Norwegian study by Nafstad et al. (2003). The study population is a cohort of 16,209 men who enrolled in a study of cardiovascular diseases in 1972. The Norwegian cancer registry identified 422 incident cases of lung cancer. SO_2 exposure data were modeled based on residence using data for observed concentrations and emission from point sources (e.g., industry and heating of buildings and private homes) and traffic. Once again, no association was observed between long-term exposure to SO_2 and lung cancer incidence.

Three additional European cohort studies examined the associations between long-term exposure to air pollution and lung cancer mortality (Beelen et al., 2008; Filleul et al., 2005; Nafstad et al., 2004) in cohorts ranging in size from 14,284 to 120,852 subjects, who were followed for 9 to > 20 years. Consistent with the results for lung cancer incidence, none of these studies observed an association between long-term SO_2 exposure and lung cancer mortality. These studies are discussed in further detail in Section 3.5.2.2.

Similar to the European cohort studies, studies conducted in the U.S. generally did not observe an association between long-term exposure to SO_2 and lung cancer mortality. In the reanalysis of the Harvard Six Cities Study, Krewski et al. (2000) estimated a RR of 1.03 (95% CI: 0.91, 1.16) per 5 ppb increase in avg SO_2 over the study period, while Pope et al. observed a positive but not statistically significant (RR ~1.04 per 5 ppb increase in avg SO_2 from 1982 to 1998) association in the extended analysis of the American Cancer Society (ACS) cohort. The California Seventh-day Adventists study by Abbey et al. (1999) did observe a statistically significant association between lung cancer mortality and SO_2 (and most of the pollutants examined including PM_{10}, sulfate, O_3, and NO_2), but the number of lung cancer deaths in this cohort was very small (12 for female, 18 for male) and, therefore, it is difficult to interpret these estimates. More detailed discussions of these studies are provided in Section 3.5.2.1.

In conclusion, the toxicological studies indicate that SO_2 at high concentrations may cause DNA damage but fails to induce carcinogenesis, cocarcinogenesis, or tumor promotion. Furthermore, results from the limited number of epidemiologic studies examining the association between long-term exposure to ambient SO_2 and excess risk of lung cancer incidence and mortality are inconclusive.

3.4.4. Cardiovascular Effects Associated with Long-Term Exposure

The effects of SO_2 on the cardiovascular system were not addressed in the 1982 AQCD. Since then, animal toxicological studies have reported oxidation and glutathione (GSH) depletion (Langley-Evans et al., 1996; Meng et al., 2003b; Wu and Meng, 2003) in the hearts of rodents which were exposed by inhalation to SO_2. However, as concentrations of SO_2 used in these studies were 5 ppm and above, the oxidative injury observed is probably not relevant to cardiovascular effects seen at ambient levels of SO_2. These and other animal toxicology studies measuring cardiovascular endpoints are summarized in Annex Table E-9.

A recent epidemiologic study examined the association between long-term exposure to air pollution, including SO_2, and one or more fatal or nonfatal cardiovascular events. In the Women's Health Initiative cohort study, Miller et al. (2007) studied 65,893 postmenopausal women between the ages of 50 and 79 years without previous cardiovascular disease in 36 U.S. metropolitan areas from 1994 to 1998. Subjects' exposures to air pollution were estimated using residents' five-digit ZIP code, assigning the annual mean levels of air pollutants measured at the nearest monitor. A total of 1,816 women had one or more fatal or nonfatal cardiovascular events, including 261 deaths from cardiovascular causes. Hazard

ratios for the first cardiovascular event were estimated. The results for models that only included subjects with non-missing exposure data for all pollutants (n = 28,402 subjects, resulting in 879 cardiovascular events) are described here. In the single-pollutant models, $PM_{2.5}$ showed the strongest associations with cardiovascular events among the pollutants (Hazard Ratios = 1.24 [95% CI: 1.04, 1.48] per 10 $\mu g/m^3$ increase in annual avg), followed by SO_2 (1.07 [95% CI: 0.95, 1.20] per 5 ppb increase in the annual avg). In the multipollutant model where all the pollutants (i.e., $PM_{2.5}$, $PM_{10-2.5}$, CO, SO_2, NO_2, O_3) were included in the model, the $PM_{2.5}$ association with overall cardiovascular events was even stronger (1.53 [95% CI: 1.21, 1.94]). The association with SO_2 also became stronger (1.13 [95% CI: 0.98, 1.30]). Correlations among these pollutants were not described and, therefore, the extent of confounding among these pollutants in these associations could not be examined, but among all the air pollutants considered, $PM_{2.5}$ was clearly the best predictor of cardiovascular events.

The available toxicological and epidemiologic evidence to assess the effect of long-term exposure to SO_2 on cardiovascular health is too limited to make any conclusions at this time.

3.4.5. Prenatal and Neonatal Outcomes Associated with Long-Term Exposure

Several animal toxicological studies examined developmental effects of SO_2 and are summarized in Annex Table E-13. No changes in birth weight or neurobehavioral development were noted in mouse pups prenatally exposed to 5-30 ppm SO_2 (Petruzzi et al., 1996), while some behavioral modifications were seen in adults exposed prenatally to these same levels (Fiore et al., 1998). However, effects observed at such high concentrations of SO_2 are of questionable relevance.

In recent years, the effects of prenatal and neonatal exposure to air pollution have been examined in epidemiologic studies by several investigators (see Annex Table F-8). The most common endpoints studied are low birth weight, preterm delivery, and measures of intrauterine growth. Preterm birth and low birth weight may result in serious long-term health outcomes for the infant. Preterm birth is the leading cause of infant mortality and is a major determinant of a variety of adverse neurodevelopmental outcomes and chronic adverse respiratory effects (Berkowitz and Papiernik, 1993). Low birth weight has also been linked with increased risk of infant mortality and morbidity. Other studies have examined associations between maternal exposure to ambient air pollution and sudden infant death syndrome (SIDS) and neonatal hospitalizations.

These studies analyzed air pollution data and birth certificates from a given area. In evaluating the results of these studies, it is important to consider the limitations of these data. For example, the reliability and validity of birth certificate data have been reviewed (Buescher et al., 1993; Piper et al., 1993) and have been found to vary in degrees of reliability by specific variables. The variables considered the most reliable include birth weight, maternal age, race, and insurance status. Whereas gestational age, parity and delivery type (vaginal vs. cesarean) were reasonably reliable, obstetrical complications and maternal lifestyle factors such as smoking and alcohol consumption were not reliable. Another concern in these studies regards adequate control for potential confounders. While most of these studies adequately controlled for maternal education, parity, age, and sex of child, many did not adjust for SES, occupational exposures, indoor pollution levels, maternal smoking, alcohol use, prenatal care, or concurrent temperature exposures as fetal growth is associated with all of these factors. This makes overall comparisons across studies a difficult task.

While most studies analyzed avg SO_2 exposure for the whole pregnancy, many also considered exposure during specific trimesters, or other time periods (e.g., first and last months of gestation). Different exposure periods have been examined because the biological mechanisms and timing of critical exposures that link air pollution to adverse birth outcomes are yet to be determined. For example, fetal growth is much more variable during the third trimester; therefore, exposure during the third trimester would have the greatest likelihood of an association. However, insufficient placentation during the first

trimester may be associated with early environmental insult, whereby subsequent fetal growth is hindered. Similarly, it is possible that preterm delivery is associated with insufficient placentation resulting from early exposure. Furthermore, preterm delivery may be the result of acute exposures just prior to delivery.

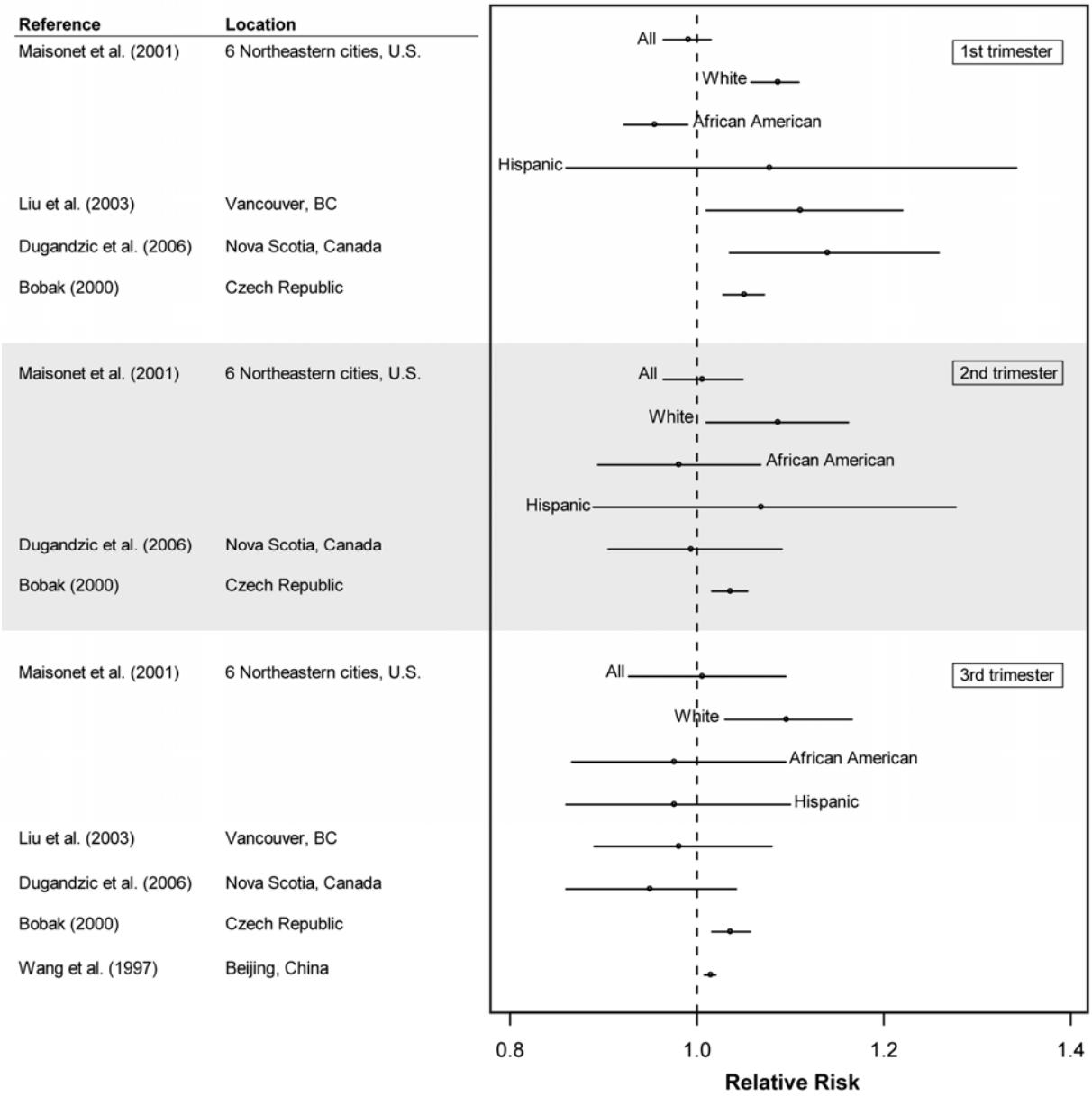


Figure 3-13. Relative risks (95% CI) for low birth weight, grouped by trimester of SO_2 exposure. Risk estimates are standardized per 5 ppb increase in SO_2 concentrations.

Epidemiologic studies examining the effects of air pollutants on low birth weight are summarized in Figure 3-13. Maisonet et al. (2001) examined the association between air pollution and low birth weight in six northeastern cities: Boston, MA; Hartford, CT; Philadelphia, PA; Pittsburgh, PA; Springfield, MA; and Washington, DC. The study population consisted of 89,557 singleton, full-term, live

births (37-44 weeks of gestation) born between January 1994 and December 1996. Low birth weight was classified as < 2,500 g (5.5 lbs.). This study observed an association between low birth weight and SO_2 concentrations during each trimester among Caucasians; however, the association was not consistent in other races and ethnicities.

An excess risk for low birth weight associated with ambient SO_2 concentrations was reported by Dugandzic et al. (2006) in a large cohort study of 74,284 women with full-term, singleton births from 1988–2000 in Nova Scotia, Canada. The mean 24-h avg SO_2 concentration over the study period was 10 ppb (IQR 7). These investigators found that exposure only during the first trimester was associated with increased risk of low birth weight. The RR was 1.14 (95% CI: 1.04, 1.26) per 5 ppb increase in SO_2 level.

Liu and Krewski (2003) found similar results in a study of pregnancy outcomes and air pollution in Vancouver, Canada. The mean 24-h avg SO_2 concentration was 4.9 ppb (IQR 7.7) from 1985 to 1998. Maternal exposure during the first month was associated with an increased risk of low birth weight (OR 1.11 [95% CI: 1.01, 1.22]). Additional studies from the U.S., Europe, Latin America and Asia have reported positive associations between low birth weight and maternal exposure to SO_2 during the first (Bell et al., 2007; Bobak, 2000; Ha et al., 2001; Mohorovic, 2004; Yang et al., 2003a), second (Bobak, 2000; Gouveia et al., 2003; Lee et al., 2003a) and third (Bobak, 2000; Lin et al., 2004b; Wang et al., 1997) trimesters.

Preterm delivery, intrauterine growth retardation (IUGR), and birth defects are additional adverse birth outcomes that have been associated with ambient SO_2 levels. In a time-series analysis using data from four Pennsylvania counties, Sagiv et al. (2005) reported that the mean 6-week SO_2 exposure prior to birth was associated with increased risk of preterm birth, with a RR of 1.05 (95% CI: 1.00, 1.10) per 5 ppb increase in SO_2. A 5 ppb increase in SO_2 concentrations three days before birth was associated with a RR of 1.02 (95% CI: 0.99, 1.05). The authors discussed two plausible mechanisms for the effects of air pollution on preterm birth: (1) changes in blood viscosity due to inflammation as a result of air pollution (Peters et al., 1997); and (2) maternal infection during pregnancy as a consequence of impaired immunity from air pollution exposure. Liu and Krewski (2003) reported that SO_2 exposure during the last month of pregnancy was associated with preterm birth, with an OR of 1.09 (95% CI: 1.01, 1.19) for a 5 ppb increase in SO_2, in Vancouver, Canada. Similar results were found for studies conducted in the Czech Republic (Bobak, 2000), Korea (Leem et al., 2006), and Beijing (Xu et al., 1995).

Liu and Krewski (2003) further reported that SO_2 exposure during the last month of pregnancy was associated with IUGR (OR 1.07 [95% CI: 1.01, 1.13]). However, in a later study in the Canadian cities of Calgary, Edmonton and Montreal, Liu et al. (2007) did not observe associations between maternal exposure to SO_2 and increased risk of IUGR.

Two Brazilian studies examined exposure to SO_2 and neonatal deaths. Pereira et al. (1998) found a positive association between SO_2 and intrauterine mortality in São Paulo during a 2-year period, though the effect was sensitive to model specifications and did not support a concentration-response relationship. The most robust association with intrauterine mortality was observed for an index of three gaseous pollutants (NO_2, SO_2, CO). Lin et al. (2004b) found that a 5 ppb increase in SO_2 was associated with an increase of 8.8% (95% CI: 5.8, 11.8). A similar relationship was found for PM_{10}. The creation of an index containing both PM_{10} and SO_2 allowed the observation of their cumulative effects on daily death counts. The result of this analysis was similar in magnitude to the effect of SO_2 alone. An ecologic cohort study of infant mortality in the U.S. found no association with annual averages of SO_2 concentration (Lipfert et al., 2000a).

Gilboa et al. (2005) conducted a population-based case-control study to investigate the association between maternal exposure and air pollutant exposure during weeks 3-8 of pregnancy, the risk of selected cardiac birth defects and oral clefts in live births, and fetal deaths between 1997 and 2000 in seven Texas counties. When the highest quartile of exposure was compared to the lowest, the authors observed a positive association between SO_2 and isolated ventricular septal defects (OR 2.16 [95% CI: 1.51, 3.09]). Although this is the only study to have examined the effect of maternal exposure to SO_2 on birth defects, it supports the notion that the developing embryo and growing fetus are susceptible to maternal air pollution exposure.

Several studies examined adverse health outcomes in relation to SO_2 concentrations during the neonatal period. Dales et al. (2006) evaluated hospitalizations for respiratory disorders in neonates < 4 weeks of age from hospitals in 11 large Canadian cities during a 15-year study period (population-weighted avg 24-h avg SO_2 of 4.3 ppb). The researchers observed a 5.5% (95% CI: 2.8, 8.3) excess risk in respiratory hospitalizations associated with a 10 ppb increase in 24-h avg SO_2 concentrations with a 2-d lag. This effect was slightly attenuated after adjusting for PM_{10} and gaseous copollutants. To investigate the influence of ambient SO_2 concentrations on SIDS, Dales et al. (2004) conducted a time-series analysis comparing daily rates of SIDS and daily SO_2 concentrations from 12 large, Canadian cities during a 16-year period. The mean 24-h avg SO_2 level across the 12 cities was 5.51 ppb (IQR 4.92). There was an 18.0% (95% CI: 4.4, 33.4) excess risk in SIDS incidence for a 10 ppb increase in 24-h avg SO_2 levels. The authors concluded that the effect of SO_2 was independent of sociodemographic factors, temporal trends, and weather.

In summary, epidemiologic studies on birth outcomes have observed positive associations between SO_2 exposure and low birth weight; however, toxicological studies provide very little biological plausibility for reproductive outcomes related to SO_2 exposure. The inconsistent results across trimesters of pregnancy and the lack of evidence regarding confounding by copollutants further limit the interpretation of these studies. The limited number of studies addressing preterm delivery, IUGR, birth defects, neonatal hospitalizations, and infant mortality make it difficult to draw conclusions regarding the effect of SO_2 on these outcomes.

3.4.6. Other Organ System Effects Associated with Long-Term Exposure

The 1982 AQCD presented only one chronic exposure study which was relevant to nervous system effects. Dogs were exposed for 68 months to a mixture of SO_2 and H_2SO_4 (Stara et al., 1980). No effects on visual-evoked brain potentials during or immediately after exposure to the SO_X mixture were observed. Since then, numerous studies have examined brain lipid content, lipid peroxidation and glutathione content and antioxidant enzymes following inhalation exposure of rodents to SO_2 at concentrations of 10 ppm or higher. Concentrations of 5 ppm or higher SO_2 were used in studies examining neurobehavior and neurodevelopment in mice. These studies are summarized in Annex Table E-12.

In the past 25 years, numerous animal toxicological studies have evaluated the effects of long-term SO_2 exposure on other organ systems such as reproductive, hematological, gastrointestinal, renal, lymphatic, and endocrine systems. Most of these studies used concentrations of SO_2 of 5 ppm or higher. Many of these studies examined alteration profiles of lipid peroxidation and antioxidant levels (Langley-Evans et al., 1996; Meng et al., 2003c; 2004) and are summarized in Annex Table E-10, E-13 through E-16, and E-21.

3.5. Mortality Associated with Long-Term SO_2 Exposure

3.5.1. Summary of Findings from the Previous Review

At the time of the 1982 AQCD, the available studies on the effects of long-term exposure to SO_2 on mortality were all ecological cross-sectional studies. This study design could not take into consideration such confounders as cigarette smoking, occupational exposures, and social status. In addition, there were

questions regarding how representative the aerometric data used were for community exposure. Therefore, it was concluded that the epidemiologic studies did not provide valid quantitative data relating respiratory disease or other types of mortality to long-term (annual avg) exposures to SO_2 or PM.

The 1986 Secondary Addendum reviewed more studies of this type, with information on more detailed components of PM (inhalable and fine particles, and particulate sulfate). While some studies suggested importance of the size of PM, the fundamental problem of the study design made it difficult to interpret the effect estimates. The 1986 Secondary Addendum also reviewed a Japanese study in which the death rates from asthma and chronic bronchitis in a highly polluted section of Yokkaichi, an industrial city with large SO_2 emissions from the largest oil-fired power plant in Japan, were compared with those in a less polluted area of the same city (Imai et al., 1986). SO_X levels (measured using the lead peroxide method) averaged across several monitoring sites in the polluted harbor area ranged from around 1.0 to 2.0 mg/day (annual avg) during 1964 through 1972 and then steadily declined to less than 0.5 mg/day in 1982. This is in contrast to levels consistently < 0.3 mg/day in the low pollution areas throughout 1967 through 1982. Annual avg levels for other pollutants (i.e., NO_2, TSP, oxidants) monitored in the high pollution area were consistently low from 1974 through 1982. The results indicated elevated rates of chronic bronchitis mortality in the highly polluted area compared to the less polluted area, but the 1986 Secondary Addendum could not conclude that this was due to SO_2 alone, because sulfate or other particulate SO_X such as H_2SO_4 could have been responsible.

Several, more recent studies have examined long-term exposure effects of air pollution, including SO_2, on mortality. These studies are summarized in Annex Table F-9. As with short-term exposure studies, the focus of most of these studies was mainly on PM though some focused on traffic-related air pollution. They all used Cox proportional hazards regression models with adjustment for potential confounders. The designs of these studies were better than earlier cross-sectional studies as the outcome and most of the potential confounders (e.g., smoking history, occupational exposure) were measured on an individual basis. However, the geographic scale and method for exposure estimates varied across these studies.

3.5.2. Associations of Mortality and Long-Term Exposure in Key Studies

3.5.2.1. U.S. Cohort Studies

Harvard Six Cities Studies

Dockery et al. (1993) conducted a prospective cohort study to study the effects of air pollution with the main focus on PM components in six U.S. cities. These cities were chosen based on levels of air pollution, with Portage, WI and Topeka, KS representing the least polluted cities and Steubenville, OH representing the most polluted city. Mean SO_2 levels ranged from 1.6 ppb in Topeka to 24.0 ppb in Steubenville from 1977 to 1985. Cox proportional hazards regression was conducted with data from a 14- to 16-year follow-up study of 8,111 adults in the six cities. Dockery et al. (1993) reported that lung cancer and cardiopulmonary mortality were more strongly associated with the concentrations of inhalable and fine PM, and sulfate particles, than with the levels of TSP, SO_2, NO_2, or acidity of the aerosol.

Krewski et al. (2000) conducted a sensitivity analysis of the Harvard Six Cities Study and examined associations between gaseous pollutants (i.e., O_3, NO_2, SO_2, and CO) and mortality. SO_2 showed positive associations with total mortality (RR = 1.05 [95% CI: 1.02, 1.09] per 5 ppb increase in avg SO_2 over the study period) and cardiopulmonary deaths (1.05 [95% CI: 1.00, 1.10]), but in this dataset SO_2 was highly correlated with $PM_{2.5}$ (r = 0.85), sulfate (r = 0.85), and NO_2 (r = 0.84).

American Cancer Society Cohort Studies

Pope et al. (1993) investigated associations between long-term exposure to PM and the mortality outcomes in the ACS cohort. Ambient air pollution data from 151 U.S. metropolitan areas in 1981 were linked with individual risk factors in 552,138 adults who resided in these areas when enrolled in the prospective study in 1982. Death outcomes were ascertained through 1989. $PM_{2.5}$ and sulfate were associated with total, cardiopulmonary, and lung cancer mortality, but not with mortality for all other causes. Gaseous pollutants were not analyzed in this study.

Krewski and co-investigators (Jerrett et al., 2003a; Krewski et al., 2000) conducted an extensive sensitivity analysis of the Pope et al. (1993) ACS data, augmented with additional gaseous pollutants data. The mean SO_2 concentrations were 7.18 ppb in the warm season (April to September) and 11.24 ppb in the cool season (October to March). Among the gaseous pollutants examined, only SO_2 showed positive associations with mortality. The RR for total mortality was 1.06 (95% CI: 1.05, 1.07) per 5 ppb increase in the annual avg SO_2. Analysis using SO_2 measured in different seasons produced a somewhat higher estimate for the warm season than that for the cool season (7% compared to 5% excess risk per 5 ppb increase). Although the subjects in the ACS cohort came from all regions of the U.S., the majority of the 151 cities were located in the eastern U.S., where both SO_2 and sulfate tend to be higher. $PM_{2.5}$ levels are also higher in the east. To address the influence of these spatial patterns, which may confound associations between mortality and these pollutants, Krewski et al. (2000) conducted extensive two-stage regression modeling. In these models, the association between SO_2 and mortality was diminished but persisted after adjusting for sulfate, $PM_{2.5}$, and other variables. For example, in the spatial filtering model (which resulted in the largest reduction of the SO_2 effect estimate when sulfate was included), the SO_2 total mortality RR estimate was 1.07 (95% CI: 1.03, 1.11) in the single-pollutant model and 1.04 (95% CI: 1.02, 1.06) with sulfate in the two-pollutant model. The effect estimates for $PM_{2.5}$ and sulfate also were diminished when SO_2 was included in the models. The result further showed that SO_2 effect estimates were generally insensitive to adjustment for spatial correlation. Thus, these results suggest that the association between SO_2 and mortality may be confounded with PM, but the association cannot be accounted for by $PM_{2.5}$ or sulfate alone. Krewski et al. (2000) noted that their reanalysis of the ACS and Harvard Six Cities studies suggested that mortality might be attributed to more than one component of the complex mixture of ambient air pollutants in urban areas in the U.S..

The original Pope et al. (1993) study and the Krewski et al. (2000) reanalysis both used the air pollution exposure estimates that are based on the average over the Metropolitan Statistical Area (MSA), which consists of multiple counties. To investigate the effects of geographic scale over which the air pollution exposures are averaged, (Willis et al., 2003), reanalyzed the ACS cohort data using the exposure estimates averaged over the county scale, and compared the results with those based on the MSA-scale avg exposure. Less than half of the cohort used in the MSA-based study was used in the county-scale based analysis, because of the limited availability of sulfate monitors and the reduced sample size due to the loss of subjects when using the five-digit ZIP codes. The mean (9.3 ppb versus 10.7 ppb) and range (0.0 to 29.3 ppb versus 0.0 to 27.2 ppb) of the MSA- and county-level SO_2 data sets were similar. In the analysis comparing the two-pollutant model with sulfate and SO_2, they found that the inclusion of SO_2 reduced sulfate effect estimates substantially (> 25%) in the MSA-scale model but not substantially (< 25%) in the county-scale model. In the MSA-level analysis (with 113 MSAs), the SO_2 RR estimate was 1.04 (95% CI: 1.02, 1.06) per 5 ppb increase, with sulfate in the model. In the county-level analysis (91 counties) with sulfate in the model, the corresponding estimate was smaller (1.02 [95% CI: 1.00, 1.05]). It should also be noted that the correlation between covariates were different between the MSA-level data and county-level data. The correlation between SO_2 and sulfate was 0.48 in the MSA-level data, but it was 0.56 in the county-level data. The correlation between poverty rate and SO_2 was -0.16 in the MSA-level data, but it was 0.15 in the county-level data. Thus, the extent of confounding between SO_2 and PM components as well as among other covariates in the model can be affected by the geographic scale of aggregation of exposure estimates. It is not clear, however, if the smaller geographic scale increases or decreases exposure characterization error for SO_2, because a certain extent of smoothing

(averaging) over distance may reduce very local concentration peaks that are not relevant to the city-wide population.

Pope et al. (2002) extended analysis of the ACS cohort with double the follow-up time (to 1998) and triple the number of deaths compared to the original Pope et al. (1993) study. In addition to $PM_{2.5}$, all the gaseous pollutant data were retrieved for the extended period and analyzed for their associations with death outcomes. As in the 1995 analysis, the air pollution exposure estimates were based on the MSA-level averages. $PM_{2.5}$ was associated with total, cardiopulmonary, and lung cancer mortality but not with deaths for all other causes. SO_2 was associated with all the mortality outcomes, including all other causes of deaths. The SO_2 RR estimate for total mortality was 1.03 (95% CI: 1.02, 1.05) per 5 ppb increase (1982 to 1998 avg). The association of SO_2 with mortality for all other causes (sulfate also showed this pattern) makes it difficult to interpret the effect estimates. This lack of specificity for SO_2 (in contrast to PM) is not consistent with causal inference.

The EPRI-Washington University Veterans' Cohort Mortality Studies

Lipfert et al. (2000b) conducted an analysis of a national cohort of ~70,000 male U.S. military veterans who were diagnosed as hypertensive in the mid 1970s and were followed up for about 21 years (up to 1996). This cohort was 35% black and 57% were current smokers (81% of the cohort had been smokers at one time). $PM_{2.5}$, PM_{10}, $PM_{10-2.5}$, TSP, sulfate, CO, O_3, NO_2, SO_2, and lead were examined in this analysis. No mean or median level of SO_2 was reported. The county of residence at the time of entry to the study was used to estimate exposures. Four exposure periods (from 1960 to 1996) were defined, and deaths during each of the three most recent exposure periods were considered. The results for SO_2 were presented only qualitatively as part of their preliminary screening regression results. Lipfert et al. (2000b) noted that lead and SO_2 were not found to be associated with mortality, thus were not considered further. They also noted that the pollution effect estimates were sensitive to the regression model specification, exposure periods, and the inclusion of ecological and individual variables. The authors reported that indications of concurrent mortality risks were found for NO_2 and peak O_3.

Lipfert et al. (2006b) examined associations between traffic density and mortality in the same cohort, whose follow-up period was extended to 2001. As in their 2000 study, four exposure periods were considered but included more recent years. The 95th percentiles of daily avg in each of the exposure periods were considered for SO_2. For the 1997–2001 data period, the estimated mortality RR for SO_2 was 0.99 (95% CI: 0.97, 1.01) per 5 ppb increase in a single-pollutant model. They reported that traffic density was a better predictor of mortality than ambient air pollution variables with the possible exception of O_3. The log-transformed traffic density variable was only weakly correlated with SO_2 ($r = 0.32$) and $PM_{2.5}$ ($r = 0.50$) in this data set.

Lipfert et a. (2006a) further extended analysis of the veterans' cohort data to include the EPA's Speciation Trends Network (STN) data, which collected chemical components of $PM_{2.5}$. They analyzed the STN data for year 2002, again using county-level averages. $PM_{2.5}$ and gaseous pollutants data for 1999 through 2001 were also analyzed. As in the previous Lipfert et al. (2006b) study, traffic density was the most important predictor of mortality, but associations were also seen for elemental carbon, vanadium, nickel, and nitrate. O_3, NO_2, and PM_{10} also showed positive but weaker associations. Once again, no associations were observed between long-term exposure to SO_2 and mortality.

Seventh-day Adventist Study

Abbey et al. (1999) investigated associations between long-term ambient concentrations of PM_{10}, sulfate, SO_2, O_3, and NO_2 (1973 through 1992) and mortality (1977 through 1992) in a cohort of 6,338 nonsmoking California Seventh-day Adventists. Monthly indices of ambient air pollutant concentrations at 348 monitoring stations throughout California were interpolated to ZIP codes according to home or work location of study participants, cumulated, and then averaged over time. They reported associations between PM_{10} and total mortality for males and nonmalignant respiratory mortality for both sexes. SO_2

was not associated with total mortality (RR 1.07 [95% CI: 0.92, 1.24] for males and 1.00 [95% CI: 0.88, 1.14] for females per 5 ppb increase in multiyear avg SO_2), cardiopulmonary deaths, or respiratory mortality for either gender.

3.5.2.2. European Cohort Studies

A study by Beelen et al. (2008) examined associations between traffic-related air pollution and mortality. They analyzed data from the Netherlands Cohort Study on Diet and Cancer with 120,852 subjects who were followed from 1987 to 1996. BS, NO_2, SO_2, $PM_{2.5}$, and four types of traffic-exposure estimates were analyzed. While the local traffic component was estimated for BS, NO_2, and $PM_{2.5}$, no such attempt was made for SO_2, because there was "virtually no traffic contributions to this pollutant." Thus, only "background" SO_2 levels were reflected in the exposure estimates. Traffic intensity on the nearest road was associated with all-cause mortality and a larger RR was observed for respiratory mortality. Results were similar for BS, NO_2 and $PM_{2.5}$, but no associations were found for SO_2 (RR = 0.98 [95% CI: 0.93, 1.03] per 5 ppb increase in multiyear avgSO_2).

Nafstad et al. (2004) investigated the association between mortality and long-term exposure to air pollution exposure in a cohort of Norwegian men followed from 1972–1973 through 1998. Data from 16,209 males (aged 0 to 49 years) living in Oslo, Norway, in 1972–1973 were linked with data from the Norwegian Death Register and with estimates of the avg annual air pollution levels at the participants' home addresses. PM was not considered in this study because measurement methods changed during the study period. Exposure estimates for NO_X and SO_2 were constructed using models based on subject addresses, emission data for industry, heating, and traffic, and measured concentrations. While NO_X was associated with total, respiratory, lung cancer, and ischemic heart disease deaths, SO_2 did not show any associations with mortality. The authors noted that the SO_2 levels were reduced by a factor of 7 during the study period (from 5.6 ppb in 1974 to 0.8 ppb in 1995), whereas NO_X did not show any clear downward trend.

Filleul et al. (2005) investigated long-term effects of air pollution on mortality in 14,284 adults who resided in 24 areas from seven French cities when enrolled in the Air Pollution and Chronic Respiratory Diseases (PAARC) survey in 1974. Daily measurements of SO_2, TSP, BS, NO_2, and NO were made in the 24 areas for 3 years (1974 through 1976). Models were run before and after exclusion of six area monitors influenced by local traffic as determined by a NO:NO_2 ratio of > 3. Before exclusion of the six areas, none of the air pollutants was associated with mortality outcomes. After exclusion of these areas, analyses showed associations between total mortality and TSP, BS, NO_2, and NO but not SO_2 (RR = 1.01 [95% CI: 0.97, 1.06] per 5 ppb multiyear average) or acidimetric measurements. It should be noted that SO_2 levels in these French cities declined markedly between the 1974 through 1976 period and the 1990 through 1997 period by a factor of 2 to 3, depending on the city. The changes in air pollution levels over the study period complicate interpretation of reported effect estimates.

3.5.2.3. Cross-Sectional Analysis Using Small Geographic Scale

Elliott et al. (2007) examined associations of BS and SO_2 with mortality in Great Britain using a cross-sectional analysis. However, unlike the earlier ecological cross-sectional mortality analyses in the U.S. in which mortality rates and air pollution levels were compared using large geographic boundaries (i.e., MSAs or counties), in the Elliot et al. analysis, the mortality rates and air pollution were compared using a much smaller geographic unit, the electoral ward, with a mean area of 7.4 km^2 and a mean population of 5,301 per electoral ward. Death rates were computed for four successive 4-year periods from 1982 to 1994 and associated with 4-year exposure periods from 1966 to 1994. The number of deaths from all causes in the 10,520 wards was 420,776. Of note, SO_2 levels declined from 41.4 ppb in the 1966 to 1970 period to 12.2 ppb in 1990 to 1994. This type of analysis does not allow adjustments for

individual risk factors, but the study did adjust for SES data available for each ward from the 1991 census. Social deprivation and air pollution were more highly correlated in the earlier exposure windows. They observed associations for both BS and SO_2 and mortality outcomes. The estimated effects were stronger for respiratory illness than other causes of mortality for the most recent exposure period and most recent mortality period (when pollution levels were lower). The adjustment for social deprivation reduced the effect estimates for both pollutants. The adjusted mortality RRs for SO_2 for the pooled mortality periods using the most recent exposure windows were 1.021 (95% CI: 1.018, 1.024) for all causes, 1.015 (95% CI: 1.011, 1.019) for cardiovascular, and 1.064 (95% CI: 1.056, 1.072) for respiratory causes per 5 ppb increase in SO_2. The effect estimates for the most recent mortality period using the most recent exposure windows were larger. Simultaneous inclusion of BS and SO_2 reduced effect estimates for BS but not SO_2. Elliott et al. (2007) noted that the results were consistent with those reported in the Krewski et al. (2000) reanalysis of the ACS study. This analysis was ecological, but the exposure estimates in the smaller area compared to that in the U.S. cohort studies may have resulted in less exposure misclassification error, and the large underlying population appears to be reflected in the narrow confidence bands of effect estimates. The results from this study suggest an association between long-term exposures (especially in recent years) to SO_2 and mortality.

3.5.3. Summary of Evidence on the Effect of Long-Term Exposure on Mortality

The available epidemiologic evidence on the effect of long-term exposure to SO_2 on mortality is *inadequate to infer a causal relationship* at this time. The ecological cross-sectional studies examined in the 1982 AQCD and 1986 Secondary Addendum found suggestive relationships between long-term exposure to SO_2 and mortality. However, there were concerns as to whether the observed association was due to SO_2 alone, because sulfate or other particulate SO_X such as H_2SO_4 could have been responsible. In the more recent longitudinal cohort studies, once again, positive associations have been observed between long-term exposure to SO_2 and mortality; however, several issues affect the interpretation of these results.

Figure 3-14 presents all-cause mortality RR estimates associated with long-term exposure to SO_2 from the U.S. and European cohort studies. The overall range of RRs spans 0.97 to 1.07 per 5 ppb increase in the annual (or longer period) avgSO_2. The analyses of the Harvard Six Cities and the ACS cohort data, which likely provide effect estimates that are most useful for evaluating possible health effects in the U.S., observed RRs of 1.02 to 1.07. Note that each of the U.S. cohort data has its own advantages and limitations. The Harvard Six Cities data have a small number of exposure estimates, but the study cities were carefully chosen to represent a range of air pollutant exposures. The ACS cohort had far more subjects, but the population was more highly educated than the representative U.S. population. Since educational status appeared to be an important effect modifier of air pollution effects in both studies, the overall effect estimate for the ACS cohort may underestimate that for the more general population. However, it should also be noted that several other U.S. and European studies did not observe an association between long-term exposure to SO_2 and mortality.

The geographic scale of analysis appears to influence SO_2 effect estimates and exposure error. In a reanalysis of the ACS data, the county-level analysis showed a smaller SO_2 effect estimate than MSA-level analysis. For sulfate, the opposite pattern was found. Thus, the impact of the geographic scale of analysis may also depend on the spatial distribution of air pollutants. The cross-sectional analysis in Great Britain using small-scale electoral wards observed an effect estimate similar to the lower end of the range of effect estimates for all-cause mortality from U.S. cohort studies, though it is not clear if the effect estimates from this cross-sectional study are directly comparable to those from cohort studies.

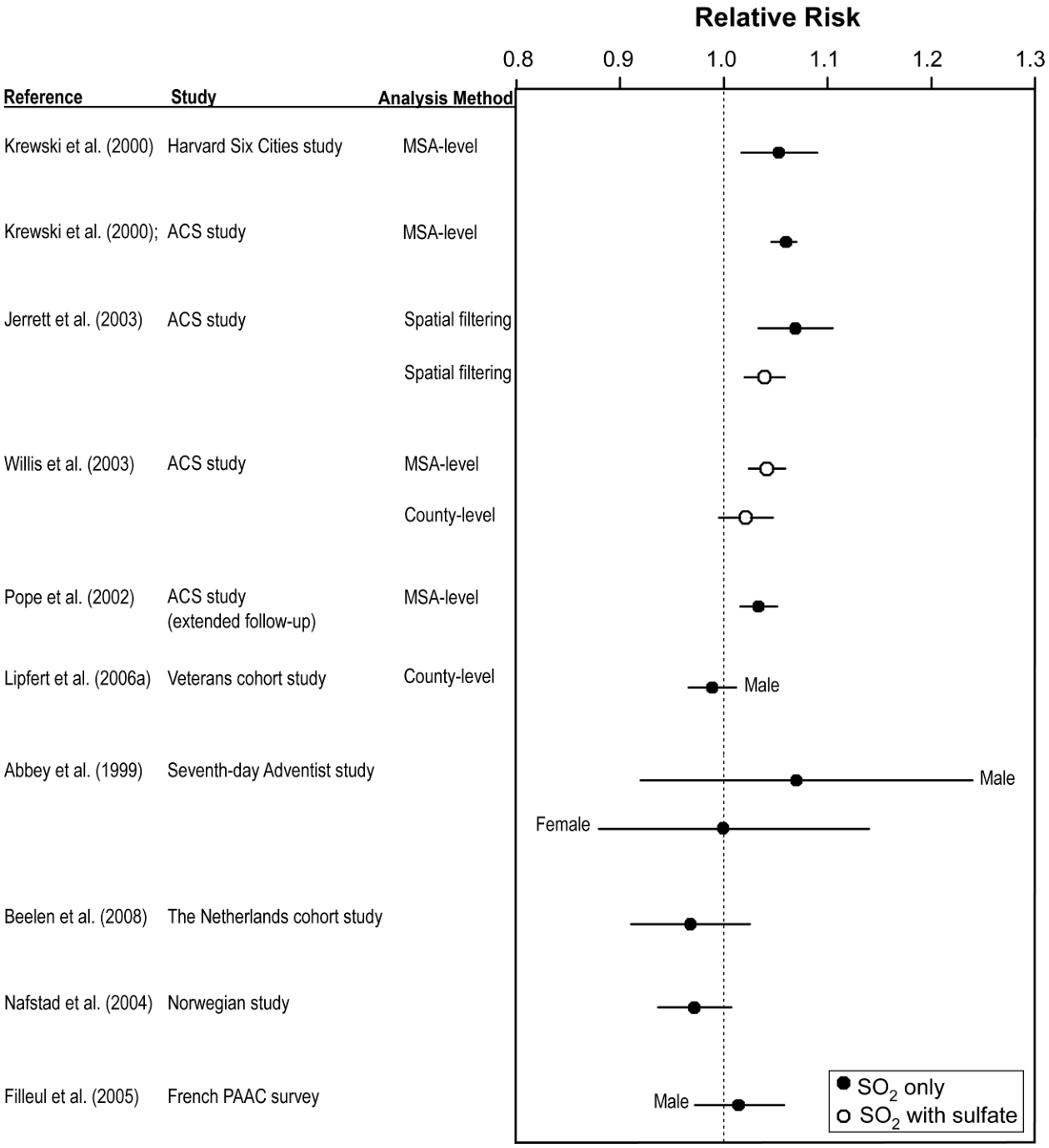


Figure 3-14. Relative risks (95% CI) of SO_2-associated all-cause (nonaccidental) mortality, with and without adjustment for sulfate, from longitudinal cohort studies. Effect estimates are standardized per 5 ppb increase in SO_2 concentrations. The exposure estimates for Krewski et al. (2000) and Pope et al. (2002) are based on MSA (Metropolitan Statistical Area)-level averaging; Lipfert et al. (2006b) used county-level averaging.

Another important issue that these studies could not resolve was the possible confounding and/or interaction among PM indices and SO_2. The possibility that the observed effects may not be due to SO_2, but other constituents that come from the same source as SO_2, or that PM may be more toxic in the presence of SO_2 or other components associated with SO_2, cannot be ruled out. For example, the ACS cohort came from all regions of the U.S., but a major fraction of the ACS cities were located in the eastern U.S., where both SO_2 and sulfate levels tend to be higher. Therefore, even with sophisticated spatial modeling, separating possible confounding of SO_2 effects by PM is challenging. Future and on-going studies that take into consideration within- versus between-city variation of these pollutants may help elucidate this issue.

Overall, the results from two major U.S. epidemiologic studies observe an association between long-term exposure to SO_2 or sulfur-containing particulate air pollution and mortality. However, several other U.S. and European cohort studies did not observe an association. The lack of consistency across studies, inability to distinguish potential confounding by copollutants, and uncertainties regarding the geographic scale of analysis limit the interpretation of a causal relationship.

Chapter 4. Public Health Impact

This chapter addresses several issues relating to the broader public health impact from exposure to ambient SO_2. The first section discusses the shape of the concentration-response relationship for SO_2, with consideration of interindividual variability in responses and evaluation of the limited evidence available to assess threshold values for health effects. The next section identifies characteristics of subpopulations which may experience increased risks from SO_2 exposures, through either enhanced susceptibility (e.g., as a result of pre-existing disease, genetic factors, age) and/or differential vulnerability associated with increased exposure (e.g., close proximity to sources, activities).

4.1. Assessment of Concentration-Response Function and Potential Thresholds

An important consideration in characterizing the public health impacts associated with SO_2 exposure is whether the concentration-response relationship is linear across the full concentration range, or if there are concentration ranges where there are departures from linearity (i.e., nonlinearity). Of particular interest is the shape of the concentration-response curve at and below the level of the current SO_2 NAAQS level of a 24-h avg level of 0.14 ppm or the annual avg of 0.03 ppm, and whether a threshold of effect may exist among these lower concentrations. The assumption of a threshold indicates an ambient SO_2 concentration below which adverse health outcomes are not elicited. Lack of a threshold implies that exposure to even the lowest measured ambient SO_2 concentrations has the potential to cause toxicity.

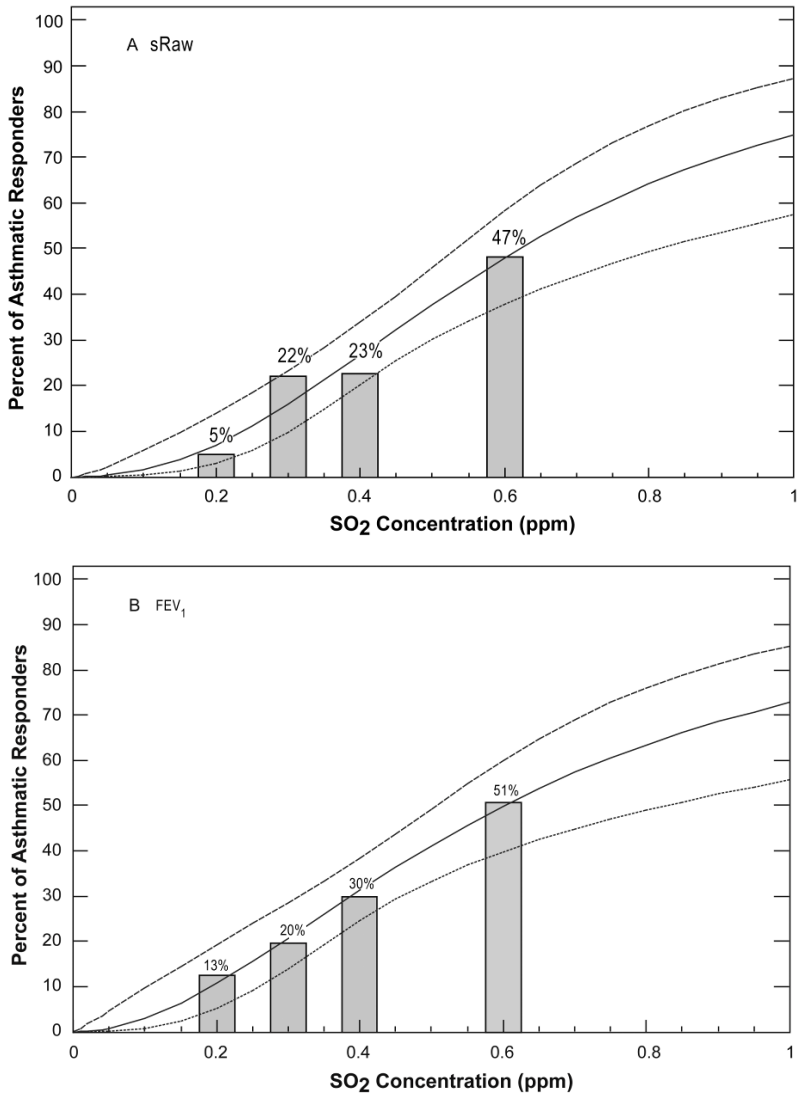
In the context of risk assessment for human health, it is important to consider the distinction between individual thresholds and population thresholds. There is wide variability in the human population, and a threshold for a population is defined by the threshold for the most sensitive individual in that population (Gaylor et al., 1988). Some human clinical studies provide individual-level response data in relation to different levels of SO_2 exposure; this allows evaluation of both the percentage of individuals showing responses across the range of exposures as well as the concentration at which an individual begins to indicate a response. Very few epidemiologic studies, and no human clinical studies, evaluate whether there is a population-level threshold, which is the concentration of SO_2 that must be exceeded to elicit a health response in the study population.

Human clinical and epidemiologic studies that examined the shape of the concentration-response function are presented below. The discussion focuses on respiratory morbidity effects associated with short-term exposure to SO_2, for which the strongest causal evidence exists.

4.1.1. Evidence from Human Clinical Studies

In human clinical studies of exercising asthmatics, moderate SO_2-induced decrements in lung function have been observed at the lowest levels tested (i.e., 0.2 to 0.3 ppm, 5 to 10 min exposures) in some individuals (approximately 5-30% of subjects). Statistically significant respiratory effects have been consistently observed at concentrations of 0.4-0.6 ppm, with 20-60% of asthmatics experiencing moderate to large decrements in lung function following 5-10 min exposures (see Table 3-1). Smaller, yet statistically significant decrements in lung function have also been demonstrated at SO_2 concentrations < 0.2 ppm when preceded by exposure to O_3 (see Section 3.1.3). Human clinical studies are valuable in characterizing the concentration-response relationship in relatively healthy asthmatics, but cannot be used

to evaluate potential population threshold directly, as controlled human exposure studies have not been conducted at SO_2 concentrations below 0.1 ppm and do not include the most sensitive asthmatics.



Source: Linn et al. (1987; 1988; 1990); Smith (1994)

Figure 4-1. Percent of mild and moderate asthmatics ($\dot{V}_E$ = 40-50 L/min) experiencing an SO_2-induced increase in (a) sRaw of ≥ 100% or a decrease in (b) FEV_1 of ≥ 15%, adjusted for effects of moderate to heavy exercise in clean air. The data represents lung function measurements from 40, 41, 40, and 81 subjects at concentrations of 0.2, 0.3, 0.4, and 0.6 ppm, respectively. A two parameter logistic model was fit to the data using Bayesian estimation with noninformative priors (Lunn et al., 2000).[1]

[1] The form of the logistic model was $p = 1/(1+\exp(-\alpha-\beta*\log(SO_2)))$, where p is the fraction of asthmatics who experienced a moderate or greater decrement in lung function as defined above. Median estimates are presented along with upper and lower 95% confidence intervals.

With increasing exposure concentration between 0.2 and 1.0 ppm, there is a clear increase both in magnitude of respiratory effect and percent of asthmatics affected (Table 3-1). A subset of the data presented in this table was taken from a series of studies conducted by Linn et al. (1987; 1988; 1990) and is presented graphically in Figures 4-1 through 4-3. In these studies, mild and moderate asthmatics were exposed for 10 min to SO_2 concentrations between 0 and 0.6 ppm during moderate to heavy exercise. These particular studies were selected for inclusion in this meta-analysis owing to similarities between exposure protocols, with all subjects being exposed to multiple concentrations of SO_2. In the 1987 study, subjects were exposed to SO_2 concentrations of 0, 0.2, 0.4, and 0.6 ppm, while in the 1988 and 1990 studies, subjects were exposed to concentrations of 0, 0.3, and 0.6 ppm. The percent of asthmatics experiencing moderate or greater SO_2-induced decrements in lung function (increase in sRaw $\geq$ 100% or decrease in $FEV_1 \geq 15\%$) is shown in Figure 4-1. At 0.2 ppm, between 5 and 13% of subjects are affected, and this fraction increases with increasing concentration, with approximately 50% of subjects experiencing respiratory effects at a concentration of 0.6 ppm.

Figures 4-2 and 4-3 present the concentration-response relationship between SO_2 and decrements in lung function among asthmatics in the Linn et al. (1987; 1988; 1990) studies. Concentration response relationships are presented for all asthmatics, as well as for SO_2-sensitive asthmatics, i.e., those asthmatics experiencing significant decrements in lung function at the highest exposure concentration used (0.6 ppm). This analysis demonstrates a clear increase in the magnitude of respiratory effects with increasing exposure concentration, with more marked effects observed at lower concentrations among the SO_2-sensitive asthmatics. The results of a study by Gong et al. (1995) support this conclusion: the authors observed a linear relationship between SO_2 concentration (0, 0.5, and 1.0 ppm) and both lung function (decrease in FEV_1, and increase in sRaw) and respiratory symptoms.

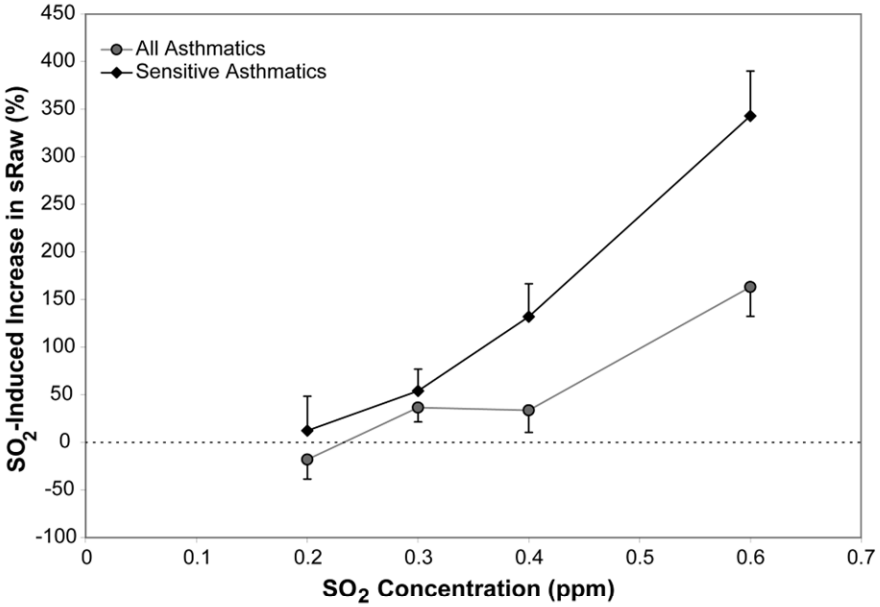


Figure 4-2. SO_2-induced increase in sRaw among mild and moderate asthmatics following 10 min exposures with moderate to heavy exercise (V_E = 40-50 L/min). Responses presented for all asthmatics as well as SO_2-sensitive asthmatics, defined here as asthmatics experiencing a ≥100% SO_2 induced increase in sRaw at 0.6 ppm. The analysis includes data from 40 subjects exposed to concentrations of 0.0, 0.2, 0.4, and 0.6 ppm, 14 of whom were SO_2-sensitive (Linn et al., 1987), as well as 41 subjects exposed to 0.0, 0.3, and 0.6, 25 of whom were SO_2-sensitive (Linn et al., 1988; 1990). Error bars = 1 SE.

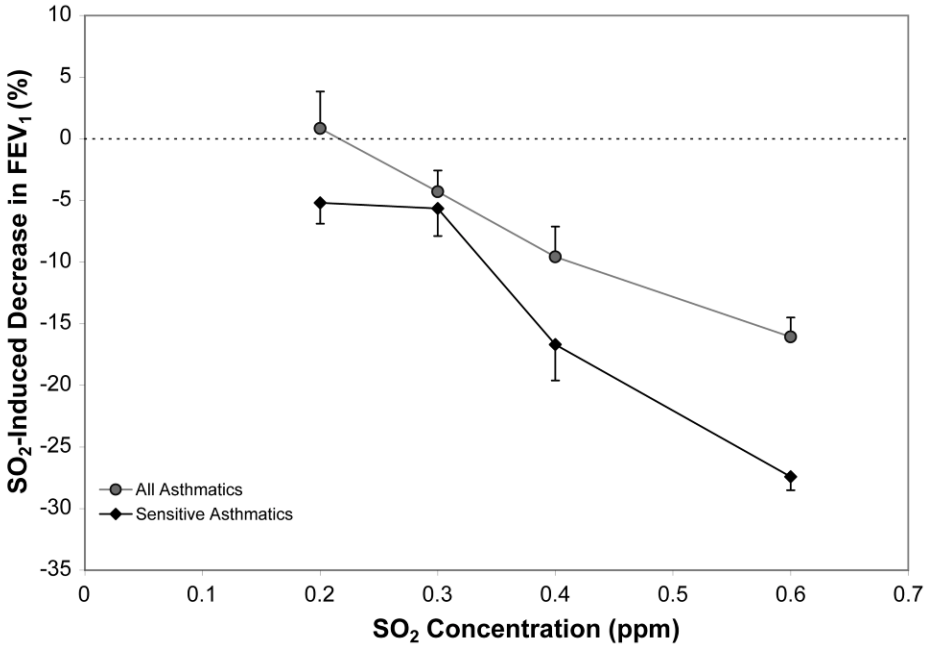


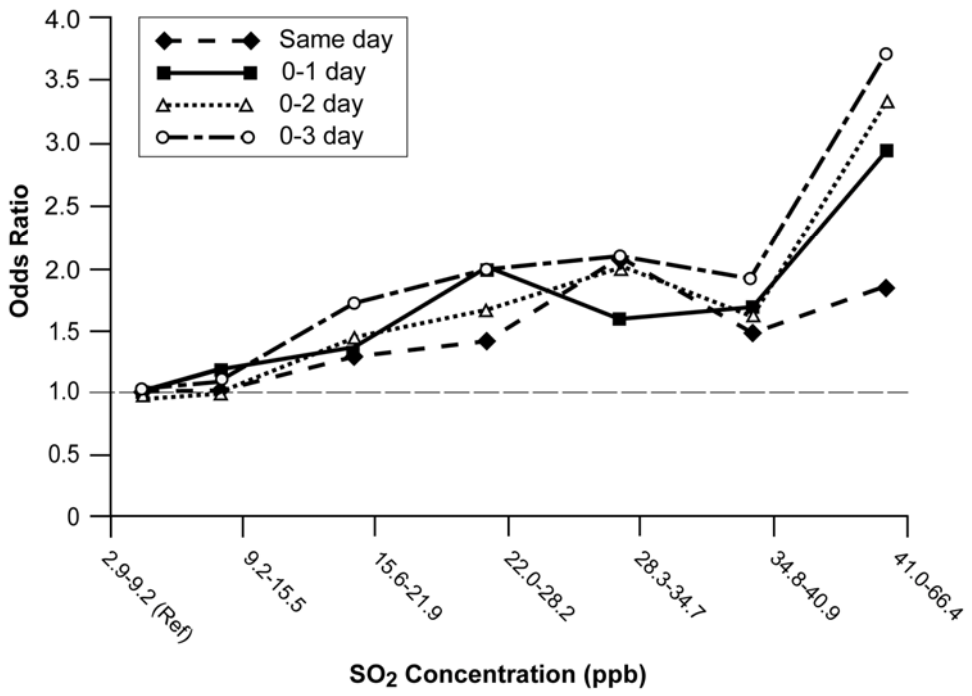
Figure 4-3. SO_2-induced decrease in FEV_1 among mild and moderate asthmatics following 10 min exposures with moderate to heavy exercise (V_E = 40-50 L/min). Responses presented for all asthmatics as well as SO_2 sensitive asthmatics, defined here as asthmatics experiencing a ≥15% SO_2 induced decrease in FEV_1 at 0.6 ppm. The analysis includes data from 40 subjects exposed to concentrations of 0.0, 0.2, 0.4, and 0.6 ppm, 21 of whom were SO_2 sensitive (Linn et al., 1987), as well as 41 subjects exposed to 0.0, 0.3, and 0.6, 20 of whom were SO_2 sensitive (Linn et al., 1988; 1990). Error bars = 1 SE.

4.1.2. Evidence from Epidemiologic Studies

Although there are numerous epidemiologic studies that examined the association between SO_2 and various health effects, only a few of these studies attempted to evaluate the concentration-response function. Most studies assumed a linear or log-linear relationship between ambient SO_2 concentrations and the health outcome in their evaluations.

Epidemiologic studies have examined the concentration-response relationship for SO_2 using various statistical methods, including the comparison of effect estimates in increasing quartiles or quintiles, plotting the risk observed against increasing SO_2 concentrations, and using nonparametric smoothed curves to assess the nonlinearity of the SO_2-effect relationship. Most of the epidemiologic studies that examined the concentration-response function between SO_2 exposure and respiratory morbidity observed that the relationship could not be distinguished from linear across the entire concentration range.

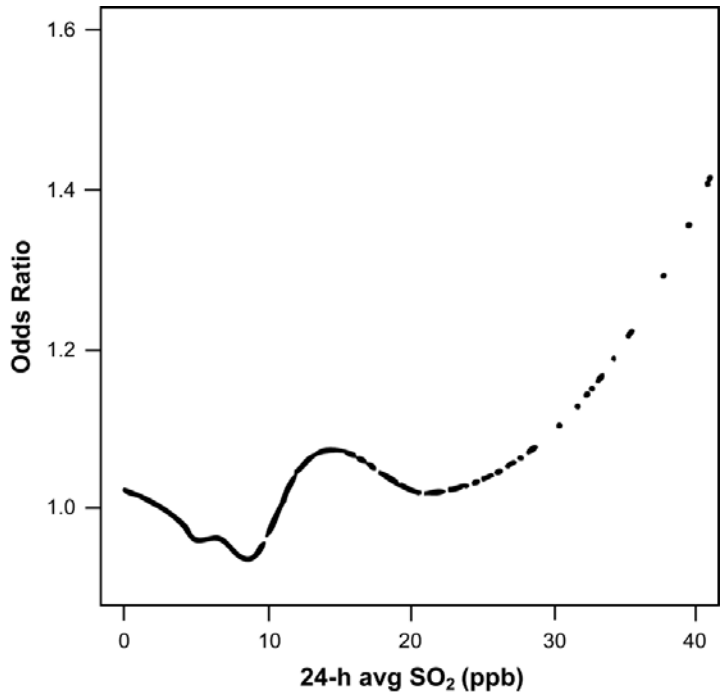
The association between asthma hospitalizations and ambient 24-h avg SO_2 concentrations was examined in a case-control study of children in Bronx County, NY (Lin et al., 2004d). The 24-h avg concentration ranged from 2.9 to 66.4 ppb. The authors categorized 24-h avg SO_2 concentrations and estimated ORs for each category using the lowest exposure group as the reference (2.9 to 9.2 ppb). They observed an increasing linear trend across the range of concentrations, with more marked effects observed at 24-h avg SO_2 concentrations greater than 40 ppb (Figure 4-4). A similar concentration-response relationship for daily 1-h max SO_2 levels was also observed. During the years 2003-2005, the 24-h avg SO_2 concentrations for the 90th and 95th percentiles were 10 and 13 ppb, respectively.



Source: Lin et al. (2004d)

Figure 4-4. Adjusted odds ratios of asthma hospitalizations by groupings of 24-h avg SO_2 concentrations in Bronx County, New York. All groups were compared with the lowest exposure group (2.9-9.2 ppb). ORs for 24-h avg SO_2 concentrations on the same day, as well as from a 2-day, 3-day, and 4-day moving average lag are presented.

The Harvard Six Cities Study by Schwartz et al. (1994) investigated the concentration-response function and observed a nonlinear relationship between SO_2 concentrations and respiratory symptoms. A figure plotting the relative odds of incidence of lower respiratory tract symptoms against SO_2 concentrations lagged 1 day indicated that no statistically significant increase in the incidence of lower respiratory tract symptoms was seen until SO_2 concentrations exceeded a 24-h avg of 22 ppb though an increasing trend was observed at concentrations as low as 10 ppb (see Figure 4-5). In a study of respiratory hospitalizations, Ponce de Leon et al. (1996) found that a weak relationship with SO_2 was only observable at 24-h avg SO_2 concentrations above 23 ppb. In both the Schwartz et al. (1994) and Ponce de Leon et al. (1996) studies, a statistically significant increased risk was observable only at 24-h avg SO_2 concentrations that were above the 90th percentile. The nonlinearity observed in these concentration-response functions is dependent on only a few influential observations; thus, should be interpreted with caution.



Source: Schwartz et al. (1994).

Figure 4-5. Relative odds ratio of incidence of lower respiratory tract symptoms smoothed against 24-h avg SO_2 concentrations on the previous day, controlling for temperature, city, and day of week.

A study by Jaffe et al. (2003) examined the association between SO_2 and ED visits for asthma in three cities in Ohio, and found significant associations only in Cincinnati using Poisson regression analysis. To examine the concentration-response function, they also conducted quintile analyses. In Cincinnati, an increasing linear trend in risk was observed across the range of concentrations. Wong et al. (2002a [using GAM with default convergence criteria]) constructed a plot of risk against 24-h avg SO_2 concentrations to examine the concentration-response relationship in Hong Kong and London. In general, a linear relationship between risk of respiratory hospitalizations and SO_2 was observed across the range of SO_2 concentrations in Hong Kong, but not in London. Several other studies that examined the concentration-response relationship found that the association between respiratory hospitalizations and SO_2 did not deviate from linearity (Atkinson et al., 1999b; Burnett et al., 1997b; Hajat et al., 1999; Hajat et al., 2002).

Discerning a possible population-level threshold for air pollution-related effects in epidemiologic studies is quite challenging. Using $PM_{2.5}$ as an example, Brauer et al. (2002a) examined the relationship between ambient concentrations and mortality risk in a simulated population with specified common individual threshold levels. They found that no population threshold was detectable when a low threshold level was specified for individuals. Other factors that may make it difficult to detect a threshold if one exists include wide interindividual variability in sensitivity to SO_2 exposure, and the inadequacy of currently deployed ambient monitors for accurate and precise measurements at lower 24-h avg SO_2 levels. Ambient concentrations of SO_2 have been declining since the 1980s and are now at or very near the limit of detection (~3 ppb) of the ambient monitors in the regulatory network. The mean 24-h avg SO_2 concentration across the metropolitan statistical areas (MSAs) from 2003 through 2005 was 4 ppb (5th–95th percentile: 1-13). Thus, there is greater uncertainty at the lower concentration range compared to the higher concentrations, which likely limits the ability to detect any potential threshold that may exist.

The overall evidence from epidemiologic studies that evaluate the concentration-response relationship is not sufficient to conclude that the relationship deviated from linearity; however, it should be noted that these studies generally lack power to distinguish between linear and non-linear response forms.

4.1.3. Summary of Evidence on Concentration-Response Functions and Thresholds

In the previous two sections, evidence from human clinical and epidemiologic studies on the concentration-response function that may inform identification of any potential population threshold was presented. Results from human clinical studies indicate wide interindividual variability in response to SO_2 exposures, with peak (5 to 10 min) exposures at levels as low as 0.2-0.3 ppm eliciting respiratory responses in some asthmatic individuals. A clear increase in the magnitude of respiratory effects was observed with increasing exposure concentrations between 0.2 and 1.0 ppm during 5-10 min SO_2 exposures.

Several epidemiologic studies that examined the concentration-response function between short-term (24-h avg or 1-h max) exposure to SO_2 and respiratory morbidity observed that the relationship could not be distinguished from linear across the entire concentration range. Given the various limitations in observing a possible threshold in population studies, the lack of evidence does not necessarily indicate that there is indeed no threshold in SO_2 health effects. Some epidemiologic studies did report that though there was generally an increasing trend at the lower SO_2 concentrations, a marked increase in SO_2-related respiratory health effects was observed at higher concentrations. However, as these observations were based on a few potentially influential data points (24-h avg SO_2 concentrations above the 90th percentile), the results should be interpreted with caution. The overall limited evidence from epidemiologic studies examining the concentration-response function of SO_2 health effects is inconclusive regarding the presence of an effect threshold at current ambient levels.

4.2. Susceptible and Vulnerable Populations

Not all individuals exposed to pollutants respond similarly. Some subpopulations are at increased risk to the detrimental effects of pollutant exposure; additionally, considerable interindividual variability exists within sensitive subpopulations. The NAAQS are intended to provide an adequate margin of safety for both general populations and sensitive subpopulations, or those subgroups potentially at increased risk for ambient air pollution health effects.

In general, a sensitive population might exhibit an adverse health effect to a pollutant at concentrations lower than those needed to elicit the same response in the general population, or exhibit a more severe adverse effect than the general population when exposed to the same pollutant concentrations. 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 SES (e.g., reduced access to health care) or particularly elevated exposure levels. Factors potentially contributing to susceptibility or vulnerability to air pollution are included in Table 4-1.

It is important to recognize that there is some overlap between the general concepts of susceptibility and vulnerability. For example, life stage is an important factor potentially determining both susceptibility and vulnerability. Children may be particularly vulnerable because of differences in exposure arising from their behavior and susceptible due to absorption or metabolism rates. Aging may also increase susceptibility to adverse effects from a pollutant because as individuals age, their bodies' ability to defend against and respond to injury may diminish.

The previous review of the SO_2 NAAQS identified certain groups within the population that may be more susceptible to the effects of SO_2 exposure, including asthmatics, individuals not diagnosed as asthmatic but with atopic disorders (e.g., allergies), and individuals with COPD or cardiovascular disease. Recent information on potentially susceptible or vulnerable subpopulations is assessed below.

Table 4-1. Factors Potentially Contributing to Susceptibility or Vulnerability to Air Pollution

Susceptibility Factors	Vulnerability Factors
Respiratory diseases (e.g., asthma)	Increased activity patterns
Cardiovascular diseases	Decreased air conditioning use
Genetic factors	Increased level of exertion
Age, Gender	Work environment (e.g., outdoor workers)
Race/ethnicity	Lower SES
Pro-inflammatory conditions, e.g., diabetes	Lower education level
Obesity	Residential location (e.g., proximity to roadways)
Adverse birth outcomes (e.g., low birth weight)	Geographic location (West vs. East)

4.2.1. Pre-existing Disease

A recent report of the NRC (2004) emphasized the need to evaluate the effect of air pollution on susceptible groups, including those with respiratory illnesses and cardiovascular diseases. Generally, asthma, COPD, conduction disorders, CHF, diabetes, and MI are conditions believed to put persons at greater risk of adverse events associated with air pollution. Asthmatics are known to be one of the most SO_2-responsive subgroups in the population; the evidence related to respiratory illness, including asthma and other factors, is discussed in further detail below.

4.2.1.1. Pre-existing Respiratory Diseases

The 1982 AQCD concluded that asthmatics are more susceptible to respiratory effects from SO_2 exposures than the general public. This conclusion was primarily drawn from the strong human clinical evidence. Recent epidemiologic studies have strengthened this conclusion, reporting associations between a range of health outcomes with both short-term and long-term SO_2 exposures in subjects with respiratory disease.

In human clinical studies, asthmatics have been shown to be more responsive to respiratory effects of SO_2 exposures than healthy non-asthmatics. While SO_2-attributable decrements in lung function generally have not been demonstrated at concentrations $\leq$ 1.0 ppm in non-asthmatics (Lawther et al., 1975; Linn et al., 1987; Schachter et al., 1984), statistically significant increases in respiratory symptoms and decreases in lung function have consistently been observed in exercising asthmatics following peak (5 to 10 min) SO_2 exposures to concentrations of 0.4-0.6 ppm (Gong et al., 1995; Horstman et al., 1986;

Linn et al., 1983b). Moderate or greater SO_2-induced decrements in lung function have also consistently been observed at lower SO_2 concentrations (0.2-0.3 ppm) in some asthmatics (Bethel et al., 1985; Linn et al., 1987; 1988; 1990; Sheppard et al., 1981). It is important to note that the most severe asthmatics in the population are excluded from participating in controlled human exposures to SO_2. Therefore, it is not unreasonable to presume that the most sensitive asthmatics would respond at lower levels than those used in human clinical studies. There is no evidence from human clinical studies that individuals with COPD have increased susceptibility to SO_2-induced respiratory effects.

A number of epidemiologic studies reported increased respiratory morbidity associated with SO_2 exposures in asthmatics. Notably, two U.S. multicity studies observed associations between ambient SO_2 concentrations and respiratory symptoms in asthmatic children (Mortimer et al., 2002; Schildcrout et al., 2006). Additional studies also have indicated generally positive associations for asthma among children and included a U.S. study (Delfino et al., 2003a) and several European studies (Higgins et al., 1995; Neukirch et al., 1998; Peters et al., 1996a; Roemer et al., 1993; Segala et al., 1998; Taggart et al., 1996; Timonen and Pekkanen, 1997; van der Zee et al., 1999). Studies of adults found no consistent association between respiratory symptoms among asthmatics and SO_2 concentrations (Desqueyroux et al., 2002a; 2002b; Romieu et al., 1996; van der Zee et al., 2000).

A positive association between ambient SO_2 concentrations and ED visits and hospitalizations provides further evidence that asthmatics are susceptible to the effects of SO_2. The associations between ambient concentrations of 24-h avg SO_2 and ED visits and hospitalizations for asthma in the U.S. are generally positive (Jaffe et al., 2003; Lin et al., 2004d; Michaud et al., 2004; Wilson et al., 2005), though a large time-series study conducted in Atlanta, GA did not find an association between ambient 1-h max SO_2 levels and asthma ED visits (Peel et al., 2005). Studies conducted outside the U.S. (Atkinson et al., 1999a; 1999b; Hajat et al., 1999; Sunyer et al., 1997; Thompson et al., 2001) also generally found positive results.

In summary, substantial evidence from epidemiologic studies suggests that individuals with preexisting respiratory diseases, particularly asthma, are more susceptible to respiratory health effects, though not mortality, from SO_2 exposures than the general public. The observations from human clinical studies indicating increased sensitivity to SO_2 exposures in asthmatic subjects compared to healthy subjects provide coherence and biological plausibility for these observations in epidemiologic studies.

4.2.1.2. Pre-existing Cardiovascular Diseases

The evidence available to evaluate the susceptibility of populations with cardiovascular disease for SO_2-related health effects is very limited. One human clinical study observed no evidence to suggest that patients with stable angina were more susceptible to SO_2-related health effects compared with healthy subjects (Routledge et al., 2006). The authors noted that this lack of response in the heart patients may be due to a drug treatment effect rather than decreased susceptibility. Liao et al. (2004) investigated short-term associations between ambient pollutants and cardiac autonomic control and observed that consistently more pronounced associations were found between SO_2 and HRV among persons with a history of coronary heart disease. In another epidemiologic study, Henneberger et al. (1996) examined the association of repolarization parameters with air pollutants in East German men with preexisting coronary heart disease. Ambient SO_2 concentrations during the 24-h preceding the ECG were associated with the QT interval duration, but not with any other repolarization parameters.

Evidence is inconsistent in studies analyzing the associations between ambient levels of air pollutants and ED visits or hospitalizations for cardiovascular diseases. A recent epidemiologic study investigated the association of SO_2 with cardiac-related hospital admissions among persons with preexisting cardiopulmonary conditions and observed no associations with ambient 1-h max SO_2 level for any cardiac disease investigated (i.e., ischemic heart disease [IHD], CHF, and dysrhythmia) across strata of comorbid disease status, including hypertension, diabetes, and COPD (Peel et al., 2007).

Goldberg et al. (2003) compared the risk estimates for death with the underlying cause of CHF and those deaths classified as having CHF one year before death and did not find associations between air pollution and those with CHF as an underlying cause of death. The authors found associations between some of the air pollutants examined (coefficient of haze [CoH], SO_2, and NO_2) and the deaths that were classified as having CHF one year before death, but the association with the specific cause of death was not unique to SO_2. This pattern of association, including but not specific to SO_2, with specific causes of death also was observed in an additional cohort of patients with CHF (Kwon et al., 2001).

In conclusion, the very limited evidence examining the susceptibility of individuals with preexisting cardiovascular disease to adverse health effects from ambient SO_2 exposures is inconclusive.

4.2.2. Genetic Factors for Oxidant and Inflammatory Damage from Air Pollutants

A consensus now exists among scientists that genetic factors related to health outcomes and ambient pollutant exposures merit serious consideration (Gilliland et al., 1999; Kauffmann, 2004). Several criteria must be satisfied in selecting and establishing useful links between polymorphisms in candidate genes and adverse respiratory effects. First, the product of the candidate gene must be significantly involved in the pathogenesis of the effect of interest, which is often a complex trait with many determinants. Second, polymorphisms in the gene must produce a functional change in either the protein product or in the level of expression of the protein. Third, in epidemiologic studies, the issue of confounding by other genes or environmental exposures must be carefully considered.

Several glutathione S-transferase (GST) families have common, functionally important polymorphic alleles (e.g., homozygosity for the null allele at the GSTM1 and GSTT1 loci, homozygosity for the A105G allele at the GSTP1 locus) that significantly reduce expression of enzyme function in the lung. Exposure to radicals and oxidants from air pollution induces decreases in GSH that increase GST transcription. Individuals with genotypes that result in enzymes with reduced or absent glutathione peroxidase activity are likely to have reduced oxidant defenses and increased susceptibility to inhaled oxidants and radicals.

Gilliland et al. (2002) examined effects of GSTM1, GSTT1, and GSTP1 genotypes and acute respiratory illness, specifically respiratory illness-related absences from school. The goal was to examine potential susceptibilities on this basis, but not specifically to air pollutants. They concluded that fourth grade schoolchildren who inherited a GSTP1 Val-105 variant allele had a decreased risk of respiratory illness-related school absences, indicating that GSTP1 genotype influences the risk and/or severity of acute respiratory infections in school-aged children.

Lee et al. (2004) studied ninth grade schoolchildren with asthma in Taiwan for a gene-environmental interaction between GSTP1-105 genotypes and outdoor pollution. They examined general district air pollution levels of low (mean SO_2 level of 3.6 ppb from 1994 to 2001), moderate (mean SO_2 of 6.2 ppb), and high (mean SO_2 of 8.6 ppb) and found that compared with individuals with any Val-105 allele in the low air pollution district, Ile-105 homozygotes in the high air pollution district had a significantly increased risk of asthma.

Gauderman et al. (2002) describe a study method that uses principal components analysis computed on single nucleotide polymorphism (SNP) markers to test for an association between a disease and a candidate gene. For example, they evaluated the association between respiratory symptoms in children and four SNPs in the GSTP1 locus, using data from the Southern California Children's Health Study (CHS). The authors observed stronger evidence of an association using the principal components approach ($p = 0.044$) than using either a genotype-based ($p = 0.13$) or haplotype-based ($p = 0.052$) approach. This method may be applied to relationships in this and other databases to evaluate aspects of air pollutants such as SO_2.

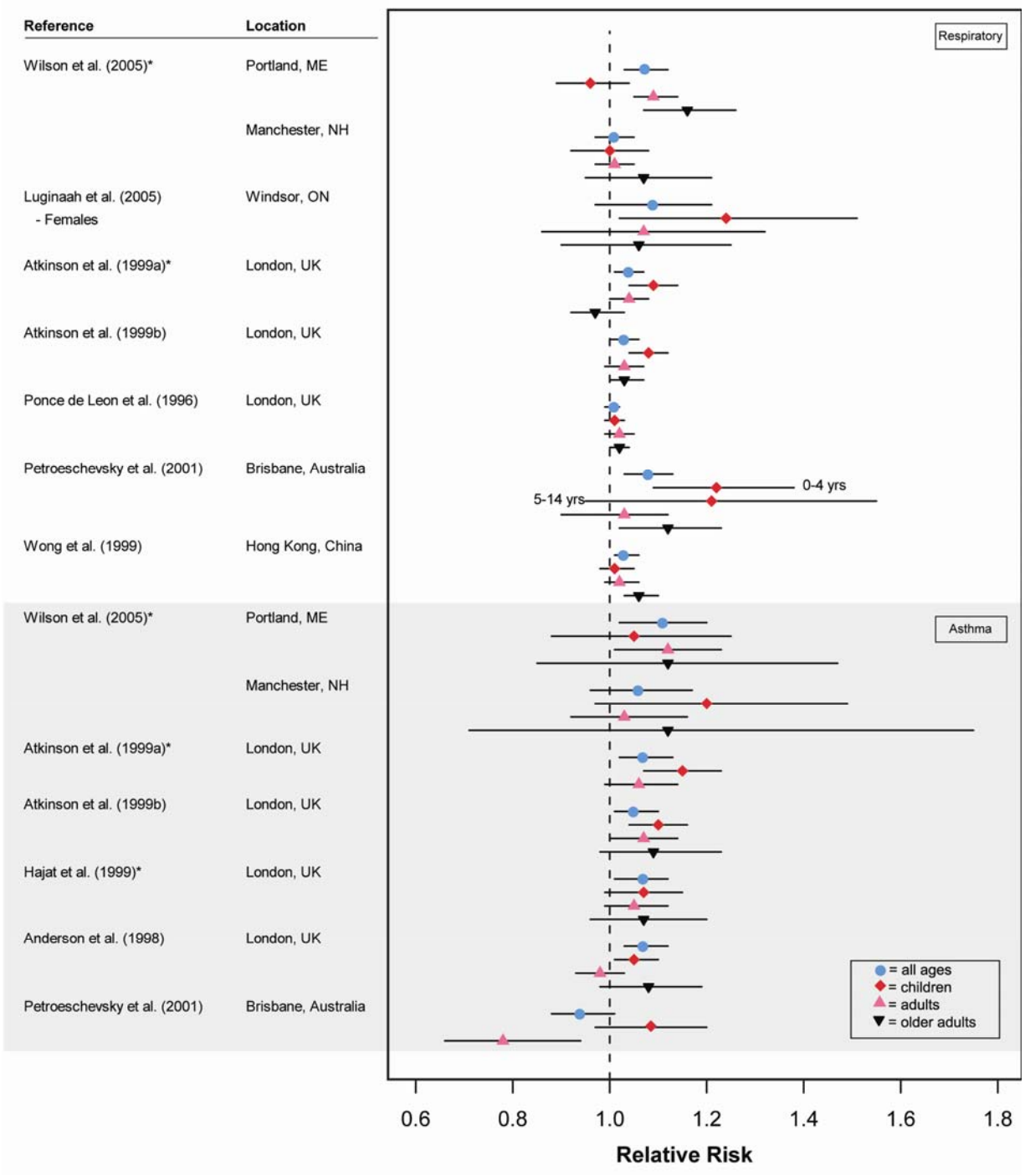


Figure 4-6. Relative risks (95% CI) of age-specific associations between short-term exposure to SO_2 and respiratory ED visits* and hospitalizations. Risk estimates are standardized per 10 ppb increase in 24-h avg SO_2 concentrations or 40 ppb increase in 1-h max SO_2.

Winterton et al. (2001) attempted to identify a genetic biomarker for susceptibility to SO_2. They screened 62 asthmatic subjects for SO_2 responsiveness using an inhalation challenge and collected genetic material via buccal swabs to test for associations between SO_2 sensitivity and specific gene

polymorphisms. Subjects inhaled 0.5 ppm SO_2 by mouthpiece for 10 min while wearing noseclips during moderate exercise on a treadmill. Subjects were defined as SO_2-sensitive if FEV_1 was decreased 12%. Genetic polymorphisms as biomarkers of susceptibility were evaluated in five regions coding for the β2-adrenergic receptor, the α subunit of the interleukin-4 (IL-4) receptor, the Clara cell secretory protein (CC16), tumor necrosis factor-α (TNF-α), and lymphotoxin-α (also known as TNF-β). The authors found a significant association between response to SO_2 and the homozygous wild-type allele of TNF-α position -308. All of the SO_2-sensitive subjects had the homozygous wild-type allele for TNF-α position -308, while 61% of the nonresponders had this genotype. Homozygosity for the TNF-1 allele was associated with a 5-fold increased risk of physician-diagnosed asthma relative to other genotypes. None of the other polymorphisms showed significant trends.

In summary, the differential effects of air pollution in general among genetically diverse subpopulations have been examined for a number of GST genes and other genotypes. The limited number of studies may provide some insight into susceptible groups and a potential genetic role in such. Only one of these studies specifically examined SO_2 as the exposure of interest, and it found a significant association with the homozygous wild-type allele for TNF-α. Khoury et al. (2000a) states that while genomics is still in its infancy, opportunities exist for developing, testing, and applying its tools to public health research of outcomes with possible environmental causes. At this time, there are insufficient data on which to base a conclusion regarding the effect of SO_2 exposure on genetically distinct subpopulations.

4.2.3. Age-Related Susceptibility

The American Academy of Pediatrics (2004) notes that children and infants are among the most susceptible to many air pollutants, including SO_2. Eighty percent of alveoli are formed postnatally and changes in the lung continue through adolescence; furthermore, the developing lung is highly susceptible to damage from exposure to environmental toxicants (Dietert et al., 2000). Children also have increased vulnerability as they spend more time outdoors, are highly active, and have high minute ventilation, which collectively increase the dose they receive (Plunkett et al., 1992; Wiley et al. 1991a, 1991b).

A number of epidemiologic studies have observed increased respiratory symptoms in children associated with increasing SO_2 exposures (Mortimer et al., 2002; Schildcrout et al., 2006; Schwartz et al. 1994), though there is no evidence from a limited number of studies suggesting this same effect in adults (Desqueyroux et al. 2002a, 2002b; van der Zee et al., 2000). Similarly, adverse respiratory effects have been observed in adolescents following SO_2 exposure in a laboratory setting (Koenig et al., 1981; 1983; 1987; 1988; 1990). However, there is no evidence from human clinical studies to suggest that the respiratory effects in adolescents are more severe than those observed in adults.

Older adults are frequently classified as being particularly susceptible to air pollution. The basis of the increased sensitivity in the older adults is not known, but one possibility is that it may be related to changes in the respiratory tract lining fluid antioxidant defense network (Kelly and Mudway, 2003) or a general reduction in immune competence.

A number of studies, investigating the association between ambient SO_2 levels and ED visits or hospital admissions for all respiratory causes or asthma, stratified their analyses by age group. Figure 4-6 summarizes the evidence of age-specific associations between SO_2 and acute respiratory ED visits and hospitalizations. Several studies demonstrated that the excess risk of ED visits or hospitalizations for all respiratory causes or asthma was higher for children (e.g. Atkinson et al., 1999a; 1999b; Petroeschevsky et al., 2001) and older adults (e.g. Petroeschevsky et al., 2001; Wilson et al., 2005; Wong et al. 1999) when compared to the risk for adults or all ages together. This is more clearly depicted in the summary density curves in Figure 4-7 and Figure 4-8, created using the effect estimates presented in Figure 4-6. As shown in these two figures, the effect estimates for children and older adults are slightly larger than that for adults or all ages for both all respiratory diseases and asthma ED visits and hospitalizations.

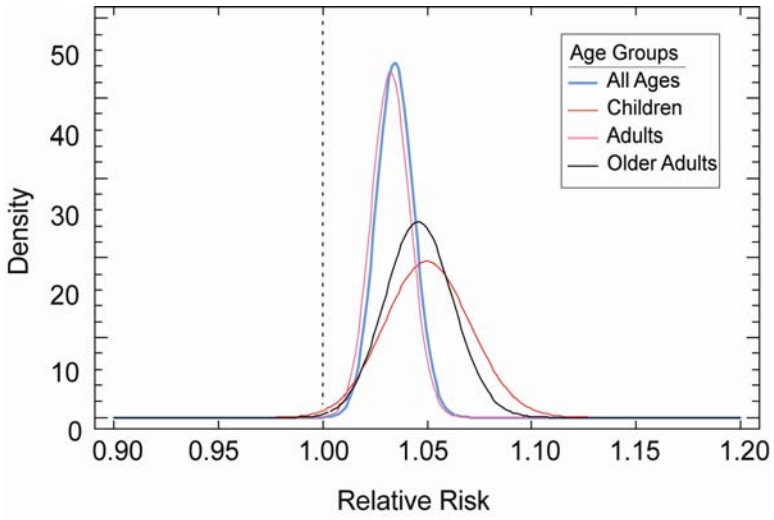


Figure 4-7. Summary density curves of the relative risks of age-specific associations between short-term exposure to SO_2 and ED visits and hospitalizations for all respiratory causes. Risk estimates are standardized per ppb increase in 24-h avg SO_2 concentrations or 40 ppb increase in 1-h max SO_2. Density curves drawn from effect estimates in Figure 4-6.

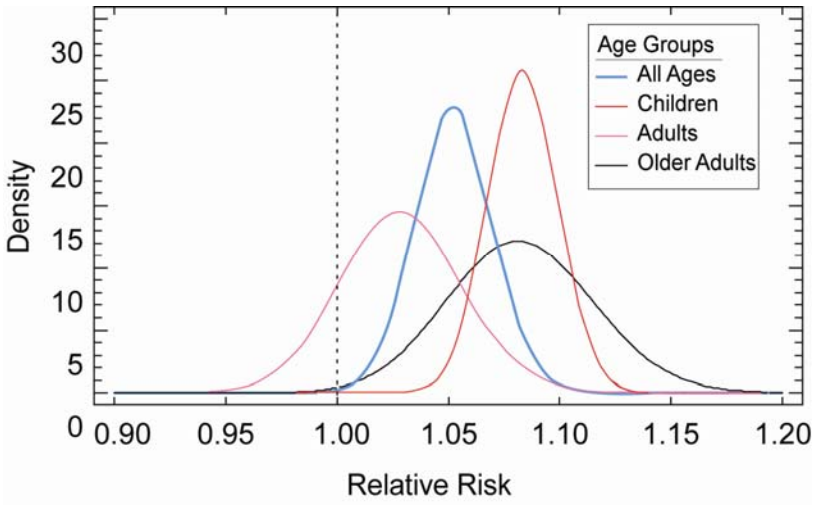


Figure 4-8. Summary density curves of the relative risks of age-specific associations between short-term exposure to SO_2 and ED visits and hospitalizations for asthma. Risk estimates are standardized per ppb increase in 24-h avg SO_2 concentrations or 40 ppb increase in 1-h max SO_2. Density curves drawn from effect estimates in Figure 4-6.

Cakmak et al. (2007b) reported that among seven Chilean urban centers, the percent increase in nonaccidental mortality associated with a 10 ppb increase in 24-h avg SO_2 was 3.4% (95% CI: 0.7, 6.1) for those < 65 years of age and 5.6% (95% CI: 2.2, 9.1) for those > 85 years of age. The authors concluded that older adults are particularly susceptible to dying from air pollution, and suggested that concentrations deemed acceptable for the general population may not adequately protect those aged > 85 years.

There is limited epidemiologic evidence to suggest that children and older adults (65+ years) are more susceptible to the adverse respiratory effects associated with ambient SO_2 concentrations when compared to the general population.

4.2.4. Other Potentially Susceptible Populations

Although data specific to SO_2 exposures is lacking for the susceptibility factors listed below, several other potentially susceptible groups deserve specific mention in this document. These include individuals in a chronic pro-inflammatory state (e.g., diabetics), obese individuals, and children born prematurely or with low birth weight.

Chronic inflammation appears to enhance susceptibility for air pollution-related cardiovascular events in older individuals, persons with diabetes, coronary artery disease, obesity, and past MIs (Bateson and Schwartz, 2004; Goldberg et al., 2001; Peel et al., 2007; Zanobetti and Schwartz, 2002). Dubowsky et al. (2006) reported that individuals with conditions associated with both chronic inflammation and increased cardiac risk were more vulnerable to the short-term pro-inflammatory effects of air pollution. This included individuals with diabetes; obesity; and concurrent diabetes, obesity and hypertension. Zanobetti and Schwartz (2001) reported more than twice the risk for hospital admissions for heart disease in persons with diabetes than in persons without diabetes associated with exposure to ambient air pollution, indicating that persons with diabetes are an important at-risk group. Data from the Third National Health and Nutrition Examination Survey indicated that 5.1% of the U.S. population older than 20 years of age has diagnosed diabetes and an additional 2.7% has undiagnosed diabetes (Harris et al., 1998). Moreover, another study found that subjects with impaired glucose tolerance without type II diabetes also had reduced HRV (Schwartz, 2001). This may indicate that the at-risk population may be even larger.

Mortimer et al. (2000) reported that among asthmatic children, birth characteristics continue to be associated with increased susceptibility to air pollution later in life, demonstrating that air pollution-induced asthma symptoms were more severe in children born prematurely or of low birth weight. Specifically, the authors revealed asthmatic children born more than three weeks prematurely or weighing less than 2,500 grams (5.5 pounds) had a six-fold decrease in breathing capacity associated with air pollution compared to full-weight, full-term children. The low birth weight and premature children also reported a five-fold greater incidence of symptoms like wheezing, coughing and tightness in the chest.

4.2.5. Factors that Potentially Increase Vulnerability to SO_2

A limited amount of information exists on exposures to SO_2 among vulnerable populations. As noted above, vulnerability is characterized by extrinsic factors that may increase a population's risk from air pollution, such as being more highly exposed than the general population, or reduced SES. Because indoor and personal SO_2 concentrations are generally much lower than outdoor or ambient measurements, individuals that spend most of their time indoors, such as older adults, are not anticipated to be vulnerable to high SO_2 exposures, though in some cases they may be more susceptible to the effects of these exposures than the general population due to preexisting health factors. Another factor that potentially alters vulnerability to SO_2 is air conditioning use due to the reduced penetration of SO_2 into buildings when windows are closed.

Other individuals with increased vulnerability include those who spend a lot of time outdoors at increased exertion levels, for example outdoor workers and individuals who exercise or play outdoor sports. Exercise may cause an increase in uptake of SO_2 resulting from an increase in ventilation rate and accompanying shift from nasal to oronasal breathing. Children, who generally spend more time playing outdoors, may qualify as both a susceptible population (due to their developing physiology) and as a

vulnerable population since ambient SO_2 concentrations are several-fold higher than indoor concentrations.

SES is a known determinant of health and there is evidence that SES modifies the effects of air pollution (Makri and Stilianakis, 2007; O'Neill et al., 2003). Both higher exposures to air pollution and greater susceptibility to its effects may contribute to a complex pattern of risk among those with lower SES. Conceptual frameworks have been proposed to explain the relationship between SES, susceptibility and exposure to air pollution. Common to these frameworks is the consideration of the broader social context in which people live and its effect on health in general (Gee and Payne-Sturges, 2004; O'Neill et al., 2003), as well as on maternal and child health (Morello-Frosch and Shenassa, 2006), and asthma (Wright et al., 2007) specifically. Multilevel modeling approaches that allow parameterization of community level stressors such as increased life stress, as well as individual risk factors, are considered by these authors. In addition, statistical methods that allow for temporal and spatial variability in exposure and susceptibility, have been discussed in the recent literature (Jerrett and Finkelstein, 2005; Kunzli, 2005).

Several studies have examined modification by SES indicators on the association between mortality and PM (Finkelstein et al., 2003; Jerrett et al., 2004; Martins et al., 2004; O'Neill et al., 2003; Romieu et al., 2004) or other indices such as traffic density, distance to roadway or a general air pollution index (Finkelstein et al., 2005; Ponce et al., 2005; Woodruff et al., 2003). However, modification of SO_2 associations has been examined in a few studies. For example, in a study conducted in 10 large Canadian cities, living in communities in which individuals have lower household education and income levels increased the individual's vulnerability to air pollution (Cakmak et al., 2006). These effects were statistically significant for several gaseous criteria pollutants, but not for SO_2. In addition, Finkelstein et al. (2003) evaluated neighborhood levels of income and air pollution in southern Ontario, Canada. They found that both income and SO_2 levels were associated with mortality differences. Specifically, among people with below-median income, the relative risk for those with above-median exposure to SO_2 was 1.18 (95% CI: 1.11, 1.26); the corresponding relative risk among subjects with above-median income was 1.03 (95% CI: 0.83, 1.28). Overall, there is very limited evidence available from which conclusions on the human health effects from the interaction between SES and SO_2 can be drawn.

Other factors that may potentially increase vulnerability to SO_2 are residential or geographic location. However, residential location is not as strong of a predictor of exposure vulnerability for SO_2 as for traffic-related pollutants, because meteorological conditions have a greater impact on pollutant plume direction from primary point sources such as coal-fired power plants.

4.2.6. Summary of Potentially Susceptible and Vulnerable Populations

In summary, subgroups considered to be potentially susceptible and/or vulnerable include children and older adults; people with other respiratory disease; genetic factors; SES; and populations experiencing heightened exposure levels (e.g., those living near roadways or other "hot spots" or engaged in outdoor work or exercise). Also of concern are individuals who generally may not be inherently susceptible to SO_2-related health effects but may experience transient increases in airways sensitivity to SO_X induced by other respiratory irritants such as recent viral respiratory infection (Stempel and Boucher, 1981). These groups comprise a large fraction of the U.S. population. Given the heterogeneity of individual responses to air pollution, the severity of health effects experienced by a susceptible subgroup may be much greater than that experienced by the population at large (Zanobetti et al., 2000).

Chapter 5. Summary and Conclusions

Previous chapters present the most policy-relevant information related to the review of the NAAQS for SO_X. This chapter integrates key findings from atmospheric sciences, ambient air data analyses, exposure assessment, dosimetry, and health evidence. The EPA framework for causal determinations described in Chapter 1 has been applied to the body of evidence in order to judge the scientific data about exposure to SO_X and health effects in a two-step process. The first step is to determine the weight of evidence in support of causation at relevant pollutant exposures and characterize the strength of any resulting causal classification. The EPA framework applied here employs a five-level hierarchy for causal determination:

- Causal relationship
- Likely to be a causal relationship
- Suggestive of a causal relationship
- Inadequate to infer a causal relationship
- Suggestive of no causal relationship

The second step evaluates the entirety of policy-relevant quantitative evidence regarding the concentration-response relationships including levels and exposure durations at which effects are observed, and subpopulations that experience effects that differ from the general population. This integration of evidence results in identification of a study or set of studies that best estimates the concentration-response relationships for the U.S. population, given the current state of knowledge. Together the two steps in the framework lead to: 1) causal determinations for a range of health outcomes, and 2) characterization of the magnitude of these responses, including susceptible or vulnerable subpopulations, over a range of relevant exposures.

This chapter summarizes and integrates the newly available scientific evidence that best informs consideration of the policy-relevant questions that frame this review, presented in Chapter 1. Section 5.1 presents trends in emissions of SO_2 and provides a brief summary of the *ambient air quality at short- and long-term exposures* ranging from 5 min to one year. Section 5.2 discusses the evidence for the *occurrence and plausibility of health effects* following short- and long-term exposure to ambient SO_2, and the *levels at which these health effects occur*. Section 5.3 *integrates the evidence* and discusses *important uncertainties* identified in the interpretation of the scientific evidence. Section 5.4 presents the evidence for potentially *susceptible and vulnerable populations* to health effects from SO_2 exposure. Finally, conclusions based on the available scientific evidence for human health effects associated with SO_2 exposure are presented in Section 5.5.

5.1. Emissions and Ambient Concentrations of SO_2

Anthropogenic SO_2 is emitted mainly by fossil fuel combustion (chiefly coal and oil) and metal smelting. The largest source of emissions is from elevated point sources such as the stacks of power plants and industrial facilities. Since 1990, in response to controls applied under the Acid Rain Program (U.S. EPA, 2006a), SO_2 emissions from these sources have declined substantially. Emissions demonstrate a strong gradient increasing from west to east, owing to the high concentration of SO_2-emitting electric generating utilities in the Ohio River Valley, the Southeast, Texas, Illinois, and Missouri. Policy Relevant Background (PRB) levels of SO_2 are estimated to be in the range of a few hundredths of a ppb (< 1% of typical ambient levels) across most of the U.S., though much higher values are found in areas affected by volcanic or geothermal activity.

The levels of the current primary NAAQS for SO_X are 0.14 ppm for 24-h avg SO_2 concentrations and 0.03 ppm for annual avg SO_2 concentrations, not to be exceeded more than once per year. Exceedances of the current primary NAAQS for SO_X have become rare in recent years, as both the mean 24-h and annual avg SO_2 concentrations in the U.S. for the years 2003 to 2005 were ~4 ppb. For the 24-h avg, 99th percentile and maximum values were ~25 ppb and ~145 ppb, respectively. The 99th percentile and maximum values of the annual avg were ~13 ppb and ~15 ppb, respectively.

Mean 1-h max concentrations in these years were ~13 ppb, with a 99th percentile value of ~95 ppb and maximum value of ~700 ppb. The large differences between 99th percentile and maximum values for the shorter term averages suggest that the maxima are strongly limited spatially and temporally and are not a major determinant of the mean values.

5-min avg SO_2 data are collected without a specific regulatory mandate. Hourly maximum 5-min avg data were voluntarily supplied from 98 monitors located in certain regions of the U.S. during the period 1997 to 2006, with only 16 monitors providing all twelve 5-min averages in each hour. The median value of the hourly maximum 5-min avg in this limited data set ranged from 1 to 8 ppb, while the 99th percentile value ranged from 21 to 184 ppb, depending on location. Because of the nonuniform spatiotemporal distribution of the existing 5-min data set across the U.S., these values are likely not representative of nationwide 5-min distributions.

5.2. Health Effects of SO_2

Evaluation of the health evidence, with consideration of issues related to atmospheric sciences, exposure assessment, and dosimetry, led to the conclusion that there is *a causal relationship between respiratory morbidity and short-term exposure to* SO_2. This conclusion is supported by the consistency, coherence, and plausibility of findings observed in the human clinical, epidemiologic, and animal toxicological studies. In human clinical studies, respiratory effects were observed following 5-10 min exposures to SO_2 at concentrations $\geq$ 0.2 ppm in asthmatics engaged in moderate to heavy levels of exercise. In the epidemiologic studies, respiratory effects were observed in areas where the maximum ambient 24-h avg SO_2 concentration was below the current 24-h avg NAAQS level of 0.14 ppm. Mean 24-h avg SO_2 levels ranged from 1 to 30 ppb in these epidemiologic studies conducted in the U.S. and abroad, with maximum 24-h avg SO_2 values ranging from 12 to 75 ppb. Animal toxicological studies indicate that repeated exposures to SO_2, at concentrations as low as 0.1 ppm in guinea pigs, may exacerbate airway inflammation and hyperresponsiveness in allergic animals.

The respiratory health effects of SO_2 are consistent with the mode of action of SO_2 as it is currently understood. The immediate effect of SO_2 on the respiratory system is bronchoconstriction. This response is mediated by chemosensitive receptors in the tracheobronchial tree. These receptors trigger reflexes at the central nervous system level resulting in bronchoconstriction, mucus secretion, mucosal vasodilation, cough, and apnea followed by rapid shallow breathing. In some cases, local nervous system reflexes also may be involved. Asthmatics are more sensitive to the effects of SO_2 likely resulting from preexisting inflammation associated with this disease. This inflammation may lead to enhanced release of mediators, alterations in the autonomic nervous system and/or sensitization of the chemosensitive receptors. These biological processes are likely to underlie decreased lung function and increased hyperresponsiveness observed in response to SO_2 exposure.

The definitive evidence for the causal relationship comes from human clinical studies reporting respiratory symptoms and decreased lung function in exercising asthmatics following 5-10 min exposures to SO_2 at concentrations which have sometimes been measured in ambient air for similarly short-time durations. With increased ventilatory rates during exercise, the pattern of SO_2 absorption shifts from the upper airways to the tracheobronchial airways in conjunction with a shift from nasal to oronasal breathing. Mode of breathing is an important determinant of the severity of SO_2-induced bronchoconstriction, with the greatest responses occurring during oral breathing followed by oronasal

breathing and the smallest responses observed during nasal breathing. In the human clinical studies, 5-30% of relatively healthy exercising asthmatics experienced moderate or greater decrements in lung function ($\geq$ 100% increase in sRaw or $\geq$ 15% decrease in FEV_1) with peak exposures to SO_2 concentrations of 0.2-0.3 ppm (see Table 5-1). At concentrations $\geq$ 0.4 ppm, a greater percentage (20-60%) of asthmatics experience SO_2-induced decrements in lung function, which are frequently accompanied by respiratory symptoms. A clear concentration-response relationship has been demonstrated following exposures to SO_2 at concentrations between 0.2 and 1.0 ppm, both in terms of increasing severity of effect and percentage of asthmatics adversely affected. Animal toxicological studies have also reported bronchoconstriction with short-term exposures of 1 ppm SO_2 (see Table 5-2). The limited 5-min SO_2 data acquired from ambient monitors located in certain regions of the U.S. during the years 1997 to 2006 indicated that 0.2% of the hourly maximum 5-min avg were greater than 0.2 ppm.

Table 5-1. Key health effects of short-term exposure to SO_2 observed in human clinical studies.

Concentration	Exposure	Effects	Study
0.2-0.3 ppm	5-10 min	Moderate to large reductions in FEV_1 and increases in sRaw observed among some asthmatic adults (5-30%) during moderate to heavy exercise. Bronchial responsiveness to SO_2 may be enhanced when preceded by exposure to O_3. Limited evidence of SO_2-induced increases in respiratory symptoms.	Bethel et al. (1985); Horstman et al. (1986);Koenig et al. (1990); Linn et al. (1983b; 1987; 1988; 1990); Schachter et al. (1984); Sheppard et al. (1981); Trenga et al. (2001)
	1-6 h	Enhanced airway responses to an inhaled allergen following exposure to SO_2 with NO_2 in resting asthmatics. No evidence of respiratory symptoms or decrements in lung function in resting asthmatics or healthy adults. The evidence that SO_2 exposure may lead to changes in heart rate variability is weak and inconsistent.	Devalia et al. (1994); Routledge et al. (2006); Rusznak et al. (1996); Tunnicliffe et al. (2001; 2003)
0.4-0.5 ppm	1-10 min	Moderate or greater decrements in lung function clearly demonstrated in asthmatics during exercise, with significant interindividual variability in response (~20-35% of asthmatics experiencing moderate or greater decrements in lung function). Respiratory effects observed following 5-10 min of exposure are generally not enhanced by repeat exposures. Respiratory symptoms (e.g., wheezing, chest tightness) are observed at concentrations as low as 0.4 ppm and have been shown to increase with increasing exposure concentrations.	Balmes et al. (1987); Gong et al. (1995); Horstman et al. (1986); Koenig et al. (1983); Linn et al. (1983b; 1987); Magnussen et al. (1990); Schachter et al. (1984); Sheppard et al. (1981); Trenga et al. (1999)
	~1-h	Decrements in lung function among asthmatics following 10 min of exercise at the end of a 60-75 min exposure are statistically significant, but less severe than effects observed following a 10 min period of exercise at the start of the exposure.	Linn et al. (1987); Roger et al. (1985)
0.6-1.0 ppm	1-10 min	Clear and consistent SO_2-induced increases in respiratory symptoms observed among exercising asthmatics. Moderate to large decrements in lung function demonstrated in 35-60% of asthmatics. Respiratory effects attributed to SO_2 among asthmatics during exercise may be diminished after cessation of exercise, even with continued SO_2 exposure. No respiratory effects reported in healthy, non-asthmatics.	Balmes et al. (1987); Gong et al. (1995); Hackney et al. (1984); Horstman et al. (1986; 1988); Koenig et al. (1983); Linn et al. (1987; 1988; 1990); Roger et al.(1985); Schachter et al. (1984)
	1-6 h	Decrements in lung function among asthmatics following 5-10 min of exercise at the end of a 1-6 h exposure are statistically significant, but less severe than effects observed following a 5-10 min period of exercise at the start of the exposure.	Linn et al. (1984; 1987); Hackney et al. (1984); Roger et al. (1985)

Table 5-2. Key respiratory health effects of exposure to SO_2 in animal toxicological studies.

Study	Exposure	Species	Effects
LUNG FUNCTION			
Amdur et al. (1983)	1 ppm (2.62 mg/m^3); 1 h; head only	Hartley guinea pigs, male, age not reported, 200-300 g, n = 18-23/ group	An 11% increase in pulmonary resistance and 12% decrease in dynamic compliance were observed. Neither effect persisted into the 1 h period following exposure. No effects were observed for breathing frequency, tidal volume, or min volume.
Barthelemy et al. (1988)	0.5 or 5 ppm (1.3 or 13.1 mg/m^3); 45 min; intratracheal	Rabbit, sex not reported, adult, mean 2.0 kg, n = 5-9/group; rabbits were mechanically ventilated	Lung resistance increased by 16% and 50% in response to 0.5 and 5 ppm SO_2, respectively.
Conner et al. (1985)	1 ppm (2.62 mg/m^3); 3-h/day for 6 days; nose only; animals evaluated for up to 48-h following exposure	Hartley guinea pig, male, age not reported, 250-320 g, n = ≤18/ group/time point	No effect was observed on residual volume, functional reserve capacity, vital capacity, total lung capacity, respiratory frequency, tidal volume, pulmonary resistance, pulmonary compliance, diffusing capacity for carbon monoxide or alveolar volume at 1 or 48 h after last exposure.
INFLAMMATION AND MORPHOLOGY			
Li et al. (2007)	2 ppm (5.24 mg/m^3); 1 h/day for 7 days; with and without exposure to ovalbumin	Wistar rats, male, age not reported	Increased number of inflammatory cells in BAL fluid, increased levels of MUC5AC and ICAM-1 and an enhanced histopathological response compared with those treated with ovalbumin or SO_2 alone
Park et al. (2001a)	0.1 ppm (0.26 mg/m^3); 5 h/day for 5 days; whole body; with and without exposure to ovalbumin	Dunkin-Hartley guinea pig, male, age not reported, 250-350 g, n = 7-12/group	After bronchial challenge, the ovalbumin/SO_2-exposed group had significantly increased eosinophil counts in BAL fluids compared with all other groups, including the SO_2–only group. The bronchial and lung tissue of the ovalbumin/SO_2–exposed group showed infiltration of inflammatory cells, bronchiolar epithelial damage, and mucus and cell plug in the lumen.
Conner et al. (1989)	1 ppm (2.62 mg/m^3); 3-h/day for 1-5 days; nose only; bronchoalveolar lavage performed each day	Hartley guinea pig, male, age not reported, 250-320 g, n = 4	No change in numbers of total cells and neutrophils, protein levels or enzyme activity in lavage fluid following SO_2 exposure.
Conner et al. (1985)	1 ppm (2.62 mg/m^3); 3 h/day/6 day; evaluated up to 72 h postexposure	Hartley guinea pigs, male, age not reported, 250-320 g, n = 18/ group/time point	No alveolar lesions.
Smith et al. (1989)	1 ppm (2.62 mg/m^3); 5-h/day, 5 day/wk up to 4 and 8 mos	Sprague-Dawley rats, male, young adult, initial weight not reported, n = 12-15 data point	Increased bronchial epithelial hyperplasia and number of nonciliated epithelial cells observed at 4 mos.
AIRWAY HYPERRESPONSIVENESS AND ALLERGIC SENSITIZATION			
Park et al. (2001a)	0.1 ppm (0.26 mg/m^3); 5-h/day for 5 days; whole body; with and without exposure to ovalbumin	Dunkin-Hartley guinea pig, male, age not reported, 250-350 g, n = 7-12/group	After bronchial challenge, the ovalbumin/SO_2-exposed group had significantly increased enhanced pause (indicator of airway obstruction) compared with all other groups, including the SO_2 group. Study authors concluded that low level SO_2 may enhance the development of ovalbumin-induced asthmatic reactions in guinea pigs.
Riedel et al. (1988)	0.1, 4.3, or 16.6 ppm (0, 0.26, 11.3, or 43.5 mg/m^3); 8-h/day for 5 days; whole body; animals were sensitized to ovalbumin on the last 3 days of exposure	Perlbright-White guinea pig, female, age not reported, 300-350 g, n = 5 or 6/group (14 controls)	Bronchial provocation with ovalbumin was conducted every other day for 2 wks, starting at 1 wk after the last exposure. Numbers of animals displaying symptoms of bronchial obstruction after ovalbumin provocation was increased in all SO_2 groups compared to air-exposed groups. Anti-ovalbumin antibodies (IgG total and IgG1) were increased in BAL fluid and serum of SO_2-exposed compared to air-exposed controls, with statistical significance attained for IgG total in BAL fluid at ≥4.3 ppm SO_2 and in serum at all SO_2 concentrations. Results indicate that in this model, repeated exposure to even low concentrations of SO_2 can potentiate allergic sensitization of the airway.

A larger body of evidence supporting this determination of causality comes from numerous epidemiologic studies published since the previous NAAQS review reporting associations with

respiratory symptoms, ED visits, and hospital admissions with short-term SO_2 exposures, generally of 24-h avg. These studies were conducted in areas where the maximum ambient 24-h avg SO_2 concentration was consistently below the current 24-h avg NAAQS level of 0.14 ppm. Mean 24-h avg SO_2 levels ranged from 1 to 30 ppb, with maximum values ranging from 12 to 75 ppb, in the epidemiologic studies,. Important new multicity studies and several other studies have found an association between 24-h avg ambient SO_2 concentrations and respiratory symptoms in children, particularly those with asthma. Furthermore, limited epidemiologic evidence indicates that atopic children and adults may be at increased risk for SO_2-induced respiratory symptoms. Generally consistent associations also were observed between ambient SO_2 concentrations and ED visits and hospitalizations for all respiratory causes, particularly among children and older adults (≥ 65 years), and for asthma. The SO_2-related changes in ED visits or hospital admissions for respiratory causes ranged from -5% to 20% excess risk.

The consistency and coherence of the epidemiologic evidence for respiratory effects associated with short-term exposure to SO_2 are illustrated in Figure 5-1 and Figure 5-2, which present effect estimates for respiratory symptoms, ED visits, and hospitalizations in children. Associations between short-term ambient SO_2 concentrations and respiratory symptoms, ED visits, and hospitalizations are largely positive, with several of the more precise effect estimates (suggestive of greater study power) indicating statistical significance. The epidemiologic findings of asthma symptoms with 24-h avg SO_2 exposures are generally coherent with increases in symptoms reported in asthmatics in human clinical studies with 5-10 min exposures; it is possible that these epidemiologic associations are determined in large part by peak exposures within a 24-h period. The effects of SO_2 on respiratory symptoms, lung function, and airway inflammation observed in the human clinical studies using peak exposures further provides a basis for a progression of respiratory morbidity resulting in increased ED visits and hospital admissions. Collectively, these findings provide biological plausibility for the observed associations between ambient SO_2 levels and ED visits and hospitalizations for all respiratory diseases and asthma, notably in children and older adults (≥ 65 years).

Overall, the epidemiologic evidence for respiratory morbidity is consistent, with associations reported in studies conducted in numerous locations using a variety of methodological approaches. The potential influence of copollutants has not been systematically considered in the epidemiologic literature. A limited subset of the studies examined potential confounding by copollutants using multipollutant regression models. These analyses indicated that although copollutant adjustment had varying degrees of influence on the SO_2 effect estimates, the effect of SO_2 on respiratory health outcomes appeared to be generally robust and independent of the effects of gaseous copollutants, including NO_2 and O_3. The evidence for PM_{10} was less consistent, though it was noted that in the limited number of studies that examined $PM_{2.5}$ and $PM_{10-2.5,}$ the SO_2 estimates were generally robust to the inclusion of these copollutants in the regression model. These findings suggest that the observed effects of SO_2 on respiratory endpoints occur independent of the effects of other ambient air pollutants.

Intervention studies provide additional evidence that supports a causal relationship between SO_2 exposure and respiratory health effects. Hill (1965) emphasized that intervention studies can provide strong support for causal inferences. Two notable studies conducted in several cities in Germany and in Hong Kong reported that decreases in SO_2 concentrations were associated with improvements in respiratory symptoms. In eastern Germany, a decrease in the prevalence of respiratory symptoms was correlated with a steep decline in ambient SO_2 concentrations of more than 90% from 1992-1993 to 1998-1999 (Heinrich et al., 2002). During this study period, decreases in other ambient air pollutants, including ~60% lower TSP concentrations, also occurred in these cities. In Hong Kong (Peters et al., 1996b), respiratory health improved with similarly large reductions in SO_2 of up to 80% in the polluted district but with much smaller reductions in TSP (less than 20%) compared with those in the cities in eastern Germany. The possibility remains that these health improvements may be partially attributable to declining concentrations of air pollutants other than SO_2, most notably PM or constituents of PM. Animal toxicological studies conducted at higher concentrations (≥ 1 mg/m^3 PM and ≥ 1 ppm SO_2) suggest that SO_2 effects may be potentiated by coexposure to PM but the relevance of these results to ambient

exposures is not clear. Hence, the improvements in respiratory health may be jointly attributable to declines in both SO_2 and PM.

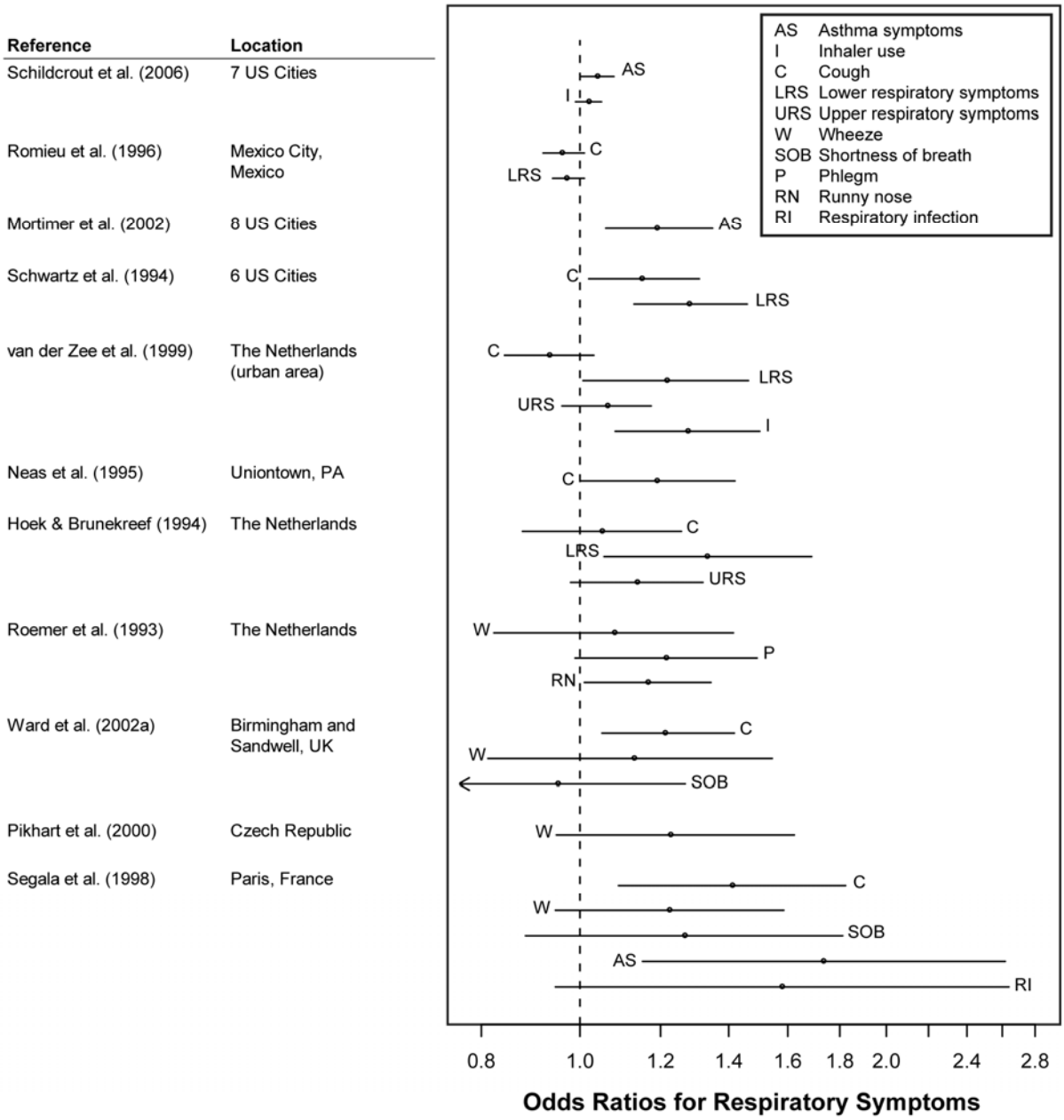


Figure 5-1. Odds ratios (95% CI) for the association between short-term exposures to ambient SO_2 and respiratory symptoms in children. Odds ratios are standardized per 10-ppb increase in 24-h avg SO_2 level. Studies are generally presented in the order of increasing width of the 95% CI.

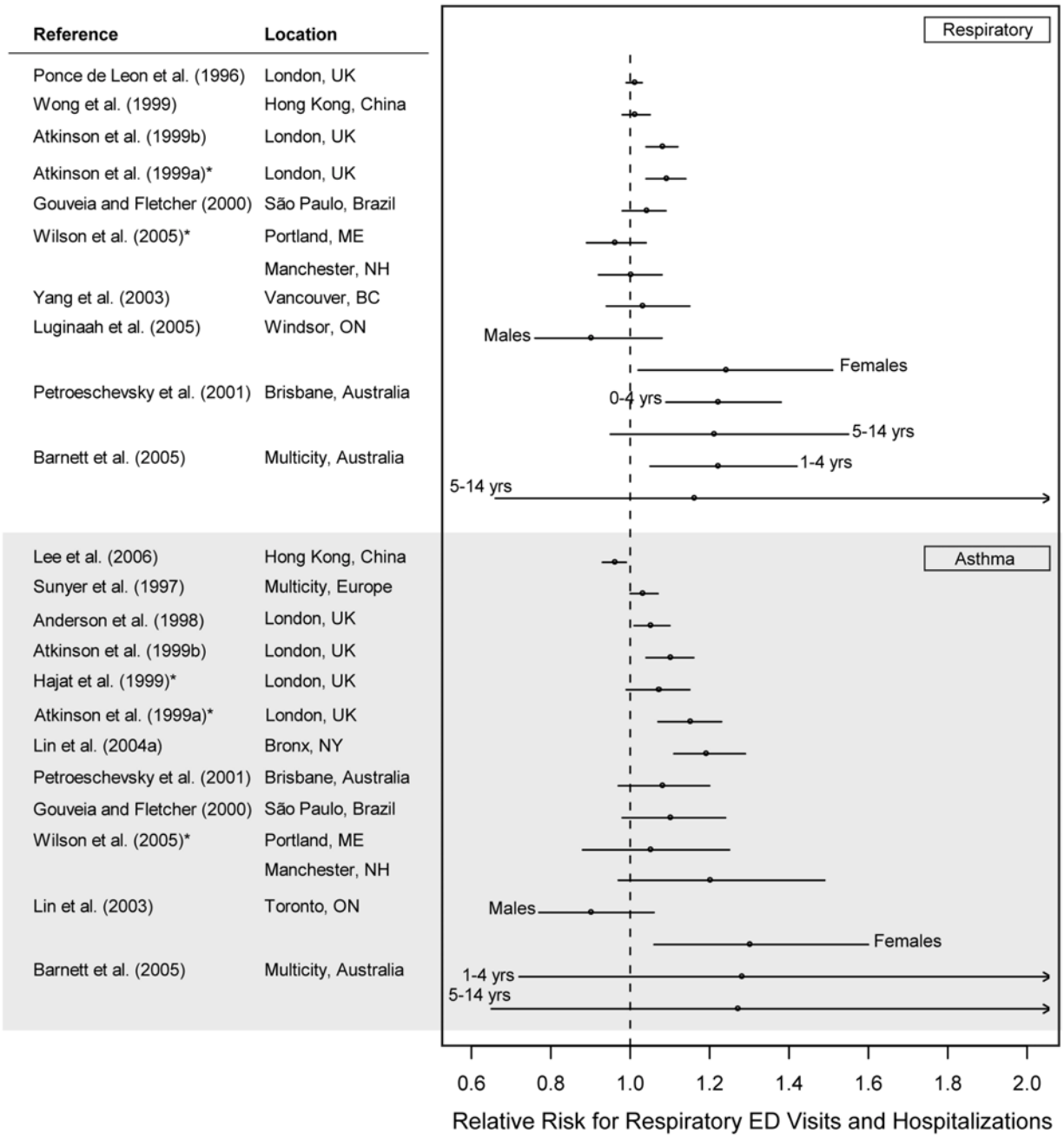


Figure 5-2. Relative risks (95% CI) for the association between short-term exposures to ambient SO_2 and emergency department (ED) visits (*) and hospitalizations for all respiratory diseases and asthma in children. Relative risks are standardized per 10-ppb increase in 24-h avg SO_2 level. The studies are generally presented in the order of increasing width of the 95% CI.

The ISA also evaluates the evidence of other health outcomes and exposure durations. For short-term exposure to SO_2 and mortality, the evidence was suggestive of a causal relationship. Recent epidemiologic studies have consistently reported positive associations between mortality and SO_2, with slightly larger effect estimates observed for respiratory mortality compared to cardiovascular mortality.

However, the SO_2 effect estimates were generally reduced after adjusting for copollutants in the regression models, indicating some extent of confounding among these pollutants. The evidence between short-term SO_2 exposure and cardiovascular effects, and morbidity and mortality with long-term SO_2 exposures is inadequate to infer a causal relationship. The key conclusions on the health effects of SO_2 exposure are briefly summarized in Section 5.5.

5.3. Integration of the Evidence

This section highlights some key considerations for the evaluation of the evidence in this ISA. As discussed above, clinical studies provide the definitive evidence that short-term SO_2 exposure is associated with respiratory morbidity. Numerous epidemiologic studies report associations for a broader range of respiratory health outcomes, at lower concentrations than the clinical studies and at levels below the current 24-h avg standard. There is, however, uncertainty about the magnitude of the epidemiologic effects estimates. Several sources of uncertainty and the implications for risk assessment are discussed below.

Although the numerous epidemiologic studies provide supportive evidence in making a causal determination for the effect of SO_2 on respiratory health, uncertainty remains in quantifying the concentration-response relationship. Exposure measurement error is a key source of this uncertainty as there are questions about the extent to which concentrations measured by the regulatory ambient monitoring network typically used in epidemiologic studies can accurately represent an individual's exposure to SO_2 of ambient origin. SO_2 monitors currently deployed in the regulatory monitoring networks are adequate to determine compliance with current standards, since both the 24-h and annual avg standards are substantially above the operating limit of detection of these monitors. However, these monitors are inadequate for accurate and precise measurements at or near the current ambient mean 24-h avg SO_2 level of ~4 ppb. Other factors contributing to exposure measurement error include the siting of ambient monitors, spatial variation in ambient SO_2, variation in time-activity patterns, infiltration characteristics of microenvironments, and instrument error.

Only a limited number of studies have focused on the relationship between personal exposure and ambient concentrations of SO_2, in part because ambient levels have declined markedly over the past few decades. Current indoor and outdoor concentrations are often beneath detection limits for passive personal monitors used in SO_2 exposure studies. In such situations, associations between ambient concentrations and personal exposures are inadequately characterized. However, in two studies with personal measurements above detection limits (Brauer et al., 1989; Sarnat et al., 2006a), a reasonably strong association (statistically significant regression slopes, with $R^2 = 0.15\text{-}0.43$) was observed between personal SO_2 exposure and ambient concentrations.

No studies have characterized the relationship between community avg exposure and ambient concentrations, which is more directly relevant to community time-series, short-term panel, and long-term cohort epidemiologic studies. Variations across a community in the fractional contribution of ambient SO_2 to exposure generally will not influence the magnitude of the observed health effect estimate in the epidemiologic studies, though the standard error of the estimate would tend to be increased by intracommunity variations. However, for community time-series and short-term panel studies, exposure and analytical measurement errors would tend to bias the effect estimate towards the null, leading to uncertainty in accurately quantifying the magnitude of the effect. In long-term exposure studies, the variable ambient measurement and exposure error could also result in bias, but the extent and direction of this bias is unclear.

Another factor that contributes to uncertainty in estimating the SO_2-related effect from epidemiologic studies is that SO_2 is one component of a complex air pollution mixture including various other components known to affect respiratory health. Several of these copollutants have been found to be

correlated with SO_2 in epidemiologic studies (e.g., PM, NO_2, CO). Of particular interest is the correlation between SO_2 and sulfate, the principal atmospheric oxidation product of SO_2. Short-term, mostly time-series epidemiologic studies generally use intracity ambient concentration data which show very little or no correlation between emitted SO_2 and transformed sulfate. In contrast, long-term epidemiologic studies using intercity data can show correlations between SO_2 and sulfate on the order of 0.8 or higher. In these studies, the fine-scale spatiotemporal variations in the intracity data are significantly reduced since sulfate has sufficient time for production from SO_2, is dispersed over a wide spatial area, and can be mixed down to ground level. Layered over these spatial and fine-scale temporal differences are seasonal and regional dissimilarities driven by cities' various SO_2 emissions profiles and differing available time and sunlight conditions for oxidation. Therefore, the relationship between SO_2 and sulfate indicates temporal and spatial discongruities that can influence exposures and related health effects.

As a consequence of these uncertainties, the epidemiologic observations of SO_2 health effects can be interpreted in different ways which are not mutually exclusive. First, the reported SO_2 effect estimates in epidemiologic studies may reflect independent SO_2 effects on respiratory health. This is supported by evidence from human clinical studies which indicate that peak exposures (5-10 min) to SO_2 at levels as low as 0.2-0.3 ppm are capable of eliciting respiratory responses in asthmatics. In the epidemiologic studies, SO_2-related effects on respiratory morbidity were observed in areas where the mean 24-h avg SO_2 levels ranged from 1 to 30 ppb, with maximum values ranging from 12 to 75 ppb. There are several factors that may explain the difference between the concentration-response relationships in the human clinical and epidemiologic studies. First, human clinical studies examine effects in groups of relatively healthy individuals who do not represent the full range of susceptibilities present in the general population. In addition, clinical studies include very small numbers of subjects as compared to the epidemiologic studies that consider large populations exposed to ambient concentrations. These two factors limit the power of human clinical studies to characterize exposure-response relationships at ambient-relevant concentrations for the general population and sensitive subpopulations. Further, comparisons are being made between 5-10 min exposures in the human clinical studies and 24-h avg exposures values reported in the epidemiologic studies. It is difficult to know if high short-term SO_2 concentrations are driving the observed associations among the general population given the limited number of ambient monitoring sites reporting short-term concentration data across the country. Among the limited number of epidemiologic studies evaluating the concentration-response function, a few studies found that a marked increase in SO_2-related respiratory health effects was only observed at higher concentrations (above 90th percentile values). However, several others reported a linear relationship across the entire range of concentrations.

Another interpretation is that ambient SO_2 may be serving as an indicator of complex ambient air pollution mixtures sharing the same source as SO_2 (i.e., combustion of sulfur-containing fuels or metal smelting). Other components of mixed emissions from these sources include trace elements such as vanadium, nickel, selenium, and arsenic. Distinguishing effects of individual pollutants in multipollutant regression models is made difficult by the possibility that a given air pollutant may be acting as a surrogate for a less-well-measured or unmeasured pollutant, or that several pollutants may all be acting as surrogates for the same mixtures of pollutants. Therefore, reported SO_2-related effects may represent those of the overall mixture or other chemical components within the mixture. Although these issues complicate the interpretation of effect estimates from multipollutant regression models, the limited available evidence indicates that the effect of SO_2 on respiratory health outcomes appeared to be generally robust and independent of the effects of gaseous copollutants, including NO_2 and O_3, as well as particulate copollutants, particularly $PM_{2.5}$.

5.4. Susceptible and Vulnerable Populations

Evidence from epidemiologic and human clinical studies, supported by animal studies, has indicated that certain subgroups within the population are more susceptible and/or vulnerable to the effects of SO_2 exposure. There is substantial evidence from epidemiologic and human clinical studies indicating that asthmatics are more susceptible to respiratory health effects from SO_2 exposures than the general public. Limited epidemiologic evidence further indicates that children and older adults (≥ 65 years) are more susceptible to the adverse respiratory effects associated with ambient SO_2 concentrations when compared to the general population. A number of potentially susceptible groups, including obese individuals, individuals having a chronic pro-inflammatory state like diabetics, and children born prematurely or with low birth weight (< 2,500 grams), may experience increased adverse effects associated with exposure to air pollution, but these relationships have not been examined specifically in relation to SO_2. The differential effects of air pollution among genetically diverse subpopulations have been examined for a number of glutathione-S-transferase (GST) genes and other genotypes. While limited in number, these studies provide some insight into a potential genetic role in the determination of susceptibility to air pollution.

Human clinical studies have clearly shown that exercising asthmatics are at greatest risk of experiencing adverse respiratory effects related to SO_2 exposure. Oronasal breathing during exercise increases vulnerability as it allows a larger fraction of inhaled SO_2 to reach the lower airways. Therefore, individuals with increased vulnerability for SO_2-related respiratory health effects include those who spend time outdoors at increased exertion levels, for example children, outdoor workers, and individuals who exercise or play sports.

5.5. Conclusions

The important findings of this ISA on the health effects of SO_2 exposure, including the levels at which effects are observed, are briefly summarized in Table 5-3. Also summarized are conclusions drawn in the 1996 NAAQS review for comparison.

Collectively, the human clinical, epidemiologic, and animal toxicological data are sufficient to conclude that there is a causal relationship between respiratory morbidity and short-term exposure to SO_2. Observed associations between SO_2 exposure and an array of respiratory outcomes, including respiratory symptoms, lung function, airway inflammation, AHR, and ED visits and hospitalizations from the human clinical, animal toxicological, and epidemiologic studies, in combination, provide clear and convincing evidence of consistency, specificity, temporal and biologic gradients, biological plausibility, and coherence.

Human clinical studies consistently demonstrate respiratory morbidity among exercising asthmatics following peak exposures (5-10 min) to SO_2 concentrations ≥ 0.4 ppm, with respiratory effects occurring at concentrations as low as 0.2 ppm in some asthmatics. In the epidemiologic studies, the SO_2-related respiratory effects were consistently observed in areas where the maximum ambient 24-h avg SO_2 concentration was below the current 24-h avg NAAQS level of 0.14 ppm (see Tables 5-4 and 5-5). Potentially susceptible and vulnerable subgroups include asthmatics, children, older adults, and individuals who spend a lot of time outdoors at increased exertion levels.

In addition to respiratory morbidity related to short-term exposure to SO_2, studies of other health outcomes and exposure durations were also evaluated in this ISA. The evidence is suggestive of a causal relationship between short-term exposure to SO_2 and mortality. The evidence linking short-term SO_2 exposure and cardiovascular effects, and morbidity and mortality with long-term exposures to SO_2 is inadequate to infer a causal relationship.

Table 5-3. Key findings on the health effects of SO_2 exposure

Short-Term Exposure: RESPIRATORY MORBIDITY

Causal relationship

RESPIRATORY SYMPTOMS

Conclusions from 1996 NAAQS Review: Among exercising asthmatics, there is a clear, statistically significant increase in respiratory symptoms following peak exposures (5-10 min) to 0.6-1.0 ppm SO_2. Significant, but less severe symptoms are associated with peak SO_2 exposures at concentrations of 0.4-0.5 ppm in human clinical studies.

In the epidemiologic studies, an association with aggravation of bronchitis is consistently observed at 24-h avg SO_2 levels of 0.19 to 0.23 ppm and in some cases at levels below 0.19 ppm.

Conclusions from Current Review: Severity and incidence of respiratory symptoms has been shown to increase with increasing concentrations between 0.2 and 0.6 ppm SO_2 in exercising asthmatic adults following peak exposures (5-10 min). Statistically significant increases in symptoms are observed at SO_2 concentrations ≥ 0.4 ppm.

Epidemiologic studies provide consistent evidence of an association between ambient SO_2 exposure and increased respiratory symptoms in children, particularly those with asthma or chronic respiratory symptoms. Multicity studies have observed these associations at a median range of 17 to 37 ppb (75th percentile: ~25 to 50) across cities for 3-h avg SO_2 and 2.2 to 7.4 ppb (90th percentile: 4.4 to 14.2) for 24-h avg SO_2.

In contrast, the epidemiologic evidence on the association between SO_2 and respiratory symptoms in adults is inconsistent at current short-term avg ambient SO_2 concentrations.

LUNG FUNCTION

Conclusions from 1996 NAAQS Review: Bronchoconstriction has been found to be the most sensitive indicator of lung function effects following acute exposure to SO_2. Guinea pigs were found to be the most sensitive species, with bronchoconstriction observed using 0.16 ppm SO_2. In human clinical studies, ≤ 10-20% of exercising asthmatic individuals experience large decrements in lung function (i.e., sRaw increases ≥ 200% or FEV_1 decreases ≥ 20%) following 5-10 min exposures to SO_2 concentrations of 0.2-0.5 ppm. At 0.6-1.0 ppm SO_2, ≥ 20-25% of exercising asthmatics are similarly affected.

Small, reversible declines in lung function in children are observed in epidemiologic studies at levels of 0.10 to 0.18 ppm but not at levels of 0.04 to 0.08 ppm.

Conclusions from Current Review: SO_2-induces moderate or greater decrements in lung function, i.e. increases in sRaw (≥ 100%) or decreases in FEV_1 (≥ 15%) in 5-30% of exercising asthmatics at 0.2-0.3 ppm and 20-60% of exercising asthmatics at 0.4-1.0 ppm with 5-10 min exposures.

Epidemiology results are inconsistent for the association between short-term avg SO_2 and lung function in children and adults.

AIRWAYS INFLAMMATION

Conclusions from 1996 NAAQS Review: No conclusions in the previous review.

Conclusions from Current Review: A limited number of health studies have evaluated the effect of SO_2 on airway inflammation. One human clinical study observed an SO_2-induced increase in sputum eosinophil counts in exercising asthmatics 2 h after a 10 min exposure to 0.75 ppm SO_2. The results of this study provide some evidence that SO_2 may elicit an inflammatory response in the airways of asthmatics which extends beyond the short time period typically associated with SO_2 effects.

Animal toxicological studies indicate that repeated exposures to SO_2, at concentrations as low as 0.1 ppm in guinea pigs, may exacerbate inflammatory responses in allergic animals.

AIRWAYS HYPERRESPONSIVENESS

Conclusions from 1996 NAAQS Review: No conclusions in the previous review.

Conclusions from Current Review: Animal toxicological evidence indicates that repeated exposures to SO_2, at concentrations as low as 0.1 ppm in guinea pigs, can exacerbate AHR following allergic sensitization. In a human clinical study, concurrent exposure (6 h) to 0.2 ppm SO_2 and 0.4 ppm NO_2 has been observed to enhance AHR to an inhaled antigen among resting asthmatics. These findings are consistent with the very limited epidemiologic evidence that observes an association between exposure to SO_2 and AHR in atopic individuals.

ED VISITS/HOSPITALIZATIONS

Conclusions from 1996 NAAQS Review: No conclusions in the previous review.

Conclusions from Current Review: Epidemiologic studies provide evidence of an association between ambient SO_2 concentrations and ED visits and hospitalizations for all respiratory causes, particularly among children and older adults (age 65+ years), and for asthma. This finding is coherent and plausible with the increases in bronchoconstriction, decreases in lung functions, increases in respiratory symptoms, and potential increases in airway inflammation and hyperresponsiveness demonstrated in other epidemiologic, human clinical, and animal toxicological studies. The SO_2 effect estimates ranged from a 5% decreased risk to a 20% excess risk per 10-ppb increase in 24-h avg SO_2, with the large majority of studies observing an increase in risk. These effects were observed in studies with mean 24-h avg concentrations as low as 4 ppb, but two studies evaluating the concentration-response function observed that a marked increase in SO_2-related effects was only observed higher concentrations (above 90th percentile values).

Short-Term Exposure: CARDIOVASCULAR MORBIDITY

Inadequate to infer a causal relationship

CARDIOVASCULAR EFFECTS; ED VISITS/HOSPITALIZATIONS

Conclusions from 1996 NAAQS Review: No conclusions in the previous review.

Conclusions from Current Review: There was some positive evidence of an association between 24-h avg SO_2 exposure and heart rate variability in the epidemiologic studies, but the evidence from two human clinical studies were weak and inconsistent. Some epidemiologic studies have observed positive associations between ambient SO_2 concentrations and ED visits or hospital admissions for cardiovascular diseases, but results are not consistent across studies and the SO_2 effect estimate was generally not robust to copollutant adjustment.

Short-Term Exposure: MORTALITY

Suggestive of a causal relationship

NONACCIDENTAL AND CARDIOPULMONARY MORTALITY

Conclusions from 1996 NAAQS Review: Epidemiologic studies based on historical air pollution episodes observed the clearest mortality associations when both BS and SO_2 concentrations were at high levels (24-h avg values exceeding 1,000 μg/m^3 [~400 ppb for SO_2]). Later studies observed that an increased risk of mortality was associated with exposure to BS and SO_2 levels in the range of 0.19 to 0.38 ppm. Because of the high colinearity between BS and SO_2 levels, it is difficult to readily separate the effects of these pollutants on mortality.

Conclusions from Current Review: Recent epidemiologic studies have consistently reported positive associations between mortality and SO_2, often at mean 24-h avg levels < 10 ppb. The range of SO_2 excess risk estimates for nonaccidental mortality is 0.4 to 2% per 10 ppb increase in 24-h avg SO_2 in several multicity studies and meta-analyses. SO_2 effect estimates for respiratory mortality were generally larger than the cardiovascular mortality estimates, suggesting a stronger association of SO_2 with respiratory mortality compared to cardiovascular mortality. The SO_2 effect estimates were generally reduced when copollutants were added in the model, indicating some extent of confounding among these pollutants.

Long-Term Exposure: RESPIRATORY MORBIDITY

Inadequate to infer a causal relationship

RESPIRATORY SYMPTOMS AND LUNG FUNCTION

Conclusions from 1996 NAAQS Review: The limited available epidemiologic data indicated associations between respiratory illnesses and symptoms and persistent exposures to SO_2 in areas with long-term averages exceeding 0.04 ppm.

Conclusions from Current Review: Several epidemiologic studies that examined the effects of long-term exposure to SO_2 on asthma, bronchitis, and respiratory symptoms observed positive associations in children. However, the variety of outcomes examined and the inconsistencies in the observed results make it difficult to assess the direct impact of long-term exposure of SO_2 on respiratory symptoms. The epidemiologic and animal toxicological evidence is also inadequate to infer that long-term exposure to SO_2 has a detrimental effect on lung function.

Long-Term Exposure: OTHER MORBIDITY

Inadequate to infer a causal relationship

CARCINOGENIC EFFECTS

Conclusions from 1996 NAAQS Review: Epidemiologic evidence did not substantiate the hypothesized links between SO_2 or other SO_X and cancer, though there was some animal toxicological evidence that led to the conclusion that SO_2 may be considered a suspect carcinogen/cocarcinogen.

Conclusions from Current Review: Animal toxicological studies indicate that SO_2 at high concentrations may cause DNA damage but fails to induce carcinogenesis, cocarcinogenesis, or tumor promotion. Epidemiologic studies did not provide evidence that long-term exposure to SO_2 is associated with an increased incidence of or mortality from lung cancer.

PRENATAL AND NEONATAL OUTCOMES

Conclusions from 1996 NAAQS Review: No conclusions in the previous review.

Conclusions from Current Review: Epidemiologic studies on birth outcomes have observed positive associations between SO_2 exposure and low birth weight. However, the inconsistent results across trimesters of pregnancy and the lack of evidence to evaluate confounding by copollutants limit the interpretation of these studies.

Long-Term Exposure: MORTALITY

Inadequate to infer a causal relationship

NONACCIDENTAL AND CARDIOPULMONARY MORTALITY

Conclusions from 1996 NAAQS Review: The available studies on the effects of long-term exposure to SO_2 on mortality were all ecological cross-sectional studies which did not take into consideration potential confounders. In addition, it was concluded that effects from PM and SO_2 could not be distinguished in these studies.

Conclusions from Current Review: Two major U.S. epidemiologic studies observed associations between long-term exposure to SO_2 and mortality, but several other U.S. and European cohort studies did not observe an association. The relative risks ranged from 0.97 to 1.07 per 5-ppb increase in the long-term avgSO_2. Evaluation of these studies is further limited by the inability to distinguish potential confounding by copollutants and uncertainties regarding the geographic scale of analysis.

Table 5-4. Effects of short-term exposure to SO_2 on respiratory symptoms among children.

Study	Population	Mean Concentration (ppb)	SO_2 Range (ppb)	SO_2 Upper Percentile (ppb)	Standardized Odds Ratio (95% CI)[a]
UNITED STATES					
Schildcrout et al. (2006) Multicity, North America Seattle, WA; Baltimore, MD; St. Louis, MO (Nov 1993–Aug 1995); Denver, CO; San Diego, CA (Nov 1993–Jul 1995); Toronto, ON (Dec 1993–Jul 1995); Boston, MA (Jan 1994–Sep 1995) No SO_2 data available in Albuquerque, NM	Asthmatic children (n = 990)	24-h avg: 2.2-7.4 (range of city-specific medians)	NR	75th: 3.1-10.7 90th: 4.4-14.2 (range of city-specific estimates)	Asthma symptoms (3-day sum lag): SO_2 alone: 1.04 (1.00, 1.08) SO_2 + PM_{10}: 1.04 (0.99, 1.08) SO_2 + NO_2: 1.04 (1.00, 1.09) SO_2 + CO: 1.05 (1.00, 1.09)
Schwartz et al. (1994) Multicity, U.S. Watertown, MA (Apr-Aug 1985); Kingston-Harriman, TN; St. Louis, MO (Apr-Aug 1986); Steubenville, OH; Portage, WI (Apr-Aug 1987); Topeka, KS (Apr-Aug 1988)	Children grades 2-5 (n = 1,844)	24-h avg: 4.1 (median)	6.8 (IQR)	75th: 8.2 90th: 17.9 Max: 81.9	Cough incidence (4-day avg lag): SO_2 alone: 1.15 (1.02, 1.31) PM_{10} adjusted: 1.08 (0.93, 1.25) NO_2 adjusted: 1.09 (0.94, 1.30) O_3 adjusted: 1.15 (1.01,1.31)
Neas et al. (1995) Uniontown, PA Summer 1990	Children grades 4-5 (n = 83)	12-h avg: 10.2 Overnight: 5.9 Daytime: 14.5	11.1 (IQR)	Max: 44.9	Evening cough (lag 12-h): 1.19 (1.00, 1.42)
Delfino et al. (2003a) Los Angeles, CA Nov 1999-Jan 2000	Hispanic children w/asthma, age 10-16 yrs (n = 22)	1-h max: 7.0	2-26	90th: 11.0	Asthma symptom score >1: 1.31 (1.10, 1.55), lag 0 Asthma symptom score >2: 1.37 (0.87, 2.18), lag 0
Mortimer et al. (2002) Multicity, U.S. Bronx, NY; East Harlem, NY; Baltimore, MD; Washington, DC; Detroit, MI; Cleveland, OH; Chicago, IL; St. Louis, MO Jun-Aug 1993	Asthmatic children, age 4-9 yrs (n = 846)	3-h avg: 22 (shown in figure)	0-75 (shown in graph)	NR	Asthma symptoms (lag 1-2): SO_2 alone (8 cities): 1.19 (1.06, 1.35) O_3 adjusted (8 cities): 1.18 (1.05, 1.33) O_3 & NO_2 adjusted (7 cities): 1.19 (1.04, 1.37) O_3, NO_2 & PM_{10} adjusted (3 cities): 1.23 (0.94, 1.62)
EUROPE					
Timonen and Pekkanen (1997) Kuopio (urban and suburban) Finland Winter 1994	Children with asthma or cough symptoms, age 7-12 yrs (n = 169)	24-h avg: 2.3	1.7 (IQR)	75th: 2.7 Max: 12.3	Upper respiratory symptoms (URS): 2.70 (1.19, 6.15), lag 1 3.15 (1.22, 8.27), lag 1-4

Study	Population	Mean Concentration (ppb)	SO_2 Range (ppb)	SO_2 Upper Percentile (ppb)	Standardized Odds Ratio (95% CI)[a]
Ward et al. (2002a, 2002b) Birmingham and Sandwell, UK Jan-Mar 1997 May-Jul 1997	Children, age at enrollment 9 yrs (n = 162)	24-h avg: Winter: 5.4 (median) Summer: 4.7 (median)	Winter: 2.0-18.0 Summer: 2.0-10.0	NR	Cough (lag 0): Winter: 0.81 (0.59, 1.13) Summer: 1.21 (1.05, 1.42) Shortness of breath (lag 0): Winter: 1.05 (0.83, 1.36) Summer: 0.95 (0.71, 1.27) Wheeze (lag 0): Winter: 0.90 (0.67, 1.18) Summer: 1.13 (0.81, 1.54)
Segala et al. (1998) Paris, France Nov 1992-May 1993	Children with physician-diagnosed asthma, age 7-15 yrs (n = 84)	24-h avg: 8.3 (SD 5.2)	1.7-32.2	NR	Asthma: 1.73 (1.15, 2.60), lag 0 1.60 (1.01, 2.53), lag 1 Wheeze: 1.22 (0.95, 1.58), lag 0 1.13 (0.68, 1.88), lag 1
Boezen et al. (1999) Amsterdam and Meppel (urban and rural), the Netherlands 3 winters, 1992-1995	Children with and without BHR and high serum concentrations of total IgE, age 7-11 yrs, (n = 632)	24-h avg: 1.7-8.7 Medians: 1.4-8.3 (range of city-specific estimates)	1.9-23.6	NR	Among children with BHR and relatively high serum total IgE: Lower respiratory symptoms (LRS): 1.27 (1.09, 1.49), lag 0 1.25 (1.06, 1.48), lag 1 1.69 (1.26, 2.28), 5-day avg
Van der Zee et al. (1999) Urban and nonurban areas, The Netherlands 3 winters, 1992-1995	Children with and without chronic respiratory symptoms, age 7-11 yrs, (n = 633)	24-h avg: 1.4-8.8 (range of city-specific medians)	NR	Max: 6.5-58.5 (range of city-specific estimates)	LRS, urban: SO_2 alone: 1.22 (1.01, 1.46), lag 0 1.14 (0.95, 1.38), lag 1 1.34 (0.98, 1.82), 5-day avg PM_{10} adjusted: 1.18 (0.96, 1.45), lag 0 1.03 (0.83, 1.27), lag 1 1.08 (0.72, 1.63), 5-day avg LRS, nonurban: 0.94 (0.79, 1.12), lag 0 0.94 (0.78, 1.13), lag 1 1.10 (0.75, 1.63), 5-day avg Cough, urban: 0.93 (0.84, 1.03), lag 0 1.08 (0.98, 1.19), lag 1 1.08 (0.89, 1.30) 5-day avg Cough, nonurban: 1.05 (0.96, 1.15), lag 0 0.98 (0.90, 1.08), lag 1 1.04 (0.83, 1.30), 5-day avg
Hoek and Brunekreef (1994) The Netherlands 3 winters, 1987-1990	Children age 7-11 yrs from 1 industrial and 3 nonindustrial communities (n = 1,078)	24-h avg: 5.7 (SD 5.5)	0.2-36.0	NR	Cough: 1.05 (0.88, 1.26), lag 0 LRS: 1.33 (1.06, 1.69), lag 1 URS: 1.14 (0.98, 1.32), lag 0
Pikhart et al. (2000) Czech Republic 1993-1994	Children age 7-11 yrs from 1 industrial and 3 nonindustrial communities (n = 1,078)	24-h avg: 28.2	NR	75th: 36.5	Wheeze: 1.23 (0.95, 1.62), lag NR

Table 5-5. Effects of short-term SO_2 exposure on emergency department visits and hospital admissions for respiratory outcomes.

Study	Population	Mean Concentration (ppb)	SO_2 Range (ppb)	SO_2 Upper Percentile (ppb)	Standardized Excess Risk (95% CI)[a]
EMERGENCY DEPARTMENT VISITS – ALL RESPIRATORY					
UNITED STATES					
Wilson et al. (2005) Portland, ME Jan 1998-Dec 2000 Manchester, NH Jan 1996-Dec 2000	≈ 54,000 ED visits in Portland and ≈ 30,000 ED visits in Manchester for all respiratory causes	1-h max: Portland: 11.1 (SD 9.1) Manchester: 16.5 (SD 14.7)	NR	NR	Portland (lag 0): All ages: 7% (3, 12). 0-14: -4% (-11, 4). 15-64: 9% (5, 14) 65+: 16% (7, 26) Manchester (lag 0): All ages: 1% (-3, 5) 0-14: 0% (8, 8). 15-64: 1% (-3, 5) 65+: 7% (-5, 21)
Tolbert et al. (2007) Atlanta, GA Jan 1993-Dec 2004	> 1,000,000 ED visits for all respiratory causes from 41 hospitals	1-h max: 14.9	1.0-149.0	75th: 20.0 90th: 35.0	0.8% (-0.7, 2.3), lag 0-2
Peel et al. (2005) Atlanta, GA Jan 1993-Aug 2000	≈ 480,000 ED visits for all respiratory causes from 31 hospitals	1-h max: 16.5 (SD 17.1)	NR	90th: 39.0	1.6% (-0.6, 3.8), lag 0-2
EUROPE					
Atkinson et al. (1999a) London, UK Jan 1992-Dec 1994	98,685 ED visits from 12 hospitals	24-h avg: 8.0 (SD 2.9)	2.8-30.9	90th: 11.7	All ages: 4% (1, 7), lag 1 0-14: 9% (4, 14), lag 2 15-64: 4% (0, 8), lag 2 65+: -3% (-8, 3), lag 1
EMERGENCY DEPARTMENT VISITS – ASTHMA					
UNITED STATES					
Ito et al. (2007) New York, NY Jan 1999-Dec 2002	Asthma ED visits, all ages from 11 hospitals	24-h avg: All year: 7.8 (SD 4.6) Warm: 5.4 (SD 2.2) Cold: 10.2 (SD 5.1)	IQR: All year: 5 Warm: 3 Cold: 7	75th: All year: 10 Warm: 7 Cold: 13 95th: All year: 17 Warm: 10 Cold: 19	All year (lag 0-1): 8.9% (4.9, 13.0) Warm (lag 0-1): SO_2 alone: 35.9% (22.2, 51.2) $PM_{2.5}$ adjusted: 29.6% (14.3, 46.8) O_3 adjusted: 26.8% (13.7, 41.5) NO_2 adjusted: -1.6% (-16.7, 16.1) CO adjusted: 31.1% (16.7, 47.2) Cold (lag 0-1): 8.5% (4.8, 12.4)
NY Department of Health (2006) Bronx & Manhattan Jan 1999-Dec 2000	≈ 31,000 asthma ED visits from 8 hospitals in the Bronx and ≈ 5,000 asthma ED visits from 14 hospitals in Manhattan	24-h avg: 11 (SD 7.2)	NR	NR	Bronx (lag 0-4): SO_2 alone: 10% (5, 15) $PM_{2.5}$ adjusted: 10% (4, 16) NO_2 adjusted: 10% (4, 15) Manhattan (lag 0-4): SO_2 alone: -1% (-11, 11) $PM_{2.5}$ adjusted: -3% (-14, 10) NO_2 adjusted: 1% (-12, 14)
Jaffe et al. (2003) Cincinnati, OH Cleveland, OH Columbus, OH Jul 1991-Jun 1996, summer months only (Jun-Aug)	4,416 ED visits for asthma, age 5-34 yrs	24-h avg: Cincinnati: 14 (SD 10) Cleveland: 15 (SD 10) Columbus: 4 (SD 3)	Cincinnati: 1-50 Cleveland: 1-64 Columbus: 0-22	NR	Cincinnati: 17% (5, 31), lag 2 Cleveland: 3% (-4, 11), lag 2 Columbus: 13% (-14, 49), lag 3 All cities: 6% (1, 11), best lags

Study	Population	Mean Concentration (ppb)	SO_2 Range (ppb)	SO_2 Upper Percentile (ppb)	Standardized Excess Risk (95% CI)[a]
Wilson et al. (2005) Portland, ME Jan 1998-Dec 2000 Manchester, NH Jan 1996-Dec 2000	≈ 8,100 asthma ED visits in Portland and ≈ 4,700 asthma ED visits in Manchester	1-h max: Portland: 11.1 (SD 9.1) Manchester: 16.5 (SD 14.7)	NR	NR	Portland (lag 0): All ages: 11% (2, 20). 0-14: 5% (-12, 25) 15-64: 12% (1, 23). 65+: 12% (-15, 47) Manchester (lag 0): All ages: 6% (-4, 17). 0-14: 20% (-3, 49) 15-64: 3% (-8, 16). 65+: 12% (-29, 75)
Peel et al. (2005) Atlanta, GA Jan 1993-Aug 2000	≈ 110,000 asthma ED visits, all ages from 31 hospitals	1-h max: 16.5 (SD 17.1)	NR	90th: 39.0	0.2% (-3.2, 3.4), lag 0-2
EUROPE					
Atkinson et al. (1999a) London, UK Jan 1992-Dec 1994	28,435 asthma ED visits from 12 hospitals	24-h avg: 8.0 (SD 2.9)	2.8-30.9	50th: 7.4 90th: 11.6	All ages: 7% (2, 13), lag 1 0-14: 15% (7, 23), lag 1 15-64: 6% (-1, 14), lag 1
Hajat et al. (1999) London, UK Jan 1992-Dec 1994	General practitioner visits for asthma	24-h avg: All year: 8.0 (SD 2.9) Warm: 7.7 (SD 2.4) Cool: 8.3 (SD 3.4)	NR	90th: All year: 11.6 Warm: 10.7 Cool: 12.4	All ages: 6.6% (1.3, 11.9), lag 0-2 0-14: 6.6% (-1.0, 14.7), lag 0-3 15-64: 5.2% (-1.5, 12.3), lag 0-3 65+: 7.2% (-4.3, 20.1), lag 0-1
Boutin-Forzano et al. (2004) Marseille, France Apr 1997-Mar 1998	549 ED visits for asthma	24-h avg: 8.5	0.0-35.3	NR	3-49 yrs: 0.6% (-1.4, 2.7), lag 0
Galan et al. (2003) Madrid, Spain Jan 1995-Dec 1998	4,827 ED visits for asthma	24-h avg: 8.9 (SD 5.8)	1.9-45.6	75th: 11.8 90th: 16.5	All ages: 4.9% (-4.2, 15.0), lag 0
Tenias et al. (1998) Valencia, Spain Jan 1993-Dec 1995	734 ED visits for asthma	24-h avg: 10.0 Cold: 11.9 Warm: 8.2 1-h max: 21.2 Cold: 24.3 Warm: 18.1	NR	24-h avg: 75th: 12.9 95th: 16.0 1-h max: 75th: 27.1 95th: 35.8	> 14 yrs: 13.9% (-7.0, 39.4), lag 0
Castellsague et al. (1995) Barcelona, Spain Jan 1986-Dec 1989	ED visits for asthma from 4 hospitals	24-h avg: Summer: 15.3 Winter: 19.5	NR	Summer: 75th: 20.3 95th: 30.8 Winter: 75th: 25.2 95th: 35.3	15-64 yrs: Summer: 5.5% (-2.1, 13.8), lag 2 Winter: 2.1% (-4.2, 9.0), lag 1
HOSPITAL ADMISSIONS – ALL RESPIRATORY					
UNITED STATES					
Schwartz (1995) New Haven, CT Tacoma, WA Jan 1988-Dec 1990	≈ 8,800 admissions in New Have and ≈ 4,000 admissions in Tacoma for all respiratory causes, ages 65+ yrs	24-h avg: New Haven: 29.8 Tacoma: 16.8	IQR: New Haven: 24.8 Tacoma: 11.5	New Haven: 75th: 38.2 90th: 60.7 Tacoma: 75th: 21.4 90th: 28.2	New Haven: SO_2 alone: 2% (1, 3), lag 2 PM_{10} adjusted: 2% (1, 3), lag 2 Tacoma: SO_2 alone: 3% (1, 6), lag 0 PM_{10} adjusted: -1% (-4, 3), lag 0
Schwartz et al. (1996) Cleveland, OH 1988-1990	Hospital admissions, ages 65+ yrs	24-h avg: 35.0	IQR: 25	75th: 45.0 90th: 61.0	0.8% (-0.3, 1.5), lag 0-1

Study	Population	Mean Concentration (ppb)	SO_2 Range (ppb)	SO_2 Upper Percentile (ppb)	Standardized Excess Risk (95% CI)[a]
CANADA					
Fung et al. (2006) Vancouver, BC Jun 1995-Mar 1999	≈ 41,000 respiratory admissions for ages 65+ yrs	24-h avg: 3.46 (SD 1.82)	0.0-12.5	NR	13% (1, 26), 7-day avg
Cakmak et al. (2007a) Multicity, Canada Calgary, Edmonton, Halifax, London, Ottawa, Saint John, Toronto, Vancouver, Windsor, Winnipeg Apr 1993-Mar 2000	> 200,000 hospital admissions for all respiratory causes	24-h avg: 4.6 (all cities) 2.8-10.2 (range of city-specific means)	0-75	Max: 14-75 (range of city-specific estimates)	SO_2 alone: 2.4% (1.1, 4.0) O_3, NO_2 & CO adjusted: 1.1% (0.2, 2.0) $SO_2 + O_3 + NO_2$: 14.9% (7.8, 22.3) (best lags selected for each city)
Yang et al. (2003b) Vancouver, BC Jan 1986-Dec 1998	Respiratory hospital admissions among young children (< 3 yrs) and elderly (65+ yrs)	24-h avg: 4.84 (SD 2.84)	IQR: 3.5	75th: 6.25 Max: 24.00	< 3 yrs (lag 2): SO_2 alone: 3% (-6, 15) O_3 adjusted: 3% (-8, 12) 65+ yrs (lag 0): SO_2 alone: 6% (0, 12) O_3 adjusted: 6% (0, 12)
Burnett et al. (1997b) Toronto, ON Jun 1992-Sep 1994, summer months only (May-Sep)	All respiratory hospital admissions	1-h max: 7.9	0-26	75th: 11 95th: 18	SO_2 alone: 38.4% (13.1, 69.2), lag 0-3 $PM_{2.5}$ adj: 24.3% (-0.5, 55.2), lag 0-3 $PM_{10-2.5}$ adj: 25.5% (0.8, 56.4), lag 0-3 PM_{10} adj: 23.1% (-2.9, 56.0), lag 0-3
Luginaah et al. (2005) Windsor, ON Apr 1995-Dec 2000	All respiratory admissions from 4 hospitals	1-h max: 27.5 (SD 16.5)	0-129	NR	All ages (lag 1): Female: 8.7% (-2.7, 21.4) Male: -9.5% (-19.7, 1.9) 0-14 (lag 1): Female: 24.4% (2.3, 51.4) Male: -9.7% (-24.4, 7.8) 15-64 (lag 1): Female: 6.5% (-14.0, 32.3) Male: -5.9% (-29.5, 25.4) 65+ (lag 1): Female: 6.3% (-9.9, 25.4) Male: -11.9% (-26.9, 6.1)
EUROPE					
Oftedal et al. (2003) Drammen, Norway Jan 1994-Dec 2000	All respiratory hospital admissions	24-h avg: 1.1 (SD 0.8)	NR	NR	All ages: 71.8% (15.5, 152.7), lag NR
Llorca et al. (2005) Torrelavega, Spain Jan 1992-Dec 1995	Hospital admissions from one hospital	24-h avg: 5.0 (SD 6.3)	NR	NR	All ages: 1.0% (-2.8, 4.7), lag NR
Atkinson et al. (1999b) London, UK Jan 1992-Dec 1994	165,032 respiratory hospital admissions	24-h avg: 8.0 (SD 2.9)	2.8-30.9	90th: 11.7	All ages: 3% (0, 6), lag 1 0-14: 8% (4, 12), lag 1 15-64: 3% (-1, 7), lag 3 65+: 3% (-0, 7), lag 3
Schouten et al. (1996) Multicity, The Netherlands Amsterdam, Rotterdam Apr 1977-Sep 1989	All respiratory hospital admissions	24-h avg: Amsterdam: 10.5 Rotterdam: 15.0 1-h max: Amsterdam: 24.4 Rotterdam: 37.2	NR	NR	Amsterdam (lag 0-3): 15-64 yrs: -2.3% (-5.5, 0.9) 65+: 0.2% (-2.8, 3.3) Rotterdam (lag 0-2): 15-64: -2.9% (-6.2, 0.5)

Study	Population	Mean Concentration (ppb)	SO_2 Range (ppb)	SO_2 Upper Percentile (ppb)	Standardized Excess Risk (95% CI)[a]
Spix et al. (1998) Multicity, Europe London, UK; Amsterdam & Rotterdam, the Netherlands; Paris, France; Milan, Italy Jan 1977-Dec 1991	All respiratory hospital admissions	24-h avg: London: 10.9 Amsterdam: 7.9 Rotterdam: 9.4 Paris: 8.6 Milan: 24.8	NR	NR	15-64 yrs: 0.5% (-0.4, 1.3), lag NR 65+: 1.1% (0.3, 2.4), lag NR
Dab et al. (1996) Paris, France Jan 1987-Sep 1992	Respiratory hospital admissions from 27 hospitals	All year: 24-h avg: 11.2 1-h max: 22.5 Warm season 24-h avg: 7.6 1-h max: 16.1 Cold season 24-h avg: 15.1 1-h max: 29.4	NR	99th: All year: 24-h avg: 50.0 1-h max: 87.5 Warm: 24-h avg: 18.5 1-h max: 50.3 Cold: 24-h avg: 56.0 1-h max: 100.9	All ages: 1.1% (0.1, 2.1), lag 0-2
Ponce de Leon et al. (1996) London, UK 1987-1988; 1991-1992	All respiratory hospital admissions	24-h avg: 12.1 (SD 4.7)	NR	75th: 14.7 90th: 17.7 95th: 20.3	All ages: 0.8% (-0.7, 2.4) 0-14: 0.9% (-1.5, 3.3), lag 1 15-64: 2.0% (-0.5, 4.7), lag 1 65+: 2.0% (-0.3, 4.4), lag 2
Walters et al. (1994) Birmingham, UK Jan 1988-Dec 1990	All respiratory hospital admissions	24-h avg: All year: 14.7 Spring: 16.1 Summer: 14.2 Autumn: 15.4 Winter: 12.9	NR	Max: 47.5	All ages: Summer: 1.5% (0.3, 2.7), lag 0 Winter: 4.5% (2.3, 6.5), lag 0
Hagen et al. (2000) Drammen, Norway Jan 1994-Dec 1997	All respiratory hospital admissions	24-h avg: Winter: 21. Spring: 18 Summer:15. Autumn:19 Number of monitors: 1	Winter: 11-33 Spring: 13-29 Summer: 5-24 Autumn: 16-23	NR	All ages: 92.8% (16.8, 218.8), lag NR
Vigotti et al. (1996) Milan, Italy Jan 1980-Dec 1989	All respiratory hospital admissions	24-h avg: All year: 44.9 Winter: 94.8 Summer: 11.6	1.1-315.7	75th: All year: 62.0 Winter: 125.0 Summer: 15.0 95th: All year: 143.5 Winter: 201.0 Summer: 23.9	15-64 yrs: 1.3% (0.0, 2.5), lag 0 65+: 1.0% (0.0, 2.3), lag 0
AUSTRALIA					
Barnett et al. (2005) Multicity, Australia/New Zealand Auckland, Brisbane, Canberra, Christchurch, Melbourne, Perth, Sydney Jan 1998-Dec 2001	All respiratory hospital admissions	24-h avg: Auckland: 4.3 Brisbane: 1.8 Christchurch: 2.8 Sydney: 0.9 NA in Canberra, Melbourne, and Perth 1-h max: Brisbane: 7.6 Christchurch: 10.1 Sydney: 3.7 NA in Auckland, Canberra, Melbourne, and Perth	24-h avg: Auckland: 0-24.3 Brisbane: 0-8.2 Christchurch: 0-11.9 Sydney: 0-3.9 1-h max: Brisbane: 0-46.5 Christchurch: 0.1-42.1 Sydney: 0.1-20.2	NR	1-4 yrs: 21.8% (4.5, 41.5), lag 0-1 5-14: 15.8% (-34.2, 104.0), lag 0-1

Study	Population	Mean Concentration (ppb)	SO_2 Range (ppb)	SO_2 Upper Percentile (ppb)	Standardized Excess Risk (95% CI)[a]
Petroeschevsky (2001) Brisbane, Australia Jan 1987-Dec 1994	33,710 respiratory hospital admissions	24-h avg: 4.1 1-h max: 9.2	NR	NR	All ages: 8.0% (3.0, 13.1), lag 0 0-4: 22.4% (8.7, 37.7), lag 0-4 5-14: 21.1% (-5.5, 55.1), lag 0-4 15-64: 3.3% (-10.5, 11.8), lag 1 65+: 12.1% (1.9, 23.4), lag 0
LATIN AMERICA					
Gouveia and Fletcher (2000) São Paulo, Brazil Nov 1992-Sep 1994	All respiratory hospital admissions	24-h avg: 6.9 (SD 3.4)	1.2-22.9	75th: 8.3 95th: 13.5	<5 yrs: 3.7% (-1.7, 9.4), lag 1
ASIA					
Wong et al. (1999b) Hong Kong Jan 1994-Dec 1995	All respiratory admissions from 12 hospitals	24-h avg: 6.4	1.0-25.7	75th: 9.4	All ages: 3.5% (1.1, 5.7), lag 0 0-4: 1.3% (-2.4, 4.9), lag 0 5-64: 2.1% (-1.1, 5.7), lag 0 65+: 6.2% (3.2, 9.9), lag 0
HOSPITAL ADMISSIONS – ASTHMA					
UNITED STATES					
Lin et al. (2004d) New York, NY Jun 1991-Dec 1993	2,629 cases; 2,236 controls, aged 0-14 yrs	24-h avg: Cases: 16.78 Controls: 15.57	2.88-66.35	NR	19% (11, 29), lag NR
Sheppard et al. (1999; reanalysis 2003) Seattle, WA Jan 1987-Dec 1994	7,837 asthma hospital admissions for patients <65 yrs	24-h avg: 8.0	NR	75th: 10.0 90th: 13.0	2.1% (-4.0, 6.2), lag 0
CANADA					
Lin et al. (2003) Toronto, ON Jan 1981-Dec 1993	7,319 asthma hospital admissions among 6-12 yr olds	24-h avg: 5.36 (SD 5.90)	0-57.0	75th: 8.00	Girls (7-day avg): SO_2 alone: 29.8% (5.8, 60.1) $PM_{2.5}$ & $PM_{10-2.5}$ adj: 42.3% (11.6, 80.2) Boys (7-day avg): SO_2 alone: -9.8% (-23.4, 5.8) $PM_{2.5}$ & $PM_{10-2.5}$ adj: -12.6% (-27.3, 5.8)
EUROPE					
Atkinson et al. (1999b) London, UK Jan 1992-Dec 1994	≈ 42,000 hospital admissions for asthma	24-h avg: 8.0 (SD 2.9)	2.8-30.9	90th: 11.7	All ages: 5% (1, 10), lag 1 0-14: 10% (4, 16), lag 1 15-64: 7% (0, 14), lag 3 65+: 9% (-2, 23), lag 2y
Schouten et al. (1996) Multicity, The Netherlands Amsterdam, Rotterdam Apr 1977-Sep 1989	All hospital admissions for asthma	24-h avg: Amsterdam: 10.5 Rotterdam: 15.0 1-h max: Amsterdam: 24.4 Rotterdam: 37.2	NR	NR	Amsterdam: All ages: -6.0% (-10.7, -1.1), lag 0-3
Sunyer et al. (1997) Multicity, Europe: Barcelona, Spain; Helsinki, Finland; Paris, France; London, UK Jan 1986-Dec 1992	All hospital admissions for asthma	24-h avg: Barcelona: 15.4 Helsinki: 6.0 London: 11.6 Paris: 8.6	Barcelona: 0.8-60.2 Helsinki: 1.1-35.7 London: 3.4-37.6 Paris: 0.4-82.3	NR	0-14 yrs: 3.2% (-0.2, 6.8), best cumulative lag 15-64: 0.2% (-2.2, 2.6), best cumulative lag

Study	Population	Mean Concentration (ppb)	SO_2 Range (ppb)	SO_2 Upper Percentile (ppb)	Standardized Excess Risk (95% CI)[a]
Dab et al. (1996) Paris, France Jan 1987-Sep 1992	Hospital admissions for asthma from 27 hospitals	All year: 24-h avg: 11.2 1-h max: 22.5 Warm season 24-h avg: 7.6 1-h max: 16.1 Cold season: 24-h avg: 15.1 1-h max: 29.4	NR	99th: All year: 24-h avg: 50.0 1-h max: 87.5 Warm: 24-h avg: 18.5 1-h max: 50.3 Cold: 24-h avg: 56.0 1-h max: 100.9	All ages: 1.8% (0.1, 3.6), lag 2
Anderson et al. (1998) London, UK Apr 1987-Feb 1992	All hospital admissions for asthma	24-h avg: 12.0 (SD 4.4)	3.4-37.6	75th: 14.3 90th: 17.3 95th: 19.5	All ages: 7.4% (3.2, 11.7), lag 0-3 0-14: 5.4% (0.8, 10.3), lag 0-3 15-64: -1.8% (-6.9, 3.4), lag 0-2 65+: 8.2% (-1.9.19.3), lag 0-3
Walters et al. (1994) Birmingham, UK Jan 1988-Dec 1990	All hospital admissions for asthma	24-h avg: All year: 14.7 Spring: 16.1 Summer: 14.2 Autumn: 15.4 Winter: 12.9	NR	Max: 47.5	All ages: Summer: 0.4% (-2.8, 9.2), lag 0 Winter: 0.7% (-2.2, 1.6), lag 0
AUSTRALIA					
Barnett et al. (2005) Multicity, Australia/New Zealand Auckland, Brisbane, Canberra, Christchurch, Melbourne, Perth, Sydney Jan 1998-Dec 2001	All hospital admissions for asthma	24-h avg: Auckland: 4.3 Brisbane: 1.8 Christchurch: 2.8 Sydney: 0.9 NA in Canberra, Melbourne, and Perth 1-h max: Brisbane: 7.6 Christchurch: 10.1 Sydney: 3.7 NA in Auckland, Canberra, Melbourne, and Perth	24-h avg: Auckland: 0-24.3 Brisbane: 0-8.2 Christchurch: 0-11.9 Sydney: 0-3.9 1-h max: Brisbane: 0-46.5 Christchurch: 0.1-42.1 Sydney: 0.1-20.2	NR	1-4 yrs: 28.1% (-27.8, 125.5), lag 0-1 5-14: 27.2% (-34.7, 147.3), lag 0-1
Petroeschevsky et al. (2001) Brisbane, Australia Jan 1987-Dec 1994	13,246 hospital admissions for asthma	24-h avg: 4.1 1-h max: 9.2	NR	NR	All ages: -5.9% (-12.4, 1.1), lag 2 0-14: 8.0% (-2.9, 20.1), lag 0 15-64: -21.6% (-34.4, -6.2), lag 0
LATIN AMERICA					
Gouveia and Fletcher (2000) São Paulo, Brazil Nov 1992-Sep 1994	All hospital admissions for asthma	24-h avg: 6.9 (SD 3.4)	1.2-22.9	75th: 8.3 95th: 13.5	<5 yrs: 10.4% (-1.9, 24.2), lag 2
ASIA					
Wong et al. (1999b) Hong Kong Jan 1994-Dec 1995	Hospital admissions for asthma from 12 hospitals	24-h avg: 6.4	1.0-25.7	75th: 9.4	All ages: 4.6% (-0.5, 9.9), lag 0
Lee et al. (2006b) Hong Kong Jan 1997-Dec 2002	26,663 hospital admissions for asthma	24-h avg: 6.6 (SD 4.0)	NR	75th: 8.2	<18 yrs: -3.7% (-6.7, -0.6), lag 0

Study	Population	Mean Concentration (ppb)	SO_2 Range (ppb)	SO_2 Upper Percentile (ppb)	Standardized Excess Risk (95% CI)[a]
Ko et al. (2007b) Hong Kong Jan 2000-Dec 2005	69,716 hospital admissions for asthma from 15 hospitals	24-h avg: All year: 7.2 (SD 4.9) <20°C: 6.9 (SD 3.8) ≥20°C: 7.3 (SD 5.4)	All year: 1.1-45.6 <20°C: 1.3-28.8 ≥20°C: 1.1-45.6	75th: All year: 8.6 <20°C: 21.3 ≥20°C: 22.5	All ages: 1.1% (-1.6, 3.7), lag 0-3 0-14: Not statistically significant (estimates NR) 15-65: 4.8% (0.3, 9.4), lag 0-3 65+: Not statistically significant (estimates NR)
Tsai et al. (2006) Kaohsiung, Taiwan Jan 1996-Dec 2003	17,682 hospital admissions for asthma from 63 hospitals	24-h avg: 9.49	0.92-31.33	75th: 12.16	SO_2 alone (lag 0-2): ≥25°C: 3.1% (-7.5, 14.8) <25°C: 34.5% (12.9, 60.3) PM_{10} adjusted (lag 0-2): ≥25°C: -1.2% (-11.5, 10.2) <25°C: 4.7% (-13.2, 26.5) NO_2 adjusted (lag 0-2): ≥25°C: -5.6% (-16.2. 6.7) <25°C: -41.2% (-53.0, -26.8) CO adjusted (lag 0-2): ≥25°C: -15.0% (-24.9, -3.8) <25°C: 6.3% (4.7, 8.1) O_3 adjusted (lag 0-2): ≥25°C: 9.7% (-1.7, 22.2) <25°C: 36.0% (14.2, 62.2)

ANNEXES

Annex A. Literature Selection

This Annex includes detailed information on the methods used to identify and select studies, and on frameworks for evaluating scientific evidence relative to causality determination. While the overarching framework is outlined in the introduction to Chapter 1, this Annex provides supporting information for that framework, including excerpts from decision frameworks or criteria developed by other organizations.

A.1. Literature Search and Retrieval

Literature searches are conducted continuously, to identify studies published since the last review. The current review includes studies published subsequent to the 1982 AQCD for SO_X (EPA, 1982). Search strategies are iteratively modified in an effort to optimize the identification of pertinent publications. Additional publications are identified for inclusion in several ways: review of pre-publication tables of contents for journals in which relevant papers may be published; independent identification of relevant literature by expert authors; and identification by the public and CASAC during the external review process. Generally, only information that has undergone scientific peer review and has been published, or accepted for publication, in the open literature is considered. Studies identified are further evaluated by EPA staff and outside experts to determine if they merit inclusion. Criteria used for study selection are summarized below.

A.2. General Criteria for Study Selection

In assessing the scientific quality and relevance of epidemiologic and animal or human toxicological studies, the following considerations have been taken into account.

- Were the study populations adequately selected and are they sufficiently well defined to allow for meaningful comparisons between study groups?
- Are the statistical analyses appropriate, properly performed, and properly interpreted?
- Are likely covariates (i.e., potential confounders or effect modifiers) adequately controlled or taken into account in the study design and statistical analysis?
- Are the reported findings internally consistent, biologically plausible, and coherent with other known facts?
- To what extent are the aerometric data, exposure, or dose metrics of adequate quality and sufficiently representative to serve as indicators of exposure to ambient SO_2?

Consideration of these issues informs our judgments on the relative quality of individual studies and allows us to focus the assessment on the most pertinent studies. The following two sections describe criteria for selecting specific types of studies.

A.2.1. Criteria for Selecting Epidemiologic Studies

In selecting epidemiologic studies for this assessment, EPA considered whether a given study contains information on (1) associations with measured SO_X concentrations using short- or long-term

exposures at or near ambient levels of SO_X, (2) health effects of specific SO_X species or indicators related to SO_X sources (e.g., combustion-related particles), (3) health endpoints and populations not previously extensively researched, (4) multiple pollutant analyses and other approaches to address issues related to potential confounding and modification of effects, and/or (5) important methodological issues (e.g., lag of effects, model specifications, thresholds, mortality displacement) related to interpretation of the health evidence. Among the epidemiologic studies, particular emphasis has been placed on those most relevant to reviews of the NAAQS. Specifically, studies conducted in the U.S. or Canada may be discussed in more detail than those from other geographic regions. Particular emphasis has been placed on**:** (1) recent multicity studies that employed standardized methodological analyses for evaluating effects of SO_X and that provide overall estimates for effects based on combined analyses of information pooled across multiple cities, (2) recent studies that provide quantitative effect estimates for populations of interest, and (3) studies that consider SO_X as a component of a complex mixture of air pollutants.

Not all studies were accorded equal weight in the overall interpretive assessment of evidence regarding SO_2-associated health effects. Among studies with adequate control for confounding, increasing scientific weight is accorded in proportion to the precision of their effect estimates. Small-scale studies without a wide range of exposures generally produce less precise estimates compared to larger studies with a broad exposure gradient. For time-series studies, the size of the study, as indicated by the duration of the study period and total number of events, and the variability of SO_2 exposures are important components that help to determine the precision of the health effect estimates. In evaluating the epidemiologic evidence in this chapter, more weight is accorded to estimates from studies with narrow confidence bands.

The goal of what was a balanced and objective evaluation that summarizes, interprets, and synthesizes the most important studies and issues in the epidemiologic database pertaining to SO_X exposure, illustrated by using newly created or previously published summary tables and figures. For each study presented, the quality of the exposure and outcome data, as well as the quality of the statistical analysis methodology, are discussed. The discussion incorporates the magnitude and statistical strengths of observed associations between SO_2 exposure and health outcomes.

A.2.2. Criteria for Selecting Animal and Human Toxicological Studies

Criteria for the selection of research evaluating animal toxicological or controlled human exposure studies included a focus on those studies conducted at levels within about an order of a magnitude of ambient SO_2 concentrations and those studies that approximated expected human exposure conditions in terms of concentration and duration. Studies that elucidate mechanisms of action and/or susceptibility, particularly if the studies were conducted under atmospherically relevant conditions, were emphasized whenever possible. For controlled human exposure studies, emphasis was placed on studies that (1) investigated potentially susceptible populations such as asthmatics, particularly studies that compared responses in susceptible individuals with those in age-matched healthy controls; (2) addressed issues such as concentration-response or time-course of responses; (3) investigated exposure to SO_2 separately and in combination with other pollutants such as O_3 and NO_2; (4) included control exposures to filtered air; and (5) had sufficient statistical power to assess findings.

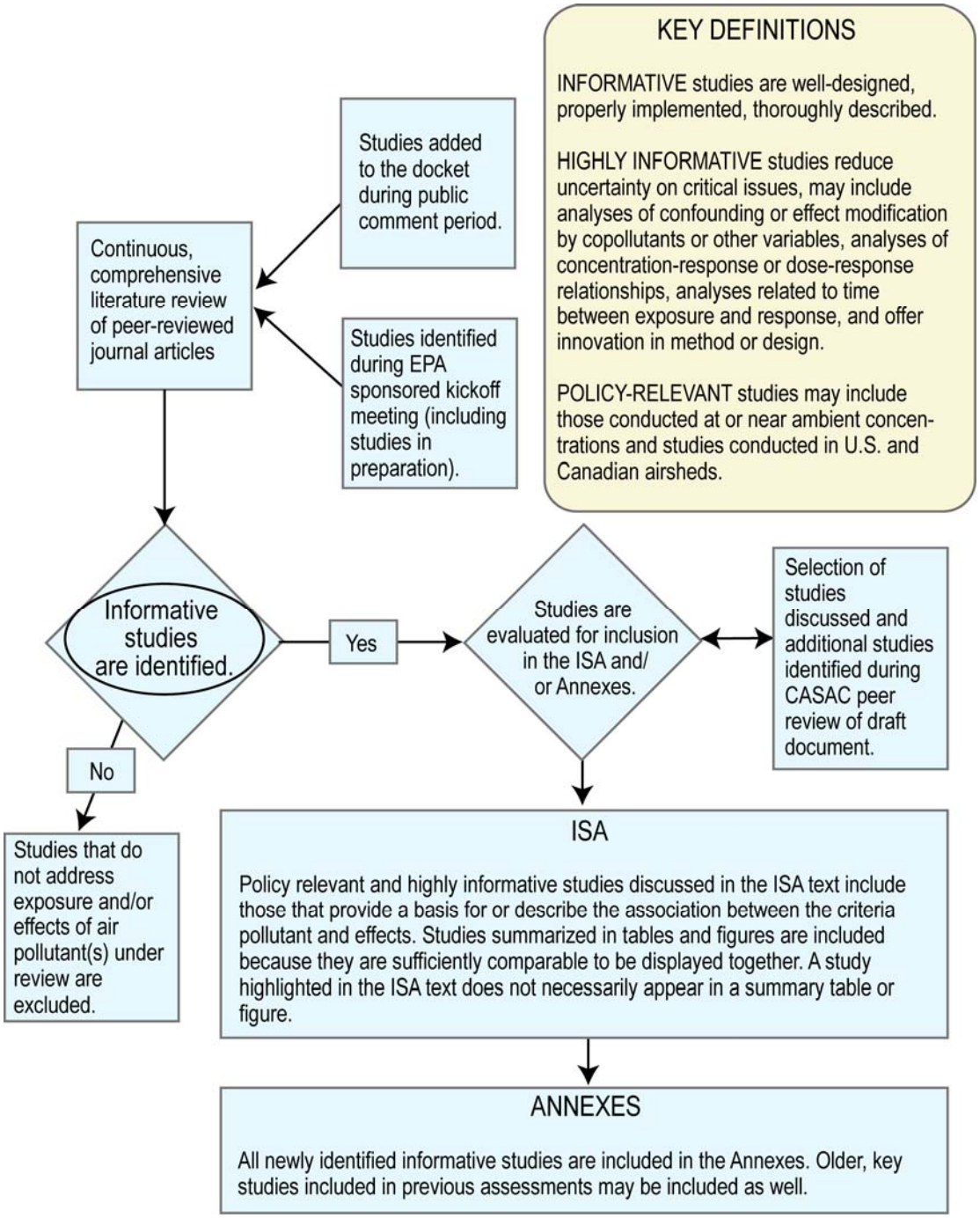


Figure A-1. Selection process for studies included in the ISA. Studies are categorized into: informative, highly informative, and policy-relevant.

A.3. Other Approaches to the Causal Determination

The following sections include excerpts from several reports that document approaches for the causality, or related decision-making processes. These sections provide supplementary documentation of approaches that are similar in nature to EPA's causal decision framework.

A.3.1. Surgeon General's Report: The Health Consequences of Smoking

The Surgeon General's Report (CDC, 2004) evaluated the health effects of smoking; building upon the first Surgeon General's report published in 1964 (PHS, 1964). It also updated the methodology for evaluating evidence that was first presented in the 1964 report. The 2004 report acknowledged the effectiveness of the previous methodology, but standardizes the language surrounding causality of associations.

The Surgeon General's Reports on Smoking played a central role in the translation of scientific evidence into policy, conveying succinctly the link between smoking and a health effect. Specifically, the report stated:

> The statement that an exposure "causes" a disease in humans represents a serious claim, but one that carries with it the possibility of prevention. Causal determinations may also carry substantial economic implications for society and for those who might be held responsible for the exposure or for achieving its prevention.

To address the issue of identifying causality, the 2004 report provided the following summary of the earlier 1964 report:

> When a relationship or an association between smoking…and some condition in the host was noted, the significance of the association was assessed.
>
> The characterization of the assessment called for a specific term. …The word *cause* is the one in general usage in connection with matters considered in this study, and it is capable of conveying the notion of a significant, effectual relationship between an agent and an associated disorder or disease in the host.
>
> No member was so naive as to insist upon mono-etiology in pathological processes or in vital phenomena. All were thoroughly aware… that the end results are the net effect of many actions and counteractions.
>
> Granted that these complexities were recognized, it is to be noted clearly that the Committee's considered decision to use the words "a cause," or "a major cause," or "a significant cause," or "a causal association" in certain conclusions about smoking and health affirms their conviction (CDC, 2004)

The 2004 report created uniformly labeled conclusions that were used throughout the document. The following excerpts from the report also include a description of the methodology and the judgments used to reach a conclusion:

Terminology of Conclusions and Causal Claims

Evidence is **sufficient** to infer a causal relationship.

Evidence is **suggestive but not sufficient** to infer a causal relationship.

Evidence is **inadequate** to infer the presence or absence of a causal relationship (which encompasses evidence that is sparse, of poor quality, or conflicting).

Evidence is **suggestive** of no causal relationship.

For this report, the summary conclusions regarding causality are expressed in this four-level classification. Use of these classifications should not constrain the process of causal inference, but rather bring consistency across chapters and reports, and greater clarity as to what the final conclusions are actually saying. As shown in Table 1.1 [see original document], without a uniform classification the precise nature of the final judgment may not always be obvious, particularly when the judgment is that the evidence falls below the "sufficient" category. Experience has shown that the "suggestive" category is often an uncomfortable one for scientists, since scientific culture is such that any evidence that falls short of causal proof is typically deemed inadequate to make a causal determination. However, it is very useful to distinguish between evidence that is truly inadequate versus that which just falls short of sufficiency.

There is no category beyond "suggestive of no causal relationship" as it is extraordinarily difficult to prove the complete absence of a causal association. At best, "negative" evidence is suggestive, either strongly or weakly. In instances where this category is used, the strength of evidence for no relationship will be indicated in the body of the text. In this new framework, conclusions regarding causality will be followed by a section on implications. This section will separate the issue of causal inference from recommendations for research, policies, or other actions that might arise from the causal conclusions. This section will assume a public health perspective, focusing on the population consequences of using or not using tobacco and also a scientific perspective, proposing further research directions. The proportion of cases in the population as a result of exposure (the population attributable risk), along with the total prevalence and seriousness of a disease, are more relevant for deciding on actions than the relative risk estimates typically used for etiologic determinations. In past reports, the failure to sharply separate issues of inference from policy issues resulted in inferential statements that were sometimes qualified with terms for action. For example, based on the evidence available in 1964, the first Surgeon General's report on

smoking and health contained the following statement about the relationship between cardiovascular diseases and smoking:

> It is established that male cigarette smokers have a higher death rate from coronary artery disease than non-smoking males. Although the causative role of cigarette smoking in deaths from coronary disease is not proven, the Committee considers it more prudent from the public health viewpoint to assume that the established association has causative meaning, than to suspend judgment until no uncertainty remains (CDC, 2004)

Using this framework, this conclusion would now be expressed differently, probably placing it in the "suggestive" category and making it clear that although it falls short of proving causation, this evidence still makes causation more likely than not. The original statement makes it clear that the 1964 committee judged that the evidence fell short of proving causality but was sufficient to justify public health action. In this report, the rationale and recommendations for action will be placed in the implications section, separate from the causal conclusions. This separation of inferential from action-related statements clarifies the degree to which policy recommendations are driven by the strength of the evidence and by the public health consequences acting to reduce exposure. In addition, this separation appropriately reflects the differences between the processes and goals of causal inference and decision making.

A.3.2. EPA: Guidelines for Carcinogen Risk Assessment

The EPA Guidelines for Carcinogen Risk Assessment, published in 2005 (EPA, 2005), was an update to the previous risk assessment document published in 1986. This document served to guide EPA staff and public about the Agency's risk assessment development and methodology. In the 1986 Guidelines, a step-wise approach was used to evaluate the scientific findings. However, this newer document was similar to the Surgeon General's Report on Smoking in that it used single integrative step after assessing all of the individual lines of evidence. Five standard descriptors were used to evaluate the weight of evidence:

1. Carcinogenic to Humans
2. Likely to Be Carcinogenic to Humans
3. Suggestive Evidence of Carcinogenic Potential
4. Inadequate Information to Assess Carcinogenic Potential
5. Not Likely to Be Carcinogenic to Humans.

The 2005 Guidelines recommend that a separate narrative be prepared on the weight of evidence and the descriptor. The Guidelines further recommend that the descriptors should only be used in the context of a weight-of-evidence discussion.

The following excerpt describes how a weight of evidence narrative should be developed and how a descriptor should be selected (EPA, 2005):

> The weight of the evidence should be presented as a narrative laying out the complexity of information that is essential to understanding the hazard and its dependence on the quality, quantity, and type(s) of data available, as well as the circumstances of exposure or the traits of an exposed population that may be required for expression of cancer. For example, the narrative can clearly state to what extent the determination was based on data from human exposure, from animal experiments, from some combination of the two, or from other data. Similarly, information on mode of action can specify to what extent the data are from *in vivo* or *in vitro* exposures or based on similarities to other chemicals. The extent to which an agent's mode of action occurs only on reaching a minimum dose or a minimum duration should also be presented. A hazard might also be expressed disproportionately in individuals possessing a specific gene; such characterizations may follow from a better understanding of the human genome. Furthermore, route of exposure should be used to qualify a hazard if, for example, an agent is not absorbed by some routes. Similarly, a hazard can be attributable to exposures during a susceptible lifestage on the basis of our understanding of human development.
>
> The weight of evidence narrative should highlight:
>
> - the quality and quantity of the data;
> - all key decisions and the basis for these major decisions; and
> - any data, analyses, or assumptions that are unusual for or new to EPA.
>
> To capture this complexity, a weight of evidence narrative generally includes
>
> - conclusions about human carcinogenic potential (choice of descriptor(s), described below)
> - a summary of the key evidence supporting these conclusions (for each descriptor used), including information on the type(s) of data (human and/or animal, in vivo and/or in vitro) used to support the conclusion(s)
> - available information on the epidemiologic or experimental conditions that characterize expression of carcinogenicity (e.g., if carcinogenicity is possible only by one exposure route or only above a certain human exposure level),
> - a summary of potential modes of action and how they reinforce the conclusions,
> - indications of any susceptible populations or lifestages, when available, and
> - a summary of the key default options invoked when the available information is inconclusive.
>
> To provide some measure of clarity and consistency in an otherwise free-form narrative, the weight of evidence descriptors are included in the first sentence of the narrative. Choosing a descriptor is a matter of judgment and cannot be reduced to a formula. Each descriptor may be applicable to a wide variety of potential data sets and weights of evidence. These descriptors and narratives are intended to permit sufficient flexibility to accommodate new scientific understanding and

new testing methods as they are developed and accepted by the scientific community and the public. Descriptors represent points along a continuum of evidence; consequently, there are gradations and borderline cases that are clarified by the full narrative. Descriptors, as well as an introductory paragraph, are a short summary of the complete narrative that preserves the complexity that is an essential part of the hazard characterization. **Users of these cancer guidelines and of the risk assessments that result from the use of these cancer guidelines should consider the entire range of information included in the narrative rather than focusing simply on the descriptor**.

In borderline cases, the narrative explains the case for choosing one descriptor and discusses the arguments for considering but not choosing another. For example, between "suggestive" and "likely" or between "suggestive" and "inadequate," the explanation clearly communicates the information needed to consider appropriately the agent's carcinogenic potential in subsequent decisions.

Multiple descriptors can be used for a single agent, for example, when carcinogenesis is dose-or route-dependent. For example, if an agent causes point-of-contact tumors by one exposure route but adequate testing is negative by another route, then the agent could be described as likely to be carcinogenic by the first route but not likely to be carcinogenic by the second. Another example is when the mode of action is sufficiently understood to conclude that a key event in tumor development would not occur below a certain dose range. In this case, the agent could be described as likely to be carcinogenic above a certain dose range but not likely to be carcinogenic below that range.

Descriptors can be selected for an agent that has not been tested in a cancer bioassay if sufficient other information, e.g., toxicokinetic and mode of action information, is available to make a strong, convincing, and logical case through scientific inference. For example, if an agent is one of a well-defined class of agents that are understood to operate through a common mode of action and if that agent has the same mode of action, then in the narrative the untested agent would have the same descriptor as the class. Another example is when an untested agent's effects are understood to be caused by a human metabolite, in which case in the narrative the untested agent could have the same descriptor as the metabolite. As new testing methods are developed and used, assessments may increasingly be based on inferences from toxicokinetic and mode of action information in the absence of tumor studies in animals or humans.

When a well-studied agent produces tumors only at a point of initial contact, the descriptor generally applies only to the exposure route producing tumors unless the mode of action is relevant to other routes. The rationale for this conclusion would be explained in the narrative.

When tumors occur at a site other than the point of initial contact, the descriptor generally applies to all exposure routes that have not been adequately tested at sufficient doses. An exception occurs when there is

convincing information, e.g., toxicokinetic data that absorption does not occur by another route.

When the response differs qualitatively as well as quantitatively with dose, this information should be part of the characterization of the hazard. In some cases reaching a certain dose range can be a precondition for effects to occur, as when cancer is secondary to another toxic effect that appears only above a certain dose. In other cases exposure duration can be a precondition for hazard if effects occur only after exposure is sustained for a certain duration. These considerations differ from the issues of relative absorption or potency at different dose levels because they may represent a discontinuity in a dose-response function.

When multiple bioassays are inconclusive, mode of action data are likely to hold the key to resolution of the more appropriate descriptor. When bioassays are few, further bioassays to replicate a study's results or to investigate the potential for effects in another sex, strain, or species may be useful.

When there are few pertinent data, the descriptor makes a statement about the database, for example, "Inadequate Information to Assess Carcinogenic Potential," or a database that provides "Suggestive Evidence of Carcinogenic Potential." With more information, the descriptor expresses a conclusion about the agent's carcinogenic potential to humans. If the conclusion is positive, the agent could be described as "Likely to Be Carcinogenic to Humans" or, with strong evidence, "Carcinogenic to Humans." If the conclusion is negative, the agent could be described as "Not Likely to Be Carcinogenic to Humans."

Although the term "likely" can have a probabilistic connotation in other contexts, its use as a weight of evidence descriptor does not correspond to a quantifiable probability of whether the chemical is carcinogenic. This is because the data that support cancer assessments generally are not suitable for numerical calculations of the probability that an agent is a carcinogen. Other health agencies have expressed a comparable weight of evidence using terms such as "Reasonably Anticipated to Be a Human Carcinogen" (NTP) or "Probably Carcinogenic to Humans" (IARC). 1989).

A.3.3. Improving the NAS/IOM Presumptive Disability Decision-Making Process for Veterans Report

A recent publication by the Institute of Medicine also provided foundation for the causality framework adapted in this ISA (IOM, 2007). The Committee on Evaluation of the Presumptive Disability Decision-Making Process for Veterans was charged by the Veterans Association to describe how presumptive decisions are made for veterans with health conditions arising from military service currently, as well as recommendations for how such decisions could be made in the future. The committee proposed a multiple-element approach that includes a quantification of the extent of disease attributable to

an exposure. This process involved a review of all relevant data to decide the strength of evidence for causation, using one of four categories:

- Sufficient: the evidence is sufficient to conclude that a causal relationship exists.
- Equipoise and Above: the evidence is sufficient to conclude that a causal relationship is at least as likely as not, but not sufficient to conclude that a causal relationship exists.
- Below Equipoise: the evidence is not sufficient to conclude that a causal relationship is at least as likely as not, or is not sufficient to make a scientifically informed judgment.
- Against: the evidence suggests the lack of a causal relationship.

The following is an excerpt from the report and describes these four categories in detail:

> In light of the categorizations used by other health organizations and agencies as well as considering the particular challenges of the presumptive disability decision-making process, we propose a four-level categorization of the strength of the *overall evidence* for or against a *causal relationship* from exposure to disease.
>
> We use the term "equipoise" to refer to the point at which the evidence is in balance between favoring and not favoring causation. The term "equipoise" is widely used in the biomedical literature, is a concept familiar to those concerned with evidence-based decision-making and is used in VA processes for rating purposes as well as being a familiar term in the veterans' community.
>
> Below we elaborate on the four-level categorization which the Committee recommends.
>
> **Sufficient**
>
> If the overall evidence for a causal relationship is categorized as Sufficient, then it should be scientifically compelling. It might include:
>
> - replicated and consistent evidence of a causal association: that is, evidence of an association from several high-quality epidemiologic studies that cannot be explained by plausible noncausal alternatives (e.g., chance, bias, or confounding)
> - evidence of causation from animal studies and mechanistic knowledge
> - compelling evidence from animal studies and strong mechanistic evidence from studies in exposed humans, consistent with (i.e., not contradicted by) the epidemiologic evidence.
>
> Using the Bayesian framework to illustrate the evidential support and the resulting state of communal scientific opinion needed for reaching the Sufficient category (and the lower categories that follow), consider again the causal diagram in Figure A-2. In this model, used to help clarify matters conceptually, the observed association between exposure and health is the result of: (1) measured confounding, parameterized by α; (2) the causal relation, parameterized by β; and (3) other, unmeasured sources such as bias or unmeasured confounding, parameterized by γ. The belief of interest, after all the evidence has been weighed, is in the size of the causal parameter β. Thus, for decision making, what matters is how strongly the evidence supports the proposition that β is above 0. As

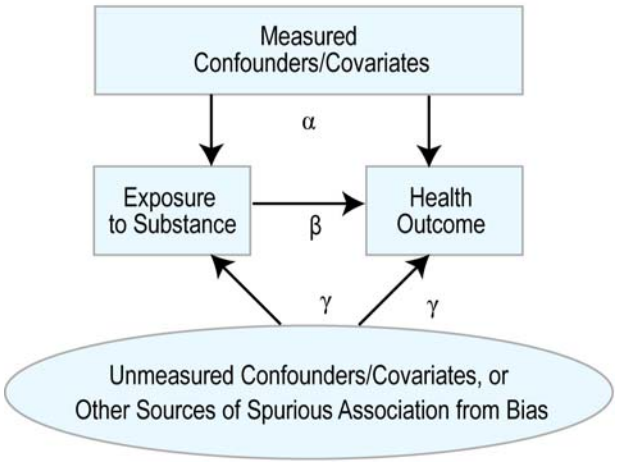
it is extremely unlikely that the types of exposures considered for presumptions reduce the risk of developing disease, we exclude values of β below 0. If we consider the evidence as supporting degrees of belief about the size of β, and we have a posterior distribution over the possible size of β, then a posterior like Figure A-2 illustrates a belief state that might result when the evidence for causation is considered Sufficient.

As the "mass" over a positive effect (the area under the curve to the right of the zero) vastly "outweighs" the small mass over no effect (zero), the evidence is considered sufficient to conclude that the association is causal. Put another way, even though the scientific community might be uncertain as to the size of β, after weighing all the evidence, it is highly confident that the probability that β is greater than zero is substantial; that is, that exposure causes disease.

Equipoise and Above

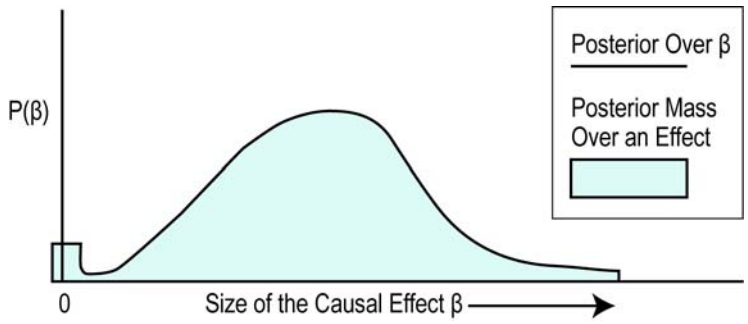
To be categorized as Equipoise and Above, the scientific community should categorize the overall evidence as making it more confident in the existence of a causal relationship than in the non-existence of a causal relationship, but not sufficient to conclude causation.

For example, if there are several high-quality epidemiologic studies, the preponderance of which show evidence of an association that cannot readily be explained by plausible noncausal alternatives (e.g., chance, bias, or confounding), and the causal relationship is consistent with the animal evidence and biological knowledge, then the overall evidence might be categorized as Equipoise and Above. Alternatively, if there is strong evidence from animal studies or mechanistic evidence, not contradicted by human or other evidence, then the overall evidence might be categorized as Equipoise and Above. Equipoise is a common term employed by VA and the courts in deciding disability claims (see Appendix D [see original document]).



Source: IOM (2008).

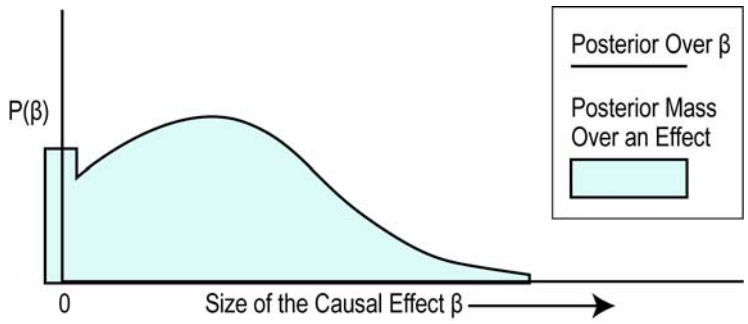
Figure A-2. Focusing on unmeasured confounders/covariates, or other sources of spurious association from bias.



Source: IOM (2008).

Figure A-3. Example posterior distribution for the determination of Sufficient.

Again, using the Bayesian model to illustrate the idea of Equipoise and Figure A-4 shows a posterior probability distribution that is an example of belief compatible with the category Equipoise and Above.



Source: IOM (2007).

Figure A-4. Example posterior distribution for the determination of *Equipoise and Above*.

In this figure, unlike the one for evidence classified as Sufficient, there is considerable mass over zero, which means that the scientific community has considerable uncertainty as to whether exposure causes disease at all; that is, whether β is greater than zero. At *least* half of the mass is to the right of the zero, however, so the community judges causation to be at least as likely as not, after they have seen and combined all the evidence available.

Below Equipoise

To be categorized as Below Equipoise, the overall evidence for a causal relationship should either be judged not to make causation at least as likely as not, or not sufficient to make a scientifically informed judgment.

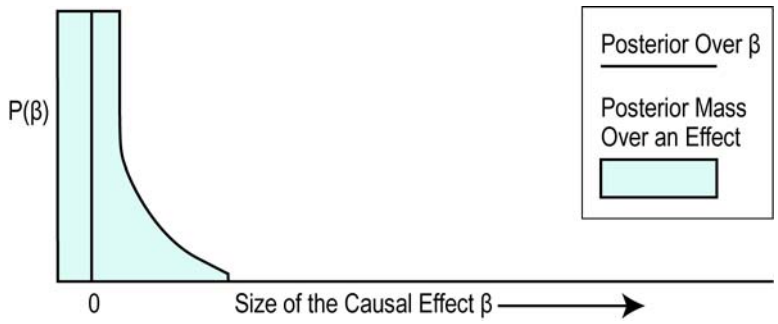
This might occur:

- when the human evidence is consistent in showing an association, but the evidence is limited by the inability to rule out chance, bias, or confounding with confidence, and animal or mechanistic evidence is weak
- when animal evidence suggests a causal relationship, but human and mechanistic
- evidence is weak or inconsistent
- when mechanistic evidence is suggestive but animal and human evidence is weak or inconsistent
- when the evidence base is very thin.

Against

To be categorized as Against, the overall evidence should favor belief that there is no causal relationship from exposure to disease. For example, if there is human evidence from multiple studies covering the full range of exposures encountered by humans that are consistent in showing no causal association, or there are is animal or mechanistic evidence supporting the lack of a causal relationship, and combining all of the evidence results in a posterior resembling Source: IOM (2008).

Figure A-5 then the scientific community should categorize the evidence as *Against* causation.



Source: IOM (2007).

Figure A-5. Example posterior distribution for the determination of *Against*.

A.3.4. National Acid Precipitation Assessment Program Guidelines

The following guidelines in the form of questions were developed and published in 1991 by the Oversight Review Board for the National Acid Precipitation Assessment Program (Washington, 1991) to assist scientists in formulating presentations of research results to be used in policy decision processes.

> Is the statement sound? Have the central issues been clearly identified? Does each statement contain the distilled essence of present scientific and technical understanding of the phenomenon or process to which it applies? Is the statement consistent with all relevant evidence – evidence developed either through NAPAP research or through analysis of research conducted outside of NAPAP? Is the statement contradicted by any important evidence developed through research inside or outside of NAPAP? Have apparent contradictions or interpretations of available evidence been considered in formulating the statement of principal findings?
>
> Is the statement directional and, where appropriate, quantitative? Does the statement correctly quantify both the direction and magnitude of trends and relationships in the phenomenon or process to which the statement is relevant? When possible, is a range of uncertainty given for each quantitative result? Have various sources of uncertainty been identified and quantified, for example, does the statement include or acknowledge errors in actual measurements, standard errors of estimate, possible biases in the availability of data, extrapolation of results beyond the mathematical, geographical, or temporal relevancy of available information, etc. In short, are there numbers in the statement? Are the numbers correct? Are the numbers relevant to the general meaning of the statement?

Is the degree of certainty or uncertainty of the statement indicated clearly? Have appropriate statistical tests been applied to the data used in drawing the conclusion set forth in the statement? If the statement is based on a mathematical or novel conceptual model, has the model or concept been validated? Does the statement describe the model or concept on which it is based and the degree of validity of that model or concept?

Is the statement correct without qualification? Are there limitations of time, space, or other special circumstances in which the statement is true? If the statement is true only in some circumstances, are these limitations described adequately and briefly?

Is the statement clear and unambiguous? Are the words and phrases used in the statement understandable by the decision makers of our society? Is the statement free of specialized jargon? Will too many people misunderstand its meaning?

Is the statement as concise as it can be made without risk of misunderstanding? Are there any excess words, phrases, or ideas in the statement which are not necessary to communicate the meaning of the statement? Are there so many caveats in the statement that the statement itself is trivial, confusing, or ambiguous?

Is the statement free of scientific or other biases or implications of societal value judgments? Is the statement free of influence by specific schools of scientific thought? Is the statement also free of words, phrases, or concepts that have political, economic, ideological, religious, moral, or other personal-, agency-, or organization-specific values, overtones, or implications? Does the choice of how the statement is expressed rather than its specific words suggest underlying biases or value judgments? Is the tone impartial and free of special pleading? If societal value judgments have been discussed, have these judgments been identified as such and described both clearly and objectively?

Have societal implications been described objectively? Consideration of alternative courses of action and their consequences inherently involves judgments of their feasibility and the importance of effects. For this reason, it is important to ask if a reasonable range of alternative policies or courses of action have been evaluated? Have societal implications of alternative courses of action been stated in the following general form?

"If this [particular option] were adopted then that [particular outcome] would be expected."

Have the professional biases of authors and reviewers been described openly? Acknowledgment of potential sources of bias is important so that readers can judge for themselves the credibility of reports and assessments.

A.3.5. IARC Guidelines for Scientific Review and Evaluation Categories

The following is excerpted from the International Agency for Research on Cancer Monographs on the evaluation of carcinogenic risks to humans (IARC, 2006)

> The available studies are summarized by the Working Group, with particular regard to the qualitative aspects discussed below. In general, numerical findings are indicated as they appear in the original report; units are converted when necessary for easier comparison. The Working Group may conduct additional analyses of the published data and use them in their assessment of the evidence; the results of such supplementary analyses are given in square brackets. When an important aspect of a study that directly impinges on its interpretation should be brought to the attention of the reader, a Working Group comment is given in square brackets.
>
> The scope of the *IARC Monographs* program has expanded beyond chemicals to include complex mixtures, occupational exposures, physical and biological agents, lifestyle factors and other potentially carcinogenic exposures. Over time, the structure of a *Monograph* has evolved to include the following sections:
>
> 1. Exposure data
>
> 2. Studies of cancer in humans
>
> 3. Studies of cancer in experimental animals
>
> 4. Mechanistic and other relevant data
>
> 5. Summary
>
> 6. Evaluation and rationale
>
> In addition, a section of General Remarks at the front of the volume discusses the reasons the agents were scheduled for evaluation and some key issues the Working Group encountered during the meeting.
>
> This part of the Preamble discusses the types of evidence considered and summarized in each section of a *Monograph*, followed by the scientific criteria that guide the evaluations.

Evaluation and rationale

> Evaluations of the strength of the evidence for carcinogenicity arising from human and experimental animal data are made, using standard terms. The strength of the mechanistic evidence is also characterized.

It is recognized that the criteria for these evaluations, described below, cannot encompass all of the factors that may be relevant to an evaluation of carcinogenicity. In considering all of the relevant scientific data, the Working Group may assign the agent to a higher or lower category than a strict interpretation of these criteria would indicate.

These categories refer only to the strength of the evidence that an exposure is carcinogenic and not to the extent of its carcinogenic activity (potency). A classification may change as new information becomes available.

An evaluation of the degree of evidence is limited to the materials tested, as defined physically, chemically or biologically. When the agents evaluated are considered by the Working Group to be sufficiently closely related, they may be grouped together for the purpose of a single evaluation of the degree of evidence.

(a) Carcinogenicity in humans

The evidence relevant to carcinogenicity from studies in humans is classified into one of the following categories:

Sufficient evidence of carcinogenicity: The Working Group considers that a causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence. A statement that there is *sufficient evidence* is followed by a separate sentence that identifies the target organ(s) or tissue(s) where an increased risk of cancer was observed in humans. Identification of a specific target organ or tissue does not preclude the possibility that the agent may cause cancer at other sites.

Limited evidence of carcinogenicity: A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

Inadequate evidence of carcinogenicity: The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure and cancer, or no data on cancer in humans are available.

Evidence suggesting lack of carcinogenicity: There are several adequate studies covering the full range of levels of exposure that humans are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent and any studied cancer at any observed level of exposure. The results from these studies alone or combined should have narrow confidence intervals with an

upper limit close to the null value (e.g. a relative risk of 1.0). Bias and confounding should be ruled out with reasonable confidence, and the studies should have an adequate length of follow-up. A conclusion of *evidence suggesting lack of carcinogenicity* is inevitably limited to the cancer sites, conditions and levels of exposure, and length of observation covered by the available studies. In addition, the possibility of a very small risk at the levels of exposure studied can never be excluded.

In some instances, the above categories may be used to classify the degree of evidence related to carcinogenicity in specific organs or tissues.

When the available epidemiologic studies pertain to a mixture, process, occupation or industry, the Working Group seeks to identify the specific agent considered most likely to be responsible for any excess risk. The evaluation is focused as narrowly as the available data on exposure and other aspects permit.

(b) Carcinogenicity in experimental animals

Carcinogenicity in experimental animals can be evaluated using conventional bioassays, bioassays that employ genetically modified animals, and other in-vivo bioassays that focus on one or more of the critical stages of carcinogenesis. In the absence of data from conventional long-term bioassays or from assays with neoplasia as the end-point, consistently positive results in several models that address several stages in the multistage process of carcinogenesis should be considered in evaluating the degree of evidence of carcinogenicity in experimental animals.

The evidence relevant to carcinogenicity in experimental animals is classified into one of the following categories:

Sufficient evidence of carcinogenicity: The Working Group considers that a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumors in both sexes of a single species in a well-conducted study, ideally conducted under Good Laboratory Practices, can also provide *sufficient evidence*.

A single study in one species and sex might be considered to provide *sufficient evidence of carcinogenicity* when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumor or age at onset, or when there are strong findings of tumors at multiple sites.

Limited evidence of carcinogenicity: The data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g. (a) the evidence of carcinogenicity is restricted to a single experiment; (b)

there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies; (c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; or (d) the evidence of carcinogenicity is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs.

Inadequate evidence of carcinogenicity: The studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect because of major qualitative or quantitative limitations, or no data on cancer in experimental animals are available.

Evidence suggesting lack of carcinogenicity: Adequate studies involving at least two species are available which show that, within the limits of the tests used, the agent is not carcinogenic. A conclusion of *evidence suggesting lack of carcinogenicity* is inevitably limited to the species, tumor sites, age at exposure, and conditions and levels of exposure studied.

(c) Mechanistic and other relevant data

Mechanistic and other evidence judged to be relevant to an evaluation of carcinogenicity and of sufficient importance to affect the overall evaluation is highlighted. This may include data on preneoplastic lesions, tumor pathology, genetic and related effects, structure–activity relationships, metabolism and toxicokinetics, physicochemical parameters and analogous biological agents.

The strength of the evidence that any carcinogenic effect observed is due to a particular mechanism is evaluated, using terms such as 'weak,' 'moderate' or 'strong.' The Working Group then assesses whether that particular mechanism is likely to be operative in humans. The strongest indications that a particular mechanism operates in humans derive from data on humans or biological specimens obtained from exposed humans. The data may be considered to be especially relevant if they show that the agent in question has caused changes in exposed humans that are on the causal pathway to carcinogenesis. Such data may, however, never become available, because it is at least conceivable that certain compounds may be kept from human use solely on the basis of evidence of their toxicity and/or carcinogenicity in experimental systems.

The conclusion that a mechanism operates in experimental animals is strengthened by findings of consistent results in different experimental systems, by the demonstration of biological plausibility and by coherence of the overall database. Strong support can be obtained from studies that challenge the hypothesized mechanism experimentally, by demonstrating that the suppression of key mechanistic processes leads to the suppression of tumor development. The Working Group considers whether multiple mechanisms might contribute to tumor development, whether different mechanisms might operate in different dose ranges, whether separate mechanisms might operate in humans and experimental

animals and whether a unique mechanism might operate in a susceptible group. The possible contribution of alternative mechanisms must be considered before concluding that tumors observed in experimental animals are not relevant to humans. An uneven level of experimental support for different mechanisms may reflect that disproportionate resources have been focused on investigating a favored mechanism.

For complex exposures, including occupational and industrial exposures, the chemical composition and the potential contribution of carcinogens known to be present are considered by the Working Group in its overall evaluation of human carcinogenicity. The Working Group also determines the extent to which the materials tested in experimental systems are related to those to which humans are exposed.

(d) Overall evaluation

Finally, the body of evidence is considered as a whole, in order to reach an overall evaluation of the carcinogenicity of the agent to humans.

An evaluation may be made for a group of agents that have been evaluated by the Working Group. In addition, when supporting data indicate that other related agents, for which there is no direct evidence of their capacity to induce cancer in humans or in animals, may also be carcinogenic, a statement describing the rationale for this conclusion is added to the evaluation narrative; an additional evaluation may be made for this broader group of agents if the strength of the evidence warrants it.

The agent is described according to the wording of one of the following categories, and the designated group is given. The categorization of an agent is a matter of scientific judgement that reflects the strength of the evidence derived from studies in humans and in experimental animals and from mechanistic and other relevant data.

Group 1: The agent is *carcinogenic to humans*.

> This category is used when there is sufficient evidence of carcinogenicity in humans. Exceptionally, an agent may be placed in this category when evidence of carcinogenicity in humans is less than sufficient but there is sufficient evidence of carcinogenicity in experimental animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity.

Group 2.

> This category includes agents for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost *sufficient*, as well as those for which, at the other extreme, there are no human data but for which there is evidence of carcinogenicity in experimental animals. Agents are assigned to either Group 2A (*probably carcinogenic to humans*) or Group 2B (*possibly carcinogenic to humans*) on the basis of

epidemiologic and experimental evidence of carcinogenicity and mechanistic and other relevant data. The terms *probably carcinogenic* and *possibly carcinogenic* have no quantitative significance and are used simply as descriptors of different levels of evidence of human carcinogenicity, with probably carcinogenic signifying a higher level of evidence than possibly carcinogenic.

Group 2A: The agent is probably carcinogenic to humans.

This category is used when there is *limited evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals. In some cases, an agent may be classified in this category when there is *inadequate evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent may be classified in this category solely on the basis of *limited evidence of carcinogenicity* in humans. An agent may be assigned to this category if it clearly belongs, based on mechanistic considerations, to a class of agents for which one or more members have been classified in Group 1 or Group 2A.

Group 2B: The agent is possibly carcinogenic to humans.

This category is used for agents for which there is *limited evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals. It may also be used when there is *inadequate evidence of carcinogenicity* in humans but there is *sufficient evidence of carcinogenicity* in experimental animals. In some instances, an agent for which there is *inadequate evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals together with supporting evidence from mechanistic and other relevant data may be placed in this group. An agent may be classified in this category solely on the basis of strong evidence from mechanistic and other relevant data.

Group 3: The agent is not classifiable as to its carcinogenicity to humans.

This category is used most commonly for agents for which the evidence of carcinogenicity is *inadequate* in humans and *inadequate* or *limited* in experimental animals.

Exceptionally, agents for which the evidence of carcinogenicity is *inadequate* in humans but *sufficient* in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans.

Agents that do not fall into any other group are also placed in this category.

An evaluation in Group 3 is not a determination of non-carcinogenicity or overall safety. It often means that further research is needed,

especially when exposures are widespread or the cancer data are consistent with differing interpretations.

Group 4: The agent is probably not carcinogenic to humans.

This category is used for agents for which there is *evidence suggesting lack of carcinogenicity* in humans and in experimental animals. In some instances, agents for which there is *inadequate evidence of carcinogenicity* in humans but *evidence suggesting lack of carcinogenicity* in experimental animals, consistently and strongly supported by a broad range of mechanistic and other relevant data, may be classified in this group.

(e) Rationale

The reasoning that the Working Group used to reach its evaluation is presented and discussed. This section integrates the major findings from studies of cancer in humans, studies of cancer in experimental animals, and mechanistic and other relevant data. It includes concise statements of the principal line(s) of argument that emerged, the conclusions of the Working Group on the strength of the evidence for each group of studies, citations to indicate which studies were pivotal to these conclusions, and an explanation of the reasoning of the Working Group in weighing data and making evaluations. When there are significant differences of scientific interpretation among Working Group Members, a brief summary of the alternative interpretations is provided, together with their scientific rationale and an indication of the relative degree of support for each alternative.

A.3.6. NTP: Report on Carcinogens

The criteria for listing an agent, substance, mixture, or exposure circumstance in the National Toxicology Program's Report on Carcinogens (NTP, 2005) as follows:

Known to Be Human Carcinogen:

There is sufficient evidence of carcinogenicity from studies in humans*, which indicates a causal relationship between exposure to the agent, substance, or mixture, and human cancer.

Reasonably Anticipated to Be Human Carcinogen:

There is limited evidence of carcinogenicity from studies in humans*, which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding factors, could not adequately be excluded,

or

there is sufficient evidence of carcinogenicity from studies in experimental animals, which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors (1) in multiple species or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site, or type of tumor, or age at onset,

or

there is less than sufficient evidence of carcinogenicity in humans or laboratory animals; however, the agent, substance, or mixture belongs to a well-defined, structurally related class of substances whose members are listed in a previous Report on Carcinogens as either known to be a human carcinogen or reasonably anticipated to be a human carcinogen, or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to, dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub-populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals, but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.

*This evidence can include traditional cancer epidemiology studies, data from clinical studies, and/or data derived from the study of tissues or cells from humans exposed to the substance in question that can be useful for evaluating whether a relevant cancer mechanism is operating in people.

Annex B. Additional Information on the Atmospheric Chemistry of SO_X

B.1. Introduction

SO_2 is chiefly but not exclusively primary in origin. Primary SO_2 is emitted directly from sources, whereas secondary SO_2 is formed as a product of atmospheric reactions. Secondary SO_2 is produced by the photochemical oxidation of reduced sulfur compounds such as dimethyl sulfide (DMS) (CH_3-S-CH_3), hydrogen sulfide (H_2S), carbon disulfide (CS_2), carbonyl sulfide (OCS), methyl mercaptan (CH_3-S-H), and dimethyl disulfide (CH_3-S-S-CH_3) which are all mainly biogenic in origin. Their sources are discussed in Section B.3. Table B-1 lists the atmospheric lifetimes of reduced sulfur species with respect to reaction with various oxidants. Except for OCS, which is lost mainly by photolysis (τ~6 months), these species are lost mainly by reaction with OH and NO_3 radicals. Because OCS is relatively long-lived in the troposphere, it can be transported upwards into the stratosphere.

Table B-1. Atmospheric lifetimes of SO_2 and reduced sulfur species with respect to reaction with OH, NO_3, and Cl radicals.

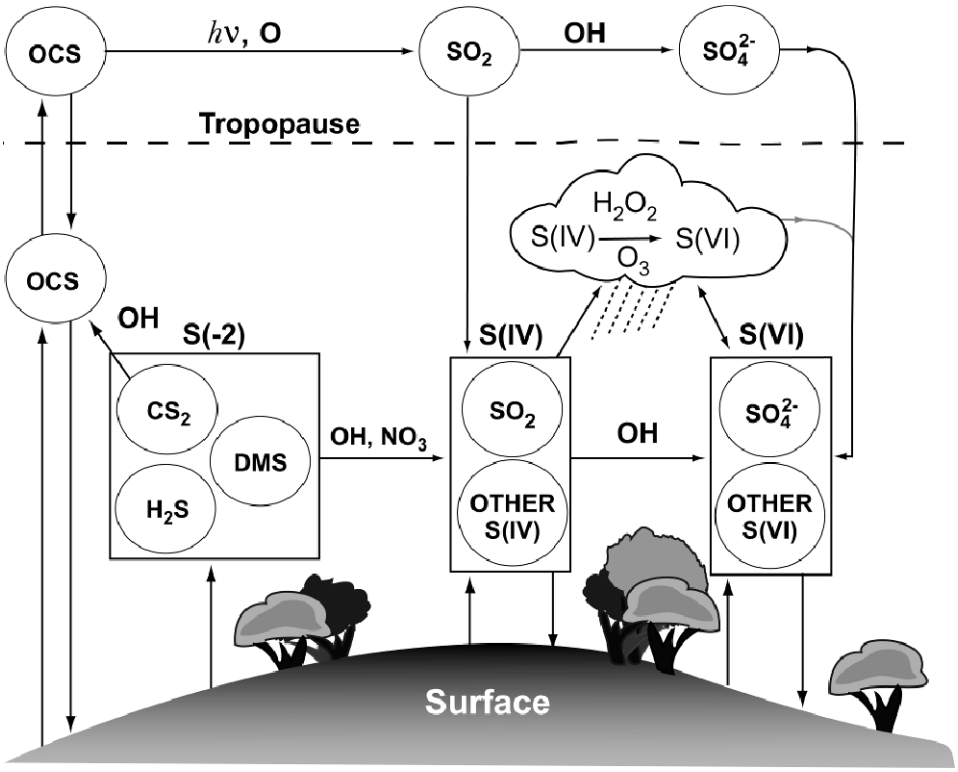
Compound	OH		NO_3		Cl	
	K X 10^{12}	T	K X 10^{12}	T	K X 10^{12}	T
SO_2	1.6	7.2d	NA		NA	
CH_3-S-CH_3	5.0	2.3 d	1.0	1.1-h	400	29 d
H_2S	4.7	2.2 d	NA		74	157 d
CS_2	1.2	9.6 d	< 0.0004	> 116 d	< 0.004	NR
OCS	0.0019	17 y	< 0.0001	> 1.3 y	< 0.0001	NR
CH_3-S-H	33	8.4 h	0.89	1.2 h	200	58 d
CH_3-S-S-CH_3	230	1.2 h	0.53	2.1-h	NA	

NA = Reaction rate coefficient not available.
NR = Rate coefficient too low to be relevant as an atmospheric loss mechanism. Rate coefficients were calculated at 298 K and 1 atmosphere.
yr = year
h = hour
OH = 1 × 10^6/cm^3
NO_3 = 2.5 × 10^8/cm^3
Cl = 1 × 10^3/cm^3.
[1]Rate coefficients were taken from JPL Chemical Kinetics Evaluation No. 14 (JPL2003)

Source: Seinfeld and Pandis (1998).

Crutzen (1976) proposed that OCS oxidation serves as the major source of sulfate (SO_4^{2-}) in the stratospheric aerosol layer sometimes referred to the "Junge layer," (Junge et al., 1961) during periods when volcanic plumes do not reach the stratosphere. However, the flux of OCS into the stratosphere is probably not sufficient to maintain this stratospheric aerosol layer. Myhre et al. (2004) proposed instead

that SO_2 transported upwards from the troposphere is the most likely source, as the upward flux of OCS is too small to sustain observed SO_4^{2-} loadings in the Junge layer. In addition, in situ measurements of the isotopic composition of sulfur (S) do not match those of OCS (Leung et al. 2002). Reaction with NO_3 radicals at night most likely represents the major loss process for DMS and methyl mercaptan. The mechanisms for the oxidation of DMS are still not completely understood. Initial attack by NO_3 and OH radicals involves H atom abstraction, with a smaller branch leading to OH addition to the S atom. The OH addition branch increases in importance as temperatures decrease, becoming the major pathway below temperatures of 285 K (Ravishankara, 1997). The adduct may either decompose to form methane sulfonic acid (MSA), or undergo further reactions in the main pathway, to yield dimethyl sulfoxide (Barnes et al., 1991). Following H atom abstraction from DMS, the main reaction products include MSA and SO_2. The ratio of MSA to SO_2 is strongly temperature dependent, varying from about 0.1 in tropical waters to about 0.4 in Antarctic waters (Seinfeld and Pandis, 1998). Excess SO_4^{2-} (over that expected from the SO_4^{2-} in seawater) in marine aerosol is related mainly to the production of SO_2 from the oxidation of DMS. Transformations among atmospheric S compounds are summarized in Figure B-1



Source: Adapted from Berresheim et al. (1995).

Figure B-1. Transformations of sulfur compounds in the atmosphere.

B.1.1. Multiphase Chemical Processes Involving SO_X and Halogens

Chemical transformations involving inorganic halogenated compounds effect changes in the multiphase cycling of SO_X in ways analogous to their effects on NO_X. Oxidation of dimethylsulfide $(CH_3)_2S$ by BrO produces dimethylsulfoxide $(CH_3)_2SO$ (Barnes et al., 1991; Toumi, 1994), and oxidation by atomic chloride leads to formation of SO_2 (Keene et al., 1996). Dimethylsulfoxide and SO_2 are precursors for methanesulfonic acid (CH_3SO_3H) and H_2SO_4. In the MBL, virtually all H_2SO_4 and

CH_3SO_3H vapor condenses onto existing aerosols or cloud droplets, which subsequently evaporate, thereby contributing to aerosol growth and acidification. Unlike CH_3SO_3H, H_2SO_4 also has the potential to produce new particles (Korhonen et al., 1999; Kulmala et al., 2000), which in marine regions is thought to occur primarily in the free troposphere. Saiz-Lopez et al. (2004) estimated that observed levels of bromine oxide (BrO) at Mace Head Atmospheric Research Station in Ireland, would oxidize $(CH_3)_2S$ about six times faster than OH and thereby substantially increase production rates of H_2SO_4 and other condensible S species in the MBL. Sulfur dioxide is also scavenged by deliquesced aerosols and oxidized to H_2SO_4 in the aqueous phase by several strongly pH-dependent pathways (Chameides and Stelson, 1992; Keene et al., 1998; Vogt et al., 1996). Model calculations indicate that oxidation of S(IV) by O_3 dominates in fresh, alkaline sea salt aerosols, whereas oxidation by hypohalous acids (primarily HOCl) dominates in moderately acidic solutions. Additional particulate non-sea salt (nss) SO_4^{2-} is generated by SO_2 oxidation in cloud droplets (Clegg and Toumi, 1998). Ion-balance calculations indicate that most nss SO_4^{2-} in short-lived (two to 48 h) sea salt size fractions accumulates in acidic aerosol solutions and/or in acidic aerosols processed through clouds (Keene et al., 2004). The production, cycling, and associated radiative effects of S-containing aerosols in marine and coastal air are regulated in part by chemical transformations involving inorganic halogens (Von Glasow et al., 2002). These transformations include: dry-deposition fluxes of nss SO_4^{2-} in marine air dominated, naturally, by the sea salt size fractions (Huebert et al., 1996; Turekian et al., 2001); HCl phase partitioning that regulates sea salt pH and associated pH-dependent pathways for S(IV) oxidation (Keene et al., 2002; Pszenny et al., 2004); and potentially important oxidative reactions with reactive halogens for $(CH_3)2S$ and S(IV). However, both the absolute magnitudes and relative importance of these processes in MBL S cycling are poorly understood.

Table B-2. Relative contributions of various reactions to the total S(IV) oxidation rate within a sunlit cloud, 10 min after cloud formation.

Reaction	% of Total [a]	% of Total [b]
GAS PHASE		
$OH + SO_2$	3.5	3.1
AQUEOUS PHASE		
$O_3 + HSO_3^-$	0.6	0.7
$O_3 + SO_3^{2-}$	7.0	8.2
$H_2O_2 + SO_3^{2-}$	78.4	82.1
$CH_3OOH + HSO_3^-$	0.1	0.1
$HNO_4 + HSO_3^-$	9.0	4.4
$HOONO + HSO_3^-$	< 0.1	< 0.1
$HSO_5^- + HSO_3^-$	1.2	< 0.1
$SO_5^- + SO_3^{2-}$	< 0.1	< 0.1
$HSO_5^- + Fe^{2+}$		0.6

[a] In the absence of transition metals. [B]in the presence of iron and copper ions.

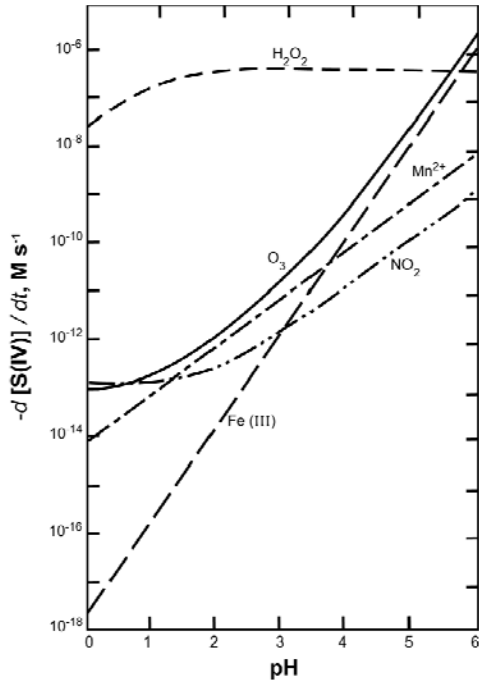
Source: Adapted from Warneck (1999).

Iodine (I) chemistry has been linked to ultrafine particle bursts at Mace Head (O'Dowd et al., 1999; O'Dowd et al., 2002). Observed bursts coincide with elevated concentrations of IO and are characterized

by particle concentrations increasing from background levels to up to 300,000/cm^3 on a time scale of seconds to minutes. This newly identified source of marine aerosol would provide additional aerosol surface area for condensation of SO_X and thereby presumably diminish the potential for nucleation pathways involving H_2SO_4. However, a subsequent investigation in polluted air along the New England, USA coast found no correlation between periods of nanoparticle growth and corresponding concentrations of I oxides (Fehsenfeld et al., 2006). The potential importance of I chemistry in aerosol nucleation and its associated influence on sulfur cycling remain highly uncertain.

B.1.2. Mechanisms for the Aqueous Phase Formation of Sulfate

Warneck (1999) constructed a box model describing the chemistry of the oxidation of SO_2 and NO_2 including the interactions of N and S species and minor processes in sunlit cumulus clouds. The relative contributions of different reactions to the oxidation of S(IV) species to S(VI) and NO_2 to NO_3^- 10 min after cloud formation are given in Table B-2. The two columns show the relative contributions with and without transition metal ions. As can be seen from Table B-2, SO_2 within a cloud (gas + cloud drops) is oxidized mainly by H_2O_2 in the aqueous phase, while the gas-phase oxidation by OH radicals is small by comparison. A much smaller contribution in the aqueous phase is made by methyl hydroperoxide (CH_3OOH) because it is formed mainly in the gas phase and its Henry's Law constant is several orders of magnitude smaller that of H_2O_2. After H_2O_2, HNO_4 is the major contributor to S(IV) oxidation. The pH dependence of the oxidation rate of S(IV) in the presence of transition metal ions is illustrated in Figure B-2.



Source: Seinfeld and Pandis (1998).

Figure B-2. Comparison of aqueous-phase oxidation paths. The rate of conversion of S(IV) to S(VI) is shown as a function of pH. Conditions assumed are: [SO_2(g)] = 5 ppb; [NO_2(g)] = 1 ppb; [H_2O_2(g)] = 1 ppb; [O_3(g)] = 50 ppb; [Fe(III)(aq)] = 0.3 µM; [Mn(II)(aq)] = 0.3 µM.

B.1.3. Multiphase Chemical Processes Involving SO_X and NH_3

The phase partitioning of ammonia (NH_3) with deliquesced aerosol solutions is controlled primarily by the thermodynamic properties of the system expressed as follows:

$$NH_{3g} \overset{K_H}{\leftrightarrow} [NH_{3aq}] \overset{K_b}{\leftrightarrow} [NH_4^+] + K_W/[H^+]$$

where K_H and K_b are the temperature-dependent Henry's Law and dissociation constants (62 M/atm and 1.8×10^{-5} M), respectively, for NH_3, and K_w is the ion product of water (1.0×10^{-14} M) (Chameides, 1984). It is evident that for a given amount of NH_X (NH_3 + particulate NH_4^+) in the system, increasing aqueous concentrations of particulate H^+ will shift the partitioning of NH_3 towards the condensed phase. Consequently, under the more polluted conditions characterized by higher concentrations of acidic sulfate aerosol, ratios of gaseous NH_3 to particulate NH_4^+ decrease (Smith et al., 2007). It also follows that in marine air, where aerosol acidity varies substantially as a function of particle size, NH_3 partitions preferentially to the more acidic sub-micron size fractions where K_H and K_b are the temperature-dependent Henry's Law and dissociation constants (62 M/atm and 1.8×10^{-5} M), respectively, for NH_3, and K_w is the ion product of water (1.0×10^{-14} M) (Chameides 1984). It is evident that for a given amount of NH_X (NH_3 + particulate NH_4^+) in the system, increasing aqueous concentrations of particulate H^+ will shift the partitioning of NH_3 towards the condensed phase. Consequently, under the more polluted conditions characterized by higher concentrations of acidic sulfate aerosol, ratios of gaseous NH_3 to particulate NH_4^+ decrease (Smith et al., 2007). Under these conditions, the roughly equal partitioning of total NH_3 between the gas and particulate phases sustains substantial dry-deposition fluxes of total NH_3 to the coastal ocean (median of 10.7 μmol//m^2/day). In contrast, heavily polluted air transported from the industrialized midwestern U.S. contains concentrations of nss SO_4^{2-} and total NH_3 that are about a factor of 3 greater, based on median values. Under these conditions, most total NH_3 (> 85%) partitions to the highly acidic sulfate aerosol size fractions and, consequently, the median dry-deposition flux of total NH_3 is 30% lower than that under the cleaner northerly flow regime. The relatively longer atmospheric lifetime of total NH_3 against dry deposition under more polluted conditions implies that, on average, total NH_3 would accumulate to higher atmospheric concentrations under these conditions and also be subject to atmospheric transport over longer distances. Consequently, the importance of NH_X removal via wet deposition would also increase. Because of the inherently sporadic character of precipitation, we might expect greater heterogeneity in NH_3 deposition fields and any potential responses in sensitive ecosystems downwind of major S-emission regions.

B.2. Transport of SO_X in the Atmosphere

Crutzen and Gidel (1983), Gidel (1983), and Chatfield and Crutzen (1984) hypothesized that convective clouds played an important role in rapid atmospheric vertical transport of trace species and first tested simple parameterizations of convective transport in atmospheric chemical models. At nearly the same time, evidence was shown of venting the boundary layer by shallow, fair weather cumulus clouds (Greenhut et al., 1984; 1986). Field experiments were conducted in 1985 which resulted in verification of the hypothesis that deep convective clouds are instrumental in atmospheric transport of trace constituents (Dickerson et al., 1987). Once pollutants are lofted to the middle and upper troposphere, they typically have a much longer chemical lifetime and with the generally stronger winds at these altitudes, they can be transported large distances from their source regions.

B.3. Emissions of SO_2

As can be seen from Table B-3, emissions of SO_2 are due mainly to the combustion of fossil fuels by electrical utilities and industry. Transportation related sources make only a minor contribution. As a result, most SO_2 emissions originate from point sources. Since S is a volatile component of fuels, it is almost quantitatively released during combustion, and emissions can be calculated on the basis of the sulfur content of fuels to greater accuracy than for other pollutants such as NO_X or primary PM.

Table B-3 Emissions of NO_X, NH_3, and SO_2 in the U.S. by source and category, 2002.

2002 Emissions (Tg/yr)	NO_X[1]	NH_3[2]	SO_2
Total all Sources	**23.19**	**4.08**	**16.87**
Fuel Combustion Total	**9.11**	**0.02**	**14.47**
Fuel Combustion Electrical Utilities	5.16	< 0.01	11.31
Coal	4.50	< 0.01	10.70
Bituminous	2.90		8.04
Subbituminous	1.42		2.14
Anthracite & Lignite	0.18		0.51
Other	< 0.01		
Oil	0.14	< 0.01	0.38
Residual	0.13		0.36
Distillate	0.01		0.01
Gas	0.30	< 0.01	0.01
Natural	0.29		
Process	0.01		
Other	0.05	< 0.01	0.21
Internal Combustion	0.17	< 0.01	0.01
Fuel Combustion Industrial	3.15	< 0.01	2.53
Coal	0.49	< 0.01	1.26
Bituminous	0.25		0.70
Subbituminous	0.07		0.10
Anthracite & Lignite	0.04		0.13
Other	0.13		0.33
Oil	0.19	< 0.01	0.59
Residual	0.09		0.40
Distillate	0.09		0.16
Other	0.01		0.02
Gas	1.16	< 0.01	0.52
Natural	0.92		
Process	0.24		
Other	< 0.01		
Other	0.16	< 0.01	0.15
Wood/Bark Waste	0.11		
Liquid Waste	0.01		
Other	0.04		
Internal Combustion	1.15	< 0.01	0.01
Fuel Combustion Other	0.80	< 0.01	0.63
Commercial/Institutional Coal	0.04	< 0.01	0.16
Commercial/Institutional Oil	0.08	< 0.01	0.28
Commercial/Institutional Gas	0.25	< 0.01	0.02
Misc. Fuel Combustion (Exc. Residential)	0.03	< 0.01	0.01
Residential Wood	0.03		< 0.01
Residential Other	0.36		0.16
Distillate Oil	0.06		0.15
Bituminous/Subbituminous	0.26		< 0.01
Other	0.04		< 0.01
Industrial Process Total	**1.10**	**0.21**	**1.54**
Chemical & Allied Product Mfg	0.12	0.02	0.36
Organic Chemical Mfg	0.02	< 0.01	0.01
Inorganic Chemical Mfg	0.01	< 0.01	0.18
Sulfur Compounds			0.17
Other			0.02
Polymer & Resin Mfg	< 0.01	< 0.01	< 0.01
Agricultural Chemical Mfg	0.05	0.02	0.05
Ammonium Nitrate/Urea Mfg.		< 0.01	
Other		0.02	
Paint, Varnish, Lacquer, Enamel Mfg	0.00		0.00
Pharmaceutical Mfg	0.00		0.00
Other Chemical Mfg	0.03	< 0.01	0.12
Metals Processing	0.09	< 0.01	0.30
Non-Ferrous Metals Processing	0.01	< 0.01	0.17
Copper			0.04
Lead			0.07
Zinc			0.01
Other			< 0.01
Ferrous Metals Processing	0.07	< 0.01	0.11
Metals Processing	0.01	< 0.01	0.02
Petroleum & Related Industries	0.16	< 0.01	.38
Oil & Gas Production	0.07	< 0.01	0.11
Natural Gas			0.11
Other			0.01
Petroleum Refineries & Related Industries	0.05	< 0.01	0.26
Fluid Catalytic Cracking Units		< 0.01	0.16
Other		< 0.01	0.07
Asphalt Manufacturing	0.04		0.01
Other Industrial Processes	0.54	0.05	0.46
Agriculture, Food, & Kindred Products	0.01	< 0.01	0.01
Textiles, Leather, & Apparel Products	< 0.01	< 0.01	< 0.01
Wood, Pulp & Paper, & Publishing Products	0.09	< 0.01	0.10
Rubber & Miscellaneous Plastic Products	< 0.01	< 0.01	< 0.01
Mineral Products	0.42	< 0.01	0.33
Cement Mfg	0.24		0.19
Glass Mfg	0.01		
Other	0.10		0.09
Machinery Products	< 0.01	< 0.01	< 0.01
Electronic Equipment	< 0.01	< 0.01	< 0.01
Transportation Equipment	< 0.01		< 0.01
Miscellaneous Industrial Processes	0.01	0.05	0.02
Solvent Utilization	0.01	< 0.01	< 0.01
Degreasing	< 0.01	< 0.01	< 0.01
Graphic Arts	< 0.01	< 0.01	< 0.01
Dry Cleaning	< 0.01	< 0.01	< 0.01
Surface Coating	< 0.01	< 0.01	< 0.01
Other Industrial	< 0.01	< 0.01	< 0.01
Nonindustrial	< 0.01		
Solvent Utilization Nec	< 0.01		
Storage & Transport	< 0.01	< 0.01	0.01
Bulk Terminals & Plants	< 0.01	< 0.01	< 0.01
Petroleum & Petroleum Product Storage	< 0.01	< 0.01	< 0.01
Petroleum & Petroleum Product Transport	< 0.01	< 0.01	< 0.01
Service Stations: Stage II	< 0.01		< 0.01
Organic Chemical Storage	< 0.01	< 0.01	< 0.01

2002 Emissions (Tg/yr)	NO_X[1]	NH_3[2]	SO_2
Organic Chemical Transport	0.01		< 0.01
Inorganic Chemical Storage	< 0.01	< 0.01	< 0.01
Inorganic Chemical Transport	< 0.01		< 0.01
Bulk Materials Storage	0.01	< 0.01	< 0.01
Waste Disposal & Recycling	0.17	0.14	0.03
Incineration	0.06	< 0.01	0.02
Industrial			
Other			< 0.01
Open Burning	0.10	< 0.01	< 0.01
Industrial			< 0.01
Land Clearing Debris			
Other			< 0.01
Public Operating Treatment Works	< 0.01	0.14	< 0.01
Industrial Waste Water	< 0.01	< 0.01	< 0.01
Treatment, Storage, And Disposal Facility	< 0.01	< 0.01	< 0.01
Landfills	< 0.01	< 0.01	< 0.01
Industrial			< 0.01
Other			< 0.01
Other	< 0.01	< 0.01	< 0.01
Transportation Total	**12.58**	**0.32**	**0.76**
Highway Vehicles	8.09	0.32	0.30
Light-Duty Gas Vehicles & Motorcycles	2.38	0.20	0.10
Light-Duty Gas Vehicles	2.36		0.10
Motorcycles	0.02		0.00
Light-Duty Gas Trucks	1.54	0.10	0.07
Light-Duty Gas Trucks 1	1.07		0.05
Light-Duty Gas Trucks 2	0.47		0.02
Heavy-Duty Gas Vehicles	0.44	< 0.01	0.01
Diesels	3.73	< 0.01	0.12
Heavy-Duty Diesel Vehicles	3.71		
Light-Duty Diesel Trucks	0.01		
Light-Duty Diesel Vehicles	0.01		
Off-Highway	4.49	< 0.01	0.46
Non-Road Gasoline	0.23	< 0.01	0.01
Recreational	0.01		
Construction	0.01		
Industrial	0.01		
Lawn & Garden	0.10		
Farm	0.01		
Light Commercial	0.04		
Logging	< 0.01		
Airport Service	< 0.01		
Railway Maintenance	< 0.01		
Recreational Marine Vessels	0.05		
Non-Road Diesel	1.76	< 0.01	0.22
Recreational	0.00		
Construction	0.84		
Industrial	0.15		
Lawn & Garden	0.05		
Farm	0.57		
Light Commercial	0.08		
Logging	0.02		
Airport Service	0.01		
Railway Maintenance	< 0.01		
Recreational Marine Vessels	0.03		
Aircraft	0.09		0.01
Marine Vessels	1.11		0.18
Diesel	1.11		
Residual Oil			
Other			
Railroads	0.98		0.05
Other	0.32	< 0.01	0.00
Liquefied Petroleum Gas	0.29		
Compressed Natural Gas	0.04		
Miscellaneous	0.39	3.53	0.10
Agriculture & Forestry	< 0.01	3.45	< 0.01
Agricultural Crops		< 0.01	
Agricultural Livestock		2.66	
Other Combustion		0.08	0.10
Health Services			
Cooling Towers			
Fugitive Dust			
Other			
Natural Sources	3.10	0.03	

[1] Emissions are expressed in terms of NO_2.
[2] Natural emissions of non-methane volatile organic compounds, carbon monoxide, and oxides.
Note: Subcategory values may not sum to category totals due to rounding.
Source: (EPA, 2006a)

The major natural sources of SO_2 are volcanoes, biomass burning, and DMS oxidation over the oceans. SO_2 constitutes a relatively minor fraction (0.005% by volume) of volcanic emissions (Holland, 1978). The ratio of H_2S to SO_2 is highly variable in volcanic gases. It is typically much less than one, as in the Mt. St. Helens' eruption (Turco et al. 1983). However, in addition to being degassed from magma, H_2S can be produced if ground waters, especially those containing organic matter, come into contact with volcanic gases. In this case, the ratio of H_2S to SO_2 can be greater than one. H_2S produced this way would more likely be emitted through side vents than through eruption columns (Pinto et al., 1989). Primary particulate SO_4^{2-} is a component of marine aerosol and is also produced by wind erosion of surface soils.

Volcanic sources of SO_2 in the U.S. are limited to the Pacific Northwest, Alaska, and Hawaii. Since 1980, the Mt. St. Helens volcano in the Washington Cascade Range (46.20ºN, 122.18ºW, summit 2549 m asl) has been a variable source of SO_2. Its major effects came in the explosive eruptions of 1980, which primarily affected the Northwest. The Augustine volcano near the mouth of the Cook Inlet in southwestern Alaska (59.363ºN, 153.43°W, summit 1252 m asl) has had variable SO_2 emission since its last major eruptions in 1986. Volcanoes in the Kamchatka peninsula of eastern Siberia do not significantly affect surface SO_2 concentrations in northwestern North America. The most serious effects in the U.S. from volcanic SO_2 occur on the island of Hawaii. Nearly continuous venting of SO_2 from Mauna Loa and Kilauea produces SO_2 in such large amounts that > 100 km downwind of the island SO_2 concentrations can exceed 30 ppb (Thornton and Bandy, 1993). Depending on wind direction, the west coast of Hawaii

(Kona region) has had significant deleterious effects from SO_2 and acidic sulfate aerosols for the past decade.

Emissions of SO_2 from burning vegetation are generally in the range of 1 to 2% of the biomass burned (e.g., Levine and Pinto, 1998). Gaseous emissions are mainly in the form of SO_2 with much smaller amounts of H_2S and OCS. The ratio of gaseous N to S emissions is about 14, very close to their ratio in plant tissue (Andrea et al., 1991). Gaseous emissions are mainly in the form of SO_2 with much smaller amounts of H_2S and OCS. The ratio of reduced N and S species such as NH_3 and H_2S to their more oxidized forms, such as NO and SO_2, increases from flaming to smoldering phases of combustion, as emissions of reduced species are favored by lower temperatures and reduced O_2 availability.

Emissions of reduced S species are associated typically with marine organisms living either in pelagic or coastal zones and with anaerobic bacteria in marshes and estuaries. Mechanisms for their oxidation were discussed in Section B.1. Emissions of DMS from marine plankton represent the largest single source of reduced S species to the atmosphere (e.g., Berresheim et al., 1995).

However, it should be noted that reduced S species are also produced by industry. For example, DMS is used in petroleum refining and in petrochemical production processes to control the formation of coke and carbon monoxide. In addition, it is used to control dusting in steel mills. It is also used in a range of organic syntheses. It also has a use as a food flavoring component. It can also be oxidized by natural or artificial means to dimethyl sulfoxide (DMSO), which has several important solvent properties.

B.4. Methods Used to Calculate SO_x and Chemical Interactions in the Atmosphere

Atmospheric chemistry and transport models are the major tools used to calculate the relations among O_3, other oxidants, and their precursors, the transport and transformation of air toxics, the production of secondary organic aerosol, the evolution of the particle size distribution, and the production and deposition of pollutants affecting ecosystems. Chemical transport models are driven by emissions inventories for primary species such as the precursors for O_3 and PM and by meteorological fields produced by other numerical models. Emissions of precursor compounds can be divided into anthropogenic and natural source categories. Natural sources can be further divided into biotic (vegetation, microbes, animals) and abiotic (biomass burning, lightning) categories. However, the distinction between natural sources and anthropogenic sources is often difficult to make as human activities affect directly, or indirectly, emissions from what would have been considered natural sources during the preindustrial era. Emissions from plants and animals used in agriculture have been referred to as anthropogenic or natural in different applications. Wildfire emissions may be considered to be natural, except that forest management practices may have led to the buildup of fuels on the forest floor, thereby altering the frequency and severity of forest fires. Needed meteorological quantities such as winds and temperatures are taken from operational analyses, reanalyses, or circulation models. In most cases, these are off-line analyses, i.e., they are not modified by radiatively active species such as O_3 and particles generated by the model.

A brief overview of atmospheric chemistry-transport models is given in Section B.5. Uncertainties in emissions estimates have also been discussed in AQCD for PM (EPA, 1996). Chemistry-transport model evaluation and an evaluation of the reliability of emissions inventories are also presented in Section B.5.

B.5. Chemical-transport Models

Atmospheric chemical transport models (CTMs) have been developed for application over a wide range of spatial scales ranging from neighborhood to global. Regional scale CTMs are used: (1) to obtain better understanding of the processes controlling the formation, transport, and destruction of gas and particle phase criteria and hazardous air pollutants; (2) to understand the relations between O_3 concentrations and concentrations of its precursors such as NO_X and VOCs, the factors leading to acid deposition, and hence to possible damage to ecosystems; and (3) to understand relations among the concentration patterns of various pollutants that may exert adverse health effects. CTMs are also used for determining control strategies for O_3 precursors. However, this application has met with varying degrees of success because of the highly nonlinear relations between O_3 and emissions of its precursors, and uncertainties in emissions, parameterizations of transport, and chemical production and loss terms. Uncertainties in meteorological variables and emissions can be large enough to lead to significant errors in developing control strategies (e.g., Russell and Dennis, 2000; Sillman, 1995).

Global scale CTMs are used to address issues associated with climate change, stratospheric O_3 depletion, and to provide boundary conditions for regional scale models. CTMs include mathematical (and often simplified) descriptions of atmospheric transport, the transfer of solar radiation through the atmosphere, chemical reactions, and removal to the surface by turbulent motions and precipitation for pollutants emitted into the model domain. Their upper boundaries extend anywhere from the top of the mixing layer to the mesopause (about 80 km in height), to obtain more realistic boundary conditions for problems involving stratospheric dynamics. There is a trade-off between the size of the modeling domain and the grid resolution used in the CTM that is imposed by computational resources.

There are two major formulations of CTMs in current use. In the first approach, grid-based, or Eulerian, air quality models, the region to be modeled (the modeling domain) is subdivided into a three-dimensional array of grid cells. Spatial derivatives in the species continuity equations are cast in terms of finite-differences. A system of equations for the concentrations of all the chemical species in the model are solved numerically at each grid point. Time dependent continuity (mass conservation) equations are solved for each species including terms for transport, chemical production and destruction, and emissions and deposition (if relevant), in each cell. Chemical processes are simulated with ordinary differential equations, and transport processes are simulated with partial differential equations. Because of a number of factors such as the different time scales inherent in different processes, the coupled, nonlinear nature of the chemical process terms, and computer storage limitations, all of the terms in the equations are not solved simultaneously in three dimensions. Instead, operator splitting, in which terms in the continuity equation involving individual processes are solved sequentially, is used. In the second CTM formulation, trajectory or Lagrangian models, a large number of hypothetical air parcels are specified as following wind trajectories. In these models, the original system of partial differential equations is transformed into a system of ordinary differential equations.

A less common approach is to use a hybrid Lagrangian/Eulerian model, in which certain aspects of atmospheric chemistry and transport are treated with a Lagrangian approach and others are treaded in an Eulerian manner (Stein et al., 2000). Each approach has its advantages and disadvantages. The Eulerian approach is more general in that it includes processes that mix air parcels and allows integrations to be carried out for long periods during which individual air parcels lose their identity. There are, however, techniques for including the effects of mixing in Lagrangian models such as FLEXPART (e.g., Zanis et al., 2003), ATTILA (Reithmeier and Sausen, 2002), and CLaMS (McKenna et al., 2002).

B.5.1. Regional Scale Chemical-Transport Models

Major modeling efforts within the EPA center on the Community Multiscale Air Quality modeling system (CMAQ) (Byun and Ching, 1999; Byun and Schere, 2006). A number of other modeling platforms

using Lagrangian and Eulerian frameworks have been reviewed in the 1996 AQCD for O_3 (U.S. EPA, 1997) and in Russell and Dennis (2000). The capabilities of a number of CTMs designed to study local- and regional-scale air pollution problems are summarized by Russell and Dennis (2000). Evaluations of the performance of CMAQ are given in Arnold et al. (2003), Eder and Yu (2006), and Fuentes and Raftery (2005). The domain of CMAQ can extend from several hundred km to the hemispherical scale. In addition, both of these classes of models allow the resolution of the calculations over specified areas to vary. CMAQ is most often driven by the MM5 mesoscale meteorological model (Seaman, 2000), though it may be driven by other meteorological models (e.g., WRF, RAMS). Simulations of O_3 episodes over regional domains have been performed with a horizontal resolution as low as 1 km, and smaller calculations over limited domains have been accomplished at even finer scales. However, simulations at such high resolutions require better parameterizations of meteorological processes such as boundary layer fluxes, deep convection and clouds (Seaman, 2000), and finer-scale emissions. Finer spatial resolution is necessary to resolve features such as urban heat island circulations; sea, bay, and land breezes; mountain and valley breezes, and the nocturnal low-level jet.

The most common approach to setting up the horizontal domain is to nest a finer grid within a larger domain of coarser resolution. However, there are other strategies such as the stretched grid (e.g., Fox-Rabinovitz et al., 2002) and the adaptive grid. In a stretched grid, the grid's resolution continuously varies throughout the domain, thereby eliminating any potential problems with the sudden change from one resolution to another at the boundary. Caution should be exercised in using such a formulation, because certain parameterizations that are valid on a relatively coarse grid scale (such as convection) may not be valid on finer scales. Adaptive grids are not fixed at the start of the simulation, but instead adapt to the needs of the simulation as it evolves. They have the advantage that they can resolve processes at relevant spatial scales. However, they can be very slow if the situation to be modeled is complex. Additionally, if adaptive grids are used for separate meteorological, emissions, and photochemical models, there is no reason a priori why the resolution of each grid should match, and the gains realized from increased resolution in one model will be wasted in the transition to another model. The use of finer horizontal resolution in CTMs will necessitate finer-scale inventories of land use and better knowledge of the exact paths of roads, locations of factories, and, in general, better methods for locating sources and estimating their emissions.

The vertical resolution of these CTMs is variable, and usually configured to have higher resolution near the surface and decreasing aloft. Because the height of the boundary layer is of critical importance in simulations of air quality, improved resolution of the boundary layer height would likely improve air quality simulations. Additionally, current CTMs do not adequately resolve fine scale features such as the nocturnal low-level jet.

CTMs require time-dependent, three-dimensional wind fields for the period of simulation. The winds may be either generated by a model using initial fields alone or with four-dimensional data assimilation to improve the model's performance; fields (i.e., model equations can be updated periodically or "nudged," to bring results into agreement with observations. Modeling efforts typically focus on simulations of several days' duration, the typical time scale for individual O_3 episodes, but there have been several attempts at modeling longer periods. For example, Kasibhatla and Chameides (2000) simulated a four-month period from May to September of 1995 using MAQSIP. The current trend in modeling applications is towards annual simulations. This trend is driven in part by the need to better understand observations of periods of high wintertime PM (e.g., Blanchard et al., 2002) and the need to simulate O_3 episodes occurring outside of summer.

Chemical kinetics mechanisms (a set of chemical reactions) representing the important reactions occurring in the atmosphere are used in CTMs to estimate the rates of chemical formation and destruction of each pollutant simulated as a function of time. Unfortunately, chemical mechanisms that explicitly treat the reactions of each individual reactive species are too computationally demanding to be incorporated into CTMs. For example, a master chemical mechanism includes approximately 10,500 reactions involving 3603 chemical species (Jenkin et al., 2003). Instead, "lumped" mechanisms, that group compounds of similar chemistry together, are used. The chemical mechanisms used in existing

photochemical O_3 models contain significant uncertainties that may limit the accuracy of their predictions; the accuracy of each of these mechanisms is also limited by missing chemistry. Because of different approaches to the lumping of organic compounds into surrogate groups, chemical mechanisms can produce somewhat different results under similar conditions. The CB-IV chemical mechanism (Gery et al., 1989), the RADM II mechanism (Stockwell et al., 1990), the SAPRC (e.g., (Carter, 1990; Wang et al., 2000a; b) and the RACM mechanism (Stockwell et al. 1997) can be used in CMAQ. Jimenez et al. (2003b) provide brief descriptions of the features of the main mechanisms in use and they compared concentrations of several key species predicted by seven chemical mechanisms in a box model simulation over 24 h. The avg deviation from the avg of all mechanism predictions for O_3 and NO over the daylight period was less than 20%, and was 10% for NO_2 for all mechanisms. However, much larger deviations were found for HNO_3, PAN, HO_2, H_2O_2, C_2H_4, and C_5H_8 (isoprene). An analysis for OH radicals was not presented. The large deviations shown for most species imply differences between the calculated lifetimes of atmospheric species and the assignment of model simulations to either NO_X-limited or radical quantity limited regimes between mechanisms. Gross and Stockwell (2003) found small differences between mechanisms for clean conditions, with differences becoming more significant for polluted conditions, especially for NO_2 and organic peroxy radicals. They caution modelers to consider carefully the mechanisms they are using. Faraji et al. (2008) found differences of 40% in peak 1-h O_3 in the Houston-Galveston-Brazoria area between simulations using SAPRAC and CB4. They attributed differences in predicted O_3 concentrations to differences in the mechanisms of oxidation of aromatic hydrocarbons.

CMAQ and other CTMs (e.g., PM-CAM_X) incorporate processes and interactions of aerosol-phase chemistry (Mebust et al., 2003). There have also been several attempts to study the feedbacks of chemistry on atmospheric dynamics using meteorological models, like MM5 (e.g., Grell et al., 2000; Liu et al., 2001a; Liu et al., 2001b; Lu et al., 1997; Park et al., 2001b). This coupling is necessary to simulate accurately feedbacks such as may be caused by the heavy aerosol loading found in forest fire plumes (Lu et al., 1997; Park et al., 2001b), or in heavily polluted areas. Photolysis rates in CMAQ can now be calculated interactively with model produced O_3, NO_2, and aerosol fields (Binkowski et al., 2007).

Spatial and temporal characterizations of anthropogenic and biogenic precursor emissions must be specified as inputs to a CTM. Emissions inventories have been compiled on grids of varying resolution for many hydrocarbons, aldehydes, ketones, CO, NH_3, and NO_X. Emissions inventories for many species require the application of some algorithm for calculating the dependence of emissions on physical variables such as temperature and to convert the inventories into formatted emission files required by a CTM. For example, preprocessing of emissions data for CMAQ is done by the Spare-Matrix Operator Kernel Emissions (SMOKE) system. For many species, information concerning the temporal variability of emissions is lacking, so long-term (e.g., annual or O_3-season) averages are used in short-term, episodic simulations. Annual emissions estimates are often modified by the emissions model to produce emissions more characteristic of the time of day and season. Significant errors in emissions can occur if an inappropriate time dependence or a default profile is used. Additional complexity arises in model calculations because different chemical mechanisms are based on different species, and inventories constructed for use with another mechanism must be adjusted to reflect these differences. This problem also complicates comparisons of the outputs of these models because one chemical mechanism may produce some species not present in another mechanism yet neither may agree with the measurements.

In addition to wet deposition, dry deposition (the removal of chemical species from the atmosphere by interaction with ground-level surfaces) is an important removal process for pollutants on both urban and regional scales and must be included in CTMs. The general approach used in most models is the resistance in series method, in which where dry deposition is parameterized with a v_d , which is represented as $v_d = (r_a + r_b + r_c)^{-1}$ where r_a, r_b, and r_c represent the resistance due to atmospheric turbulence, transport in the fluid sublayer very near the elements of surface such as leaves or soil, and the resistance to uptake of the surface itself. This approach works for a range of substances, although it is inappropriate for species with substantial emissions from the surface or for species whose deposition to the surface depends on its concentration at the surface itself. The approach is also modified somewhat for aerosols: the terms r_b and r_c are replaced with a surface v_d to account for gravitational settling. In their

review, Wesely and Hicks (2000) point out several shortcomings of current knowledge of dry deposition. Among those shortcomings are difficulties in representing dry deposition over varying terrain where horizontal advection plays a significant role in determining the magnitude of r_a and difficulties in adequately determining a v_d for extremely stable conditions such as those occurring at night (e.g., Mahrt, 1998). Under the best of conditions, when a model is exercised over a relatively small area where dry deposition measurements have been made, models still commonly show uncertainties at least as large as ± 30% (e.g., Brook et al., 1996; Massman et al., 1994; Padro, 1996). Wesely and Hicks (2000) state that an important result of these comparisons is that the current level of sophistication of most dry deposition models is relatively low, and that deposition estimates therefore must rely heavily on empirical data. Still larger uncertainties exist when the surface features in the built environment are not well known or when the surface comprises a patchwork of different surface types, as is common in the eastern U.S..

The initial conditions, i.e., the concentration fields of all species computed by a model, and the boundary conditions, i.e., the concentrations of species along the horizontal and upper boundaries of the model domain throughout the simulation must be specified at the beginning of the simulation. It would be best to specify initial and boundary conditions according to observations. However, data for vertical profiles of most species of interest are sparse. The results of model simulations over larger, preferably global, domains can also be used. As may be expected, the influence of boundary conditions depends on the lifetime of the species under consideration and the time scales for transport from the boundaries to the interior of the model domain (Liu et al., 2001a; Liu et al., 2001b).

Each of the model components described above has an associated uncertainty, and the relative importance of these uncertainties varies with the modeling application. The largest errors in photochemical modeling are still thought to arise from the meteorological and emissions inputs to the model (Russell and Dennis, 2000). Within the model itself, horizontal advection algorithms are still thought to be significant source of uncertainty (e.g., Chock and Winkler, 1994), though more recently, those errors are thought to have been reduced (e.g., Odman and Ingram, 1996). There are also indications that problems with mass conservation continue to be present in photochemical and meteorological models (e.g.,(Odman and Russel, 1999); these can result in significant simulation errors. The effects of errors in initial conditions can be minimized by including several days “spin-up” time in a simulation to allow the model to be driven by emitted species before the simulation of the period of interest begins.

While the effects of poorly specified boundary conditions propagate through the model’s domain, the effects of these errors remain undetermined. Because many meteorological processes occur on spatial scales which are smaller than the model grid spacing (either horizontally or vertically) and thus are not calculated explicitly, parameterizations of these processes must be used and these introduce additional uncertainty.

Uncertainty also arises in modeling the chemistry of O_3 formation because it is highly nonlinear with respect to NO_X concentrations. Thus, the volume of the grid cell into which emissions are injected is important because the nature of O_3 chemistry (i.e., O_3 production or titration) depends in a complicated way on the concentrations of the precursors and the OH radical as noted earlier. The use of ever-finer grid spacing allows regions of O_3 titration to be more clearly separated from regions of O_3 production. The use of grid spacing fine enough to resolve the chemistry in individual power-plant plumes is too demanding of computer resources for this to be attempted in most simulations. Instead, parameterizations of the effects of sub-grid-scale processes such as these must be developed; otherwise serious errors can result if emissions are allowed to mix through an excessively large grid volume before the chemistry step in a model calculation is performed. In light of the significant differences between atmospheric chemistry taking place inside and outside of a power plant plume (Ryerson et al., 1998; Sillman, 2000), inclusion of a separate, meteorological module for treating large, tight plumes is necessary. Because the photochemistry of O_3 and many other atmospheric species is nonlinear, emissions correctly modeled in a tight plume may be incorrectly modeled in a more dilute plume. Fortunately, it appears that the chemical mechanism used to follow a plume’s development need not be as detailed as that used to simulate the rest of the domain, as the inorganic reactions are the most important in the plume see (e.g., Kumar and Russell, 1996). The need to include explicitly plume-in-grid chemistry only down to the level of the

smallest grid disappears if one uses the adaptive grid approach mentioned previously, though such grids are more computationally intensive. The differences in simulations are significant because they can lead to significant differences in the calculated sensitivity of O_3 to its precursors (e.g., Sillman, 1995).

Because the chemical production and loss terms in the continuity equations for individual species are coupled, the chemical calculations must be performed iteratively until calculated concentrations converge to within some preset criterion. The number of iterations and the convergence criteria chosen also can introduce error.

B.5.2. Intra-urban Scale Dispersion Modeling

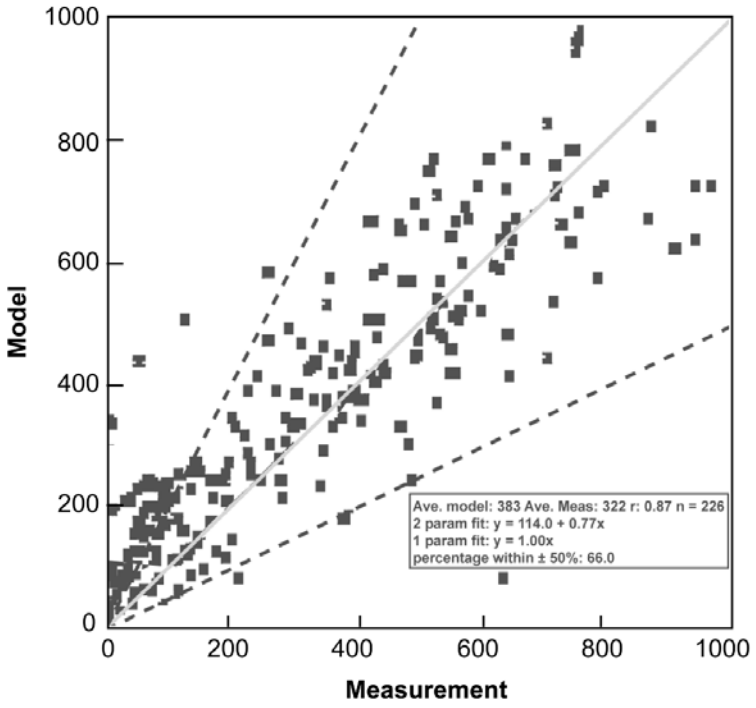
The grid spacing for regional applications of air quality CTMs, typically between 1 and 12 km^2, is usually too coarse to resolve spatial variations on urban neighborhood scales. The link between regional scale models and the population exposure models described in Annex C.2 is made with the classical dispersion models. Several models could be used to simulate concentration fields near local sources, each with its own set of strengths and weaknesses. For example, AERMOD is a steady-state plume model formulated by a committee of the American Meteorological Society and EPA as a replacement to the ISC3 dispersion model. (Technical information on the current version of AERMOD, including model evaluation databases, can be found at http://www.epa.gov/scram001/dispersion_prefrec.htm.) In the stable boundary layer (SBL), steady-state dispersion models like AERMOD assume the distributions of pollutant concentrations to be Gaussian in both the vertical and horizontal dimensions. In the convective boundary layer, the horizontal distribution is also assumed to be Gaussian, but the vertical distribution is described with a bi-Gaussian probability density function (pdf). Dispersion of emissions from line sources like highways is treated as the sum of emissions from a series of contiguous rectangular area or volume sources. AERMOD has provisions to be applied to flat and complex terrain, and with multiple source types including point, area, and volume sources in both urban and rural settings with air dispersion algorithms based on planetary boundary layer turbulence structure and scaling concepts. A large number of applications have been carried out and evaluated for both surface and elevated sources, and simple and complex terrain in rural and urban areas. However, AERMOD like similar models was not designed to treat the formation and dispersal of secondary products.

B.5.3. Global-scale CTMs

The importance of global transport of O_3 and O_3 precursors and their contribution to regional O_3 levels in the U.S. is slowly becoming apparent. There are presently on the order of 20 three-dimensional global models that have been developed by various groups to address problems in tropospheric chemistry. These models resolve synoptic meteorology, O_3-NO_X-CO-hydrocarbon photochemistry, have parameterizations for wet and dry deposition, and parameterize sub-grid scale vertical mixing processes such as convection. Global models have proven useful for testing and advancing scientific understanding beyond what is possible with observations alone. For example, they can calculate quantities of interest that cannot be measured directly, such as the export of pollution from one continent to the global atmosphere or the response of the atmosphere to future perturbations to anthropogenic emissions.

Global simulations are typically conducted at a horizontal resolution of about 200 km^2. Simulations of the effects of transport from long-range transport link multiple horizontal resolutions from the global to the local scale. Finer resolution will only improve scientific understanding to the extent that the governing processes are more accurately described at that scale. Consequently, there is a critical need for observations at the appropriate scales to evaluate the scientific understanding represented by the models.

During the recent IPCC-AR4 tropospheric chemistry study coordinated by the European Union project Atmospheric Composition Change: the European Network of excellence (ACCENT), 26 atmospheric CTMs were used to estimate the impacts of three emissions scenarios on global atmospheric composition, climate, and air quality in 2030 (Dentener et al., 2006a). All models were required to use anthropogenic emissions developed at IIASA (Dentener et al., 2005) and GFED version 1 biomass burning emissions (Van der Werf et al., 2003) as described in Stevenson et al. (2006). The base simulations from these models were evaluated against a suite of present-day observations. Most relevant to this assessment report are the evaluations with O_3 and NO_2, and for N and sulfur deposition (Dentener et al., 2006a; Stevenson et al., 2006; van Noije et al., 2006); see Figure B-3, sulfate deposition.



Source: Dentener et al. (2006a).

Figure B-3. Sulfate wet deposition (mg S/m²/yr) of the mean model versus measurements for the National Atmospheric Deposition Program (NADP) network. Dashed lines indicate factor of 2. The gray line is the result of a linear regression fitting through 0.

B.5.4. Modeling the Effects of Convection

The effects of deep convection can be simulated using cloud-resolving models, or in regional or global models in which the convection is parameterized. The Goddard Cumulus Ensemble (GCE) model (Tao and Simpson, 1993) has been used by Pickering et al. (1991; 1992; 1993; 1996), Scala et al. (1990), and Stenchikov et al. (1996) in the analysis of convective transport of trace gases. The cloud model is nonhydrostatic and contains a detailed representation of cloud microphysical processes. Two- and three-dimensional versions of the model have been applied in transport analyses. The initial conditions for the model are usually from a sounding of temperature, water vapor and winds representative of the region of storm development. Model-generated wind fields can be used to perform air parcel trajectory analyses and tracer advection calculations.

B.5.5. CTM Evaluation

The comparison of model predictions with ambient measurements represents a critical task for establishing the accuracy of photochemical models and evaluating their ability to serve as the basis for making effective control strategy decisions. The evaluation of a model's performance, or its adequacy to perform the tasks for which it was designed can only be conducted within the context of measurement errors and artifacts. Not only are there analytical problems, but there are also problems in assessing the representativeness of monitors at ground level for comparison with model values which represent typically an average over the volume of a grid box.

Evaluations of CMAQ are given in Arnold et al. (2003) and Fuentes and Raftery (2005). Discrepancies between model predictions and observations can be used to point out gaps in current understanding of atmospheric chemistry and to spur improvements in parameterizations of atmospheric chemical and physical processes. Model evaluation does not merely involve a straightforward comparison between model predictions and the concentration field of the pollutant of interest. Such comparisons may not be meaningful because it is difficult to determine if agreement between model predictions and observations truly represents an accurate treatment of physical and chemical processes in the CTM or the effects of compensating errors in complex model routines. Ideally, each of the model components (emissions inventories, chemical mechanism, meteorological driver) should be evaluated individually. However, this is rarely done in practice.

B.6. Sampling and Analysis of SO_X

B.6.1. Sampling and Analysis for SO_2

SO_2 molecules absorb ultraviolet (UV) light at one wavelength and emit UV light at longer wavelengths. This process is known as fluorescence, and involves the excitation of the SO_2 molecule to a higher energy (singlet) electronic state. Once excited, the molecule decays non-radiatively to a lower energy electronic state from which it then decays to the original, or ground, electronic state by emitting a photon of light at a longer wavelength (i.e., lower energy) than the original, incident photon. The process can be summarized by the following equations

$$SO_2 + h\nu_1 \rightarrow SO_2 *$$

$$SO_2 * \rightarrow SO_2 + h\nu_2$$

where SO_2* represents the excited state of SO_2, $h\nu_1$, and $h\nu_2$ represent the energy of the excitation and fluorescence photons, respectively, and $h\nu_2 < h\nu_1$. The intensity of the emitted light is proportional to the number of SO_2 molecules in the sample gas.

In commercial analyzers, light from a high intensity UV lamp passes through a bandwidth filter, allowing only photons with wavelengths around the SO_2 absorption peak (near 214 nm) to enter the optical chamber. The light passing through the source bandwidth filter is collimated (to improve image quality) using a UV lens and passes through the optical chamber, where it is detected on the opposite side of the chamber by the reference detector. A photomultiplier tube (PMT) is offset from and placed perpendicular to the light path to detect the SO_2 fluorescence. Since the SO_2 fluorescence (330 nm) is at a wavelength that is different from the excitation wavelength, an optical bandwidth filter is placed in front of the PMT to filter out any stray light from the UV lamp. A lens is located between the filter and the

PMT to focus the fluorescence onto the active area of the detector and optimize the fluorescence signal. The LOD for a non-trace level SO_2 analyzer is 10 ppb (CFR, 2006). The SO_2 measurement method is subject to both positive and negative interference.

B.6.1.1. Other Techniques for Measuring SO_2

A more sensitive SO_2 measurement method than the UV-fluorescence method was reported by Thornton et al. (2002), who reported use of an atmospheric pressure ionization mass spectrometer. The high measurement precision and instrument sensitivity were achieved by adding isotopically labeled SO_2 ($^{34}S^{16}O_2$) continuously to the manifold as an internal standard. Field studies showed that the method precision was better than 10% and the limit of detection was less than 1 ppt for a sampling interval of 1s.

SO_2 can be measured by LIF at around 220 nm (Matsumi et al., 2005). Because the laser wavelength is alternately tuned to an SO_2 absorption peak at 220.6 and trough at 220.2 nm, and the difference signal at the two wavelengths is used to extract the SO_2 concentration, the technique eliminates interference from either absorption or fluorescence by other species and has high sensitivity (5 ppt in 60 sec). SO_2 can also be measured by the same DOAS instrument that can measure NO_2.

Photoacoustic techniques have been employed for SO_2 detection, but they generally have detection limits suitable only for source monitoring (Gondal, 1997; Gondal and Mastromarino, 2001).

Chemical Ionization Mass Spectroscopy (CIMS) utilizes ionization via chemical reactions in the gas phase to determine an unknown sample's mass spectrum and identity. High sensitivity (10 ppt or better) has been achieved with uncertainty of ~15% when a charcoal scrubber is used for zeroing and the sensitivity is measured with isotopically labeled $^{34}SO_2$ (Hanke et al., 2003; Hennigan et al., 2006; Huey et al., 2004).

B.6.2. Sampling and Analysis for SO_4^{2-}, NO_3, and NH_4^+

Sulfate is commonly present in $PM_{2.5}$. Most $PM_{2.5}$ samplers have a size-separation device to separate particles so that only those particles approximately 2.5 μm or less are collected on the sample filter. Air is drawn through the sample filter at a controlled flow rate by a pump located downstream of the sample filter. The systems have two critical flow rate components for the capture of fine particulate: (1) the flow of air through the sampler must be at a flow rate that ensures that the size cut at 2.5 μm occurs; and (2) the flow rate must be optimized to capture the desired amount of particulate loading with respect to the analytical method detection limits.

When using the system described above to collect SO_4^{2-} sampling artifacts can occur because of: (1) positive sampling artifact for SO_4^{2-}, nitrate (NO_3), and particulate ammonium due to chemical reaction; and (2) negative sampling artifact for NO_3 and ammonium (NH_4^+) due to the decomposition and evaporation.

There are two major PM speciation ambient air-monitoring networks in the U.S.: the Speciation Trend Network (STN), and the Interagency Monitoring of Protected Visual Environments (IMPROVE) network. The current STN samplers include three filters: (1) Teflon for equilibrated mass and elemental analysis including elemental sulfur; (2) a HNO_3 denuded nylon filter for ion analysis including NO_3 and SO_4^{2-}, (3) a quartz-fiber filter for elemental and organic carbon. The IMPROVE sampler, which collects two 24-h samples per week, simultaneously collects one sample of PM_{10} on a Teflon filter, and three samples of $PM_{2.5}$ on Teflon, nylon, and quartz filters. $PM_{2.5}$ mass concentrations are determined gravimetrically from the $PM_{2.5}$ Teflon filter sample. The $PM_{2.5}$ Teflon filter sample is also used to determine concentrations of selected elements. The $PM_{2.5}$ nylon filter sample, which is preceded by a denuder to remove acidic gases, is analyzed to determine NO_3 and sulfate aerosol concentrations. Finally, the $PM_{2.5}$ quartz filter sample is analyzed for OC and EC using the thermal-optical reflectance (TOR)

method. The STN and the IMPROVE networks represent a major advance in the measurement of NO_3, because the combination of a denuder (coated with either sodium carbonate [Na_2CO_3] or MgO) to remove HNO_3 vapor and a Nylon filter to adsorb HNO_3 vapor volatilizing from the collected ammonium nitrate particles overcomes the loss of NO_3 from Teflon filters.

The extent to which sampling artifacts for particulate NH_4^+ have been adequately addressed in the current networks is not clear. Recently, new denuder-filter sampling systems have been developed to measure SO_4^{2-}, NO_3, and NH_4^+ with an adequate correction of NH_4^+ sampling artifacts. The denuder-filter system, Chembcomb Model 3500 speciation sampling cartridge developed by Rupprecht & Patashnick Co, Inc. could be used to collect NO_3, SO_4^{2-}, and NH_4^+ simultaneously. The sampling system contains a single-nozzle size-selective inlet, two honeycomb denuders, the aerosol filter and two backup filters (Keck and Wittmaack, 2005). The first denuder in the system is coated with 0.5% Na_2CO_3 and 1% glycerol and collects acid gases such as HCl, SO_2, HONO, and HNO_3. The second denuder is coated with 0.5% phosphoric acid in methanol for collecting NH_3. Backup filters collect the gases behind denuded filters. The backup filters are coated with the same solutions as the denuders. A similar system based on the same principle was applied by Possanzini et al. (1999). The system contains two NaCl-coated annular denuders followed by other two denuders coated with Na_2CO_3/glycerol and citric acid, respectively. This configuration was adopted to remove HNO_3 quantitatively on the first NaCl denuder. The third and fourth denuders remove SO_2 and NH_3, respectively. A polyethylene cyclone and a two-stage filter holder containing three filters is placed downstream of the denuders. Aerosol fine particles are collected on a Teflon membrane. A backup nylon filter and a subsequent citric acid impregnated filter paper collect dissociation products (HNO_3 and NH_3) of ammonium nitrate evaporated from the filtered particulate matter.

Several traditional and new methods could be used to quantify elemental S collected on filters: energy dispersive X-ray fluorescence, synchrotron induced X-ray fluorescence, proton induced X-ray emission (PIXE), total reflection X-ray fluorescence, and scanning electron microscopy. Energy dispersive X-ray fluorescence (EDXRF)(Method IO-3.3, EPA, 1997b; see 2004 PM CD for details) and PIXE are the most commonly used methods. Since sample filters often contain very small amounts of particle deposits, preference is given to methods that can accommodate small sample sizes and require little or no sample preparation or operator time after the samples are placed into the analyzer. X-ray fluorescence (XRF) meets these needs and leaves the sample intact after analysis so it can be submitted for additional examinations by other methods as needed. To obtain the greatest efficiency and sensitivity, XRF typically places the filters in a vacuum which may cause volatile compounds (nitrates and organics) to evaporate. As a result, species that can volatilize such as ammonium nitrate and certain organic compounds can be lost during the analysis. The effects of this volatilization are important if the PTFE filter is to be subjected to subsequent analyses of volatile species.

Polyatomic ions such as SO_4^{2-}, NO_3, and NH_4^+ are quantified by methods such as ion chromatography (IC) (an alternative method commonly used for NH_4^+ analysis is automated colorimetry). All ion analysis methods require a fraction of the filter to be extracted in deionized distilled water for SO_4^{2-} and Na_2CO_3/$NaHCO_3$ solution for NO_3 and then filtered to remove insoluble residues prior to analysis. The extraction volume should be as small as possible to avoid over-diluting the solution and inhibiting the detection of the desired constituents at levels typical of those found in ambient $PM_{2.5}$ samples. During analysis, the sample extract passes through an ion-exchange column which separates the ions in time for individual quantification, usually by an electroconductivity detector. The ions are identified by their elution/retention times and are quantified by the conductivity peak area or peak height.

In a side-by-side comparison of two of the major aerosol monitoring techniques (Hains et al., 2007), $PM_{2.5}$ mass and major contributing species were well correlated among the different methods with correlation coefficients in excess of 0.8. Agreement for mass, SO_4^{2-}, OC, TC, and NH_4^+ was good while that for NO_3 and BC was weaker. Based on reported uncertainties, however, even daily concentrations of $PM_{2.5}$ mass and major contributing species were often significantly different at the 95% confidence level. Greater values of $PM_{2.5}$ mass and individual species were generally reported from Speciation Trends Network methods than from the Desert Research Institute Sequential Filter Samplers. These differences

can only be partially accounted for by known random errors. The authors concluded that the current uncertainty estimates used in the STN network may underestimate the actual uncertainty.

The reaction of SO_2 (and other acid gases) with basic sites on glass fiber filters or with basic coarse particles on the filter leads to the formation of SO_4^{2-} (or other nonvolatile salts, e.g., NO_3, chloride). These positive artifacts lead to the overestimation of total mass, and SO_4^{2-}, and probably also NO_3 concentrations. These problems were largely overcome by changing to quartz fiber or Teflon filters and by the separate collection of $PM_{2.5}$. However, the possible reaction of acidic gases with basic coarse particles remains a possibility, especially with PM_{10} and $PM_{10-2.5}$ measurements. These positive artifacts could be effectively eliminated by removing acidic gases in the sampling line with denuders coated with NaCl or Na_2CO_3.

Positive sampling artifacts also occur during measurement of particulate NH_4^+. The reaction of NH_3 with acidic particles (e.g. $2NH_3 + H_2SO_4 \rightarrow (NH_4)_2SO_4$), either during sampling or during transportation, storage, and equilibration could lead to an overestimation of particulate NH_4^+ concentrations. Techniques have been developed to overcome this problem: using a denuder to remove NH_3 during sampling and to protect the collected PM from NH_3 (Brauer et al., 1991; Keck and Wittmaack, 2006; 1988b; Koutrakis et al., 1988a; Possanzini et al., 1999; Suh et al., 1992; Winberry et al., 1999). Hydrogen fluoride, citric acid, and phosphorous acids have been used as coating materials for the NH_3 denuder. Positive artifacts for particulate NH_4^+ can also be observed during sample handling due to contamination. No chemical analysis method, no matter how accurate or precise, can adequately represent atmospheric concentrations if the filters to which these methods are applied are improperly handled. Ammonia is emitted directly from human sweat, breath and smoking. It can then react with acidic aerosols on the filter to form ammonium sulfate, ammonium bisulfate and ammonium nitrate if the filter was not properly handled (Sutton et al., 2000). Therefore, it is important to keep filters away from NH_3 sources, such as human breath, to minimize neutralization of the acidic compounds. Also, when filters are handled, preferably in a glove box, the analyst should wear gloves that are antistatic and powder-free to act as an effective contamination barrier.

Continuous methods for the quantification of aerosol S compounds first remove gaseous S (e.g., SO_2, H_2S) from the sample stream by a diffusion tube denuder followed by the analysis of particulate S (Cobourn et al., 1978; Durham et al., 1978; Huntzicker et al., 1978; Tanner et al., 1980). Another approach is to measure total S and gaseous S separately by alternately removing particles from the sample stream. Particulate S is obtained as the difference between the total and gaseous S (Kittelson et al., 1978). The total S content is measured by a flame photometric detector (FPD) by introducing the sampling stream into a fuel-rich, hydrogen-air flame (e.g., Farwell and Rasmussen, 1976; Stevens et al., 1969) that reduces sulfur compounds and measures the intensity of the chemiluminescence from electronically excited sulfur molecules (S_2*). Because the formation of S_2* requires two S atoms, the intensity of the chemiluminescence is theoretically proportional to the square of the concentration of molecules that contain a single S atom. In practice, the exponent is between 1 and 2 and depends on the S compound being analyzed (Dagnall et al., 1967; Stevens et al., 1971). Calibrations are performed using both particles and gases as standards. The FPD can also be replaced by a chemiluminescent reaction with O_3 that minimizes the potential for interference and provides a faster response time (Benner and Stedman, 1989; 1990). Capabilities added to the basic system include in situ thermal analysis and sulfuric acid speciation (Cobourn et al., 1978; Cobourn and Husar, 1982; Huntzicker et al., 1978; Tanner et al., 1980). Sensitivities for particulate S as low as 0.1 $\mu g/m^3$, with time resolution ranging from 1 to 30 min, have been reported. Continuous measurements of particulate S content have also been obtained by on-line XRF analysis with resolution of 30 min or less (Jaklevic et al., 1981). During a field-intercomparison study of five different S instruments, Camp et al. (1982) reported four out of five FPD systems agreed to within ± 5% during a 1-week sampling period.

Annex C. Modeling Human Exposure

C.1. Introduction

Predictive (or prognostic) exposure modeling studies are assessments that start from emissions and demographic information and explicitly consider the physical and chemical processes of environmental and microenvironmental transport and fate, in conjunction with human activities, to estimate inhalation intake and uptake. This type of comprehensive modeling effort, although conducted for other pollutants, has not previously been undertaken for SO_2[1]. Previous efforts for SO_2 exposure assessment have relied on statistical (diagnostic) analyses that have been reported using data obtained in various field exposure studies. However, existing prognostic modeling systems for the assessment of inhalation exposures can in principle be directly applied to, or adapted for, SO_2 studies; specifically, such systems include APEX, SHEDS, and MENTOR-1A, to be discussed in the following sections. Nevertheless, it should be mentioned that such applications will be constrained by data limitations, such as the degree of ambient concentration characterization (e.g., concentrations at the local level) and quantitative information on indoor sources and sinks.

Predictive models of human exposure to ambient air pollutants such as SO_2 can be classified and differentiated based upon a variety of attributes. For example, exposure models can be classified as:

- models of potential (typically maximum) outdoor exposure versus models of actual exposures (the latter including locally modified microenvironmental exposures, both outdoor and indoor);
- Population Based Exposure Models (PBEM) versus Individual Based Exposure Models (IBEM);
- deterministic versus probabilistic (or statistical) exposure models; and
- observation-driven versus mechanistic air quality models (see Section C.4 for discussions about the construction, uses and limitations of this class of mathematical models.

Some points should be made regarding terminology and essential concepts in exposure modeling, before proceeding to the overview of specific developments reported in the current research literature:

First, it must be understood that there is significant variation in the definitions of many of the terms used in the exposure modeling literature; indeed, the science of exposure modeling is a rapidly evolving field and the development of a standard and commonly accepted terminology is an ongoing process (e.g., WHO, 2004).

Second, it should also be mentioned that, very often, procedures that are called exposure modeling, exposure estimation, etc. in the scientific literature, may in fact refer to only a sub-set of the complete set of steps or components required for a comprehensive exposure assessment. For example, certain self-identified exposure modeling studies focus solely on refining the sub-regional or local spatio-temporal dynamics of pollutant concentrations (starting from raw data representing monitor observations or regional grid-based model estimates). Though not exposure studies per se, such efforts have value and are included in the discussion of the next sub-section, as they provide potentially useful tools that can be used in a complete exposure assessment. On the other hand, formulations which are self-identified as exposure models but actually focus only on ambient air quality predictions, such as chemical-transport models, are not included in the discussion that follows.

Third, the process of modeling human exposures to ambient pollutants is very often identified explicitly with population-based modeling, while models describing the specific mechanisms affecting the

[1] OAQPS is proposing to apply the APEX exposure model to SO_2 as part of this NAAQS review.

exposure of an actual individual (at specific locations) to an air contaminant (or to a group of co-occurring gas and/or aerosol phase pollutants) are usually associated with studies focusing specifically on indoor air chemistry modeling.

Finally the concept of microenvironments, introduced in earlier sections of this document, should be clarified further, as it is critical in developing procedures for exposure modeling. In the past, microenvironments have typically been defined as individual or aggregate locations (and sometimes even as activities taking place within a location) where a homogeneous concentration of the pollutant is encountered. Thus a microenvironment has often been identified with an ideal (i.e. perfectly mixed) compartment of classical compartmental modeling. More recent and general definitions view the microenvironment as a control volume, either indoors or outdoors, that can be fully characterized by a set of either mechanistic or phenomenological governing equations, when appropriate parameters are available, given necessary initial and boundary conditions. The boundary conditions typically would reflect interactions with ambient air and with other microenvironments. The parameterizations of the governing equations generally include the information on attributes of sources and sinks within each microenvironment. This type of general definition allows for the concentration within a microenvironment to be non-homogeneous (non-uniform), provided its spatial profile and mixing properties can be fully predicted or characterized. By adopting this definition, the number of microenvironments used in a study is kept manageable, but variability in concentrations in each of the microenvironments can still be taken into account. Microenvironments typically used to determine exposure include indoor residential microenvironments, other indoor locations (typically occupational microenvironments), outdoors near roadways, other outdoor locations, and in-vehicles. Outdoor locations near roadways are segregated from other outdoor locations (and can be further classified into street canyons, vicinities of intersections, etc.) because emissions from automobiles alter local concentrations significantly compared to background outdoor levels. Indoor residential microenvironments (kitchen, bedroom, living room, etc. or aggregate home microenvironment) are typically separated from other indoor locations because of the time spent there and potential differences between the residential environment and the work/public environment.

Once the actual individual and relevant activities and locations (for Individual Based Modeling), or the sample population and associated spatial (geographical) domain (for Population Based Modeling) have been defined along with the temporal framework of the analysis (time period and resolution), the comprehensive modeling of individual/population exposure to SO_2 (and related pollutants) will in general require seven steps (or components, as some of them do not have to be performed in sequence) that are listed below. This list represents a composite based on approaches and frameworks described in the literature over the last twenty-five years (WHO). 2005; EPA, 1992; 1997a; Georgopoulos and Lioy, 1994; Georgopoulos et al., 2005; Georgopoulos and Lioy, 2006; Ott, 1982; Price et al., 2003) as well as on the structure of various inhalation exposure models that have been used in the past or in current studies to specifically assess inhalation exposures. Figure C-1, adapted from Georgopoulos et al. (2005), schematically depicts the sequence of steps summarized here.

1) Estimation of the background or ambient levels of both SO_2 and related pollutants. This is done through either (or a combination of):

   a) multivariate spatio-temporal analysis of fixed monitor data, or

   b) emissions-based, photochemical, air quality modeling (typically with a regional, grid-based model such as Models-3/CMAQ or CAM_X) applied in a coarse resolution mode.

2) Estimation of local outdoor pollutant levels of both SO_2 and related pollutants. These levels could typically characterize the ambient air of either an administrative unit (such as a census tract, a municipality, a county, etc.) or a conveniently defined grid cell of an urban scale air quality model. Again, this may involve either (or a combination of):

a) spatio-temporal statistical analysis of monitor data, or

b) application of either an intra-urban scale dispersion model (such as AERMOD or CALPUFF) or an urban multi-scale, grid based model (such as CMAQ or CAM_X) at its highest resolution (typically around 2-4 km), or

c) correction of the estimates of the regional model using some scheme that adjusts for observations and/or for subgrid chemistry and mixing processes.

3) Characterization of relevant attributes of the individuals or populations under study (residence and work locations, occupation, housing data, income, education, age, gender, race, weight, and other physiological characteristics). For Population Based Exposure Modeling (PBEM) one can either:

a) select a fixed-size sample population of virtual individuals in a way that statistically reproduces essential demographics (age, gender, race, occupation, income, education) of the administrative population unit used in the assessment (e.g., a sample of 500 people is typically used to represent the demographics of a given census tract, whereas a sample of about 10,000 may be needed to represent the demographics of a county), or

b) divide the population-of interest into a set of cohorts representing selected subpopulations where the cohort is defined by characteristics known to influence exposure.

4) Development of activity event (or exposure event) sequences for each member of the sample population (actual or virtual) or for each cohort for the exposure period. This could utilize:

a) study-specific information, if available

b) existing databases based on composites of questionnaire information from past studies

c) time-activity databases, typically in a format compatible with EPA's Consolidated Human Activity Database (McCurdy et al., 2000)

5) Estimation of levels and temporal profiles of both SO_2 and related pollutants in various outdoor and indoor microenvironments such as street canyons, roadway intersections, parks, residences, offices, restaurants, vehicles, etc. This is done through either:

a) linear regression of available observational data sets,

b) simple mass balance models (with linear transformation and sinks) over the volume (or a portion of the volume) of the microenvironment,

c) lumped (nonlinear) gas or gas/aerosol chemistry models, or

d) detailed combined chemistry and Computational Fluid Dynamics modeling.

6) Calculation of appropriate inhalation rates for the members of the sample population, combining the physiological attributes of the (actual or virtual) study subjects and the activities pursued during the individual exposure events.

7) Calculation of target tissue dose through biologically based modeling estimation (specifically, respiratory dosimetry modeling in the case of SO_2 and related reactive pollutants) if sufficient information is available.

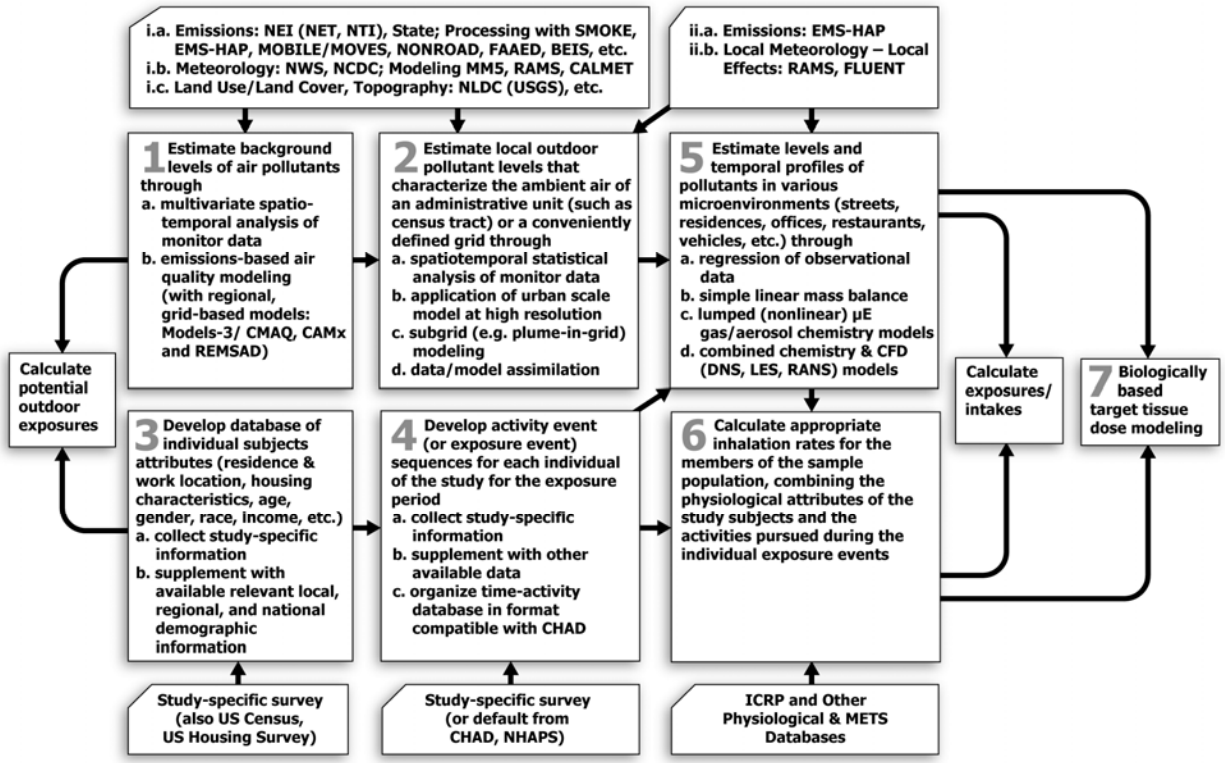


Figure C-1. Schematic description of a general framework identifying the processes (steps or components) involved in assessing inhalation exposures and doses for individuals and populations. In general terms, existing comprehensive exposure modeling systems such as SHEDS, APEX, and MENTOR-1A follow this framework.

Implementation of the above framework for comprehensive exposure modeling has benefited significantly from recent advances and expanded availability of computational technologies such as Relational Database Management Systems (RDBMS) and Geographic Information Systems (GIS) (Georgopoulos et al., 2005; Purushothaman and Georgopoulos, 1997; 1999b; a).

In fact, only relatively recently comprehensive, predictive, inhalation exposure modeling studies for O_3, PM, and various air toxics, have attempted to address/incorporate all the components of the general framework described here. In practice, the majority of past exposure modeling studies have either incorporated only subsets of these components or treated some of them in a simplified manner, often focusing on the importance of specific factors affecting exposure. Of course, depending on the objective of a particular modeling study, implementation of only a limited number of steps may be necessary. For example, in a regulatory setting, when comparing the relative effectiveness of emission control strategies, the focus can be on expected changes in ambient levels (corresponding to those observed at NAAQS monitors) in relation to the density of nearby populations. The outdoor levels of pollutants, in conjunction with basic demographic information, can thus be used to calculate upper bounds of population exposures associated with ambient air (as opposed to total exposures that would include contributions from indoor

sources) useful in comparing alternative control strategies. Though the metrics derived would not be quantitative indicators of actual human exposures, they can serve as surrogates of population exposures associated with outdoor air, and thus aid in regulatory decision making concerning pollutant standards and in studying the efficacy of emission control strategies. This approach has been used in studies performing comparative evaluations of regional and local emissions reduction strategies in the eastern U.S. (Foley et al., 2003; Georgopoulos et al., 1997; Purushothaman and Georgopoulos, 1997).

C.2. Population Exposure Models: Their Evolution and Current Status

Existing comprehensive inhalation exposure models consider the trajectories of individual human subjects (actual or virtual), or of appropriately defined cohorts, in space and time as sequences of exposure events. In these sequences, each event is defined by time, a geographic location, a microenvironment, and the activity of the subject. EPA offices (OAQPS and NERL) have supported the most comprehensive efforts in developing models implementing this general concept (see, e.g., Johnson, 2002). These families of models are the result: National Exposure Model and Probabilistic National Exposure Model (NEM/pNEM, Whitfield et al., 1997) Hazardous Air Pollutant Exposure Model (HAPEM, Rosenbaum, 2005); Simulation of Human Exposure and Dose System (SHEDS, Burke et al., 2001); Air Pollutants Exposure Model (APEX, EPA, 2006b); and Modeling Environment for Total Risk Studies (MENTOR, Georgopoulos et al., 2005; Georgopoulos and Lioy, 2006). European efforts have produced some formulations with similar general attributes as the above U.S. models but, generally, involving simplifications in some of their components. Examples of European models addressing exposures to photochemical oxidants (specifically, O_3) include the Air Pollution Exposure Model (AirPEx, Freijer et al., 1998), which basically replicates the pNEM approach and has been applied to the Netherlands, and the Air Quality Information System Model (AirQUIS, Clench-Aas et al., 1999).

The NEM/pNEM, SHEDS, APEX, and MENTOR for One-Atmosphere studies (MENTOR-1A) families of models provide exposure estimates defined by concentration and breathing rate for each individual exposure event, and then average these estimates over periods typically ranging from one hour to one year. These models allow simulation of certain aspects of the variability and uncertainty in the principal factors affecting exposure. An alternative approach is taken by the HAPEM family of models that typically provide annual avg exposure estimates based on the quantity of time spent per year in each combination of geographic locations and microenvironments. The NEM, SHEDS, APEX, and MENTOR-type models are therefore expected to be more appropriate for pollutants with complex chemistry such as SO_2, and could provide useful information for enhancing related health assessments.

More specifically, regarding the consideration of population demographics and activity patterns:

- pNEM divides the population of interest into representative cohorts based on the combinations of demographic characteristics (age, gender, and employment), home/work district, residential cooking fuel and replicate number, and then assigns an activity diary record from the CHAD to each cohort according to demographic characteristic, season, day-type (weekday/weekend) and temperature.
- HAPEM6 divides the population of interest into demographic groups based on age, gender and race, and then for each demographic group/day-type (weekday/weekend) combination, selects multiple activity patterns randomly (with replacement) from CHAD and combines them to find the averaged annual time allocations for group members in each census tract for different day types.
- SHEDS, APEX, and MENTOR-1A generate population demographic files, which contain a user-defined number of person records for each census tract of the population based on proportions of characteristic variables (age, gender, employment, and housing) obtained

from the population of interest, and then assign a matching activity diary record from CHAD to each individual record of the population based on the characteristic variables. It should be mentioned that, in the formulations of these models, workers may commute from one census tract to another census tract for work. So, with the specification of commuting patterns, the variation of exposure concentrations due to commuting between different census tracts can be captured.

The conceptual approach originated by the SHEDS models was modified and expanded for use in the development of MENTOR-1A. Flexibility was incorporated into this modeling system, such as the option of including detailed indoor chemistry and other relevant microenvironmental processes, and providing interactive linking with CHAD for consistent definition of population characteristics and activity events (Georgopoulos et al., 2005).

Table C-1. The Essential Attributes of the pNEM, HAPEM, APEX, SHEDS, and MENTOR-1A

	pNEM	HAPEM	APEX	SHEDS	MENTOR-1A
Exposure Estimate	Hourly averaged	Annual averaged	Hourly averaged	Activity event based	Activity event based
Characterization of the High-End Exposures	Yes	No	Yes	Yes	Yes
Typical Spatial Scale/Resolution	Urban areas/Census tract level	Ranging from urban to national/ Census tract level	Urban area/Census tract level	Urban areas/Census tract level	Multiscale/ Census tract level
Temporal Scale/Resolution	Annual / one hour	Annual / one hour	Annual / one hour	Annual / event based	Annual / activity event based time step
Population Activity Patterns Assembly	Top-down approach	Top-down approach	Bottom-up "person-oriented" approach	Bottom-up "person-oriented" approach	Bottom-up "person-oriented" approach
Microenvironment Concentration Estimation	Non-steady-state and steady-state mass balance equations (hard-coded)	Linear relationship method (hard-coded)	Non-steady-state mass balance and linear regression (flexibility of selecting algorithms)	Steady-state mass balance equation (residential) and linear regression (non-residential) (hard-coded)	Non-steady-state mass balance equation with indoor air chemistry module or regression methods (flexibility of selecting algorithms)
Microenvironmental (ME) Factors	Random samples from probability distributions	Random samples from probability distributions	Random samples from probability distributions	Random samples from probability distributions	Random samples from probability distributions
Specification of Indoor Source Emissions	Yes (gas-stove, tobacco smoking)	Available; set to zero in HAPEM6	Yes (multiple sources defined by the user)	Yes (gas-stove, tobacco smoking, other sources)	Yes (multiple sources defined by the user)
Commuting Patterns	Yes	Yes	Yes	Yes	Yes
Exposure Routes	Inhalation	Inhalation	Inhalation	Inhalation	Multiple (optional)
Potential Dose Calculation	Yes	No	Yes	Yes	Yes
Physiologically Based Dose	No	No	No	Yes	Yes
Variability/Uncertainty	Yes	No	Yes	Yes	Yes (Various "Tools")

The essential attributes of the pNEM, HAPEM, APEX, SHEDS, and MENTOR-1A models are elaborated in Table C-1.

NEM/pNEM implementations have been extensively applied to O_3 studies in the 1980s and 1990s. The historical evolution of the pNEM family of models of OAQPS started with the introduction of the first NEM model in the 1980s (Biller et al., 1981). The first such implementations of pNEM/O_3 in the 1980s used a regression-based relationship to estimate indoor O_3 concentrations from outdoor concentrations. The second generation of pNEM/O_3 was developed in 1992 and included a simple mass balance model to estimate indoor O_3 concentrations. A report by Johnson (2002) describes this version of pNEM/O_3 and summarizes the results of an initial application of the model to 10 cities. Subsequent enhancements to pNEM/O_3 and its input databases included revisions to the methods used to estimate equivalent ventilation rates, to determine commuting patterns, and to adjust ambient O_3 levels to simulate attainment of proposed NAAQS. During the mid-1990s, the EPA applied updated versions of pNEM/O_3 to three different population groups in selected cities: (1) the general population of urban residents, (2) outdoor workers, and (3) children who tend to spend more time outdoors than the average child. This version of pNEM/O_3 used a revised probabilistic mass balance model to determine O_3 concentrations over one-h periods in indoor and in-vehicle microenvironments (Johnson, 2002).

In recent years, pNEM has been replaced by (or "evolved to") the APEX. APEX differs from earlier pNEM models in that the probabilistic features of the model are incorporated into a Monte Carlo framework (U.S. EPA, 2006; Langstaff, 2007). Like SHEDS and MENTOR-1A, instead of dividing the population-of-interest into a set of cohorts, APEX generates individuals as if they were being randomly sampled from the population. APEX provides each generated individual with a demographic profile that specifies values for all parameters required by the model. The values are selected from distributions and databases that are specific to the age, gender, and other specifications stated in the demographic profile. The EPA has applied APEX to the study of exposures to O_3 and other criteria pollutants; APEX can be modified and used for the estimation of SO_2 exposures, if required.

Reconfiguration of APEX for use with SO_2 or other pollutants would require significant literature review, data analysis, and modeling efforts. Necessary steps include determining spatial scope and resolution of the model; generating input files for activity data, air quality and temperature data; and developing definitions for microenvironments and pollutant-microenvironment modeling parameters (penetration and proximity factors, indoor source emissions rates, decay rates, etc.) (ICF Consulting, 2005). To take full advantage of the probabilistic capabilities of APEX, distributions of model input parameters should be used wherever possible.

C.3. Ambient Concentrations of SO_2 and Related Air Pollutants

As mentioned earlier, background and regional outdoor concentrations of pollutants over a study domain may be estimated through emissions-based mechanistic modeling, through ambient data based modeling, or through a combination of both. Emissions-based models calculate the spatio-temporal fields of the pollutant concentrations using precursor emissions and meteorological conditions as inputs and using numerical representations of transformation reactions to drive outputs. The ambient data based models typically calculate spatial or spatio-temporal distributions of the pollutant through the use of interpolation schemes, based on either deterministic or stochastic models for allocating monitor station observations to the nodes of a virtual regular grid covering the region of interest. The geostatistical technique of kriging provides various standard procedures for generating an interpolated spatial distribution for a given time, from data at a set of discrete points. Kriging approaches were evaluated by Georgopoulos et al. (1997) in relation to the calculation of local ambient O_3 concentrations for exposure assessment purposes, using either monitor observations or regional/urban photochemical model outputs. It was found that kriging is severely limited by the nonstationary character of the concentration patterns of reactive pollutants; so the advantages of this method in other fields of geophysics do not apply here. The

above study showed that the appropriate semivariograms had to be hour-specific, complicating the automated reapplication of any purely spatial interpolation over an extended time period.

Spatio-temporal distributions of pollutant concentrations such as O_3, PM, and various air toxics have alternatively been obtained using methods of the Spatio-Temporal Random Field (STRF) theory (Christakos and Hristopulos, 1998). The STRF approach interpolates monitor data in both space and time simultaneously. This method can thus analyze information on temporal trends which cannot be incorporated directly in purely spatial interpolation methods such as standard kriging. Furthermore, the STRF method can optimize the use of data which are not uniformly sampled in either space or time. STRF was further extended within the Bayesian Maximum Entropy (BME) framework and applied to O_3 interpolation studies (Christakos and Hristopulos, 1998; Christakos and Kolovos, 1999; Christakos, 2000). It should be noted that these studies formulate an over-arching scheme for linking air quality with population dose and health effects; however, they are limited by the fact that they do not include any microenvironmental effects. MENTOR has incorporated STRF/BME methods as one of the steps for performing a comprehensive analysis of exposure to O_3 and PM (Georgopoulos et al., 2005).

The issue of subgrid variability (SGV) from the perspective of interpreting and evaluating the outcomes of grid-based, multiscale, photochemical air quality simulation models is discussed in Ching et al. (2006), who suggest a framework that can provide for qualitative judgments on model performance based on comparing observations to the grid predictions and its SGV distribution. From the perspective of Population Exposure Modeling, the most feasible/practical approach for treating subgrid variability of local concentrations is probably through 1) the identification and proper characterization of an adequate number of outdoor microenvironments (potentially related to different types of land use within the urban area as well as to proximity to different types of roadways) and 2) then, concentrations in these microenvironments will have to be adjusted from the corresponding local background ambient concentrations through either regression of empirical data or various types of local atmospheric dispersion/transformation models. This is discussed further in the next section.

C.4. Characterization of Microenvironmental Concentrations

Once the background and local ambient spatio-temporal concentration patterns have been derived, microenvironments that can represent either outdoor or indoor settings when individuals come in contact with the contaminant of concern (e.g., SO_2) must be characterized. This process can involve modeling of various local sources and sinks, and interrelationships between ambient and microenvironmental concentration levels. Three general approaches have been used in the past to model microenvironmental concentrations:

- Empirical (typically linear regression) fitting of data from studies relating ambient/local and microenvironmental concentration levels to develop analytical relationships.
- Parameterized mass balance modeling over, or within, the volume of the microenvironment. This type of modeling has ranged from very simple formulations, i.e. from models assuming ideal (homogeneous) mixing within the microenvironment (or specified portions of it) and only linear physicochemical transformations (including sources and sinks), to models incorporating analytical solutions of idealized dispersion formulations (such as Gaussian plumes), to models that take into account aspects of complex multiphase chemical and physical interactions and nonidealities in mixing.
- Detailed Computational Fluid Dynamics (CFD) modeling of the outdoor or indoor microenvironment, employing either a Direct Numerical Simulation (DNS) approach, a Reynolds Averaged Numerical Simulation (RANS) approach, or a Large Eddy Simulation

(LES) approach, the latter typically for outdoor situations (see, e.g., Chang and Meroney, 2003; Chang, 2006; Milner et al., 2005).

Parameterized mass balance modeling is the approach currently preferred for exposure modeling for populations. As discussed earlier, the simplest microenvironmental setting corresponds to a homogeneously mixed compartment, in contact with possibly both outdoor/local environments as well as other microenvironments. The air quality of this idealized microenvironment is affected mainly by the following processes:

- Transport processes: These can include advection/convection and dispersion that are affected by local processes and obstacles such as vehicle induced turbulence, street canyons, building structures, etc.
- Sources and sinks: These can include local outdoor emissions, indoor emissions, surface deposition, etc.
- Transformation processes: These can include local outdoor as well as indoor gas and aerosol phase chemistry, such as formation of secondary organic and inorganic aerosols.

Exposure modeling also requires information on activity patterns to determine time spent in various microenvironments and estimates of inhalation rates to characterize dose. The next two subsections describe recent work done in these areas.

C.4.1. Characterization of Activity Events

An important development in inhalation exposure modeling has been the consolidation of existing information on activity event sequences in the Consolidated Human Activity Database (CHAD) (McCurdy et al., 2000; McCurdy, 2000). Indeed, most recent exposure models are designed (or have been re-designed) to obtain such information from CHAD which incorporates 24-h time/activity data developed from numerous surveys. The surveys include probability-based recall studies conducted by EPA and the California Air Resources Board, as well as real-time diary studies conducted in individual U.S. metropolitan areas using both probability-based and volunteer subject panels. All ages of both genders are represented in CHAD. The data for each subject consist of one or more days of sequential activities, in which each activity is defined by start time, duration, activity type (140 categories), and microenvironment classification (110 categories). Activities vary from one min to one h in duration, with longer activities being subdivided into clock-hour durations to facilitate exposure modeling. A distribution of values for the ratio of oxygen uptake rate to body mass (referred to as metabolic equivalents or METs) is provided for each activity type listed in CHAD. The forms and parameters of these distributions were determined through an extensive review of the exercise and nutrition literature. The primary source of distributional data was Ainsworth et al. (1993), a compendium developed specifically to facilitate the coding of physical activities and to promote comparability across studies.

C.4.2. Characterization of Inhalation Intake and Uptake

Use of the information in CHAD provides a rational way for incorporating realistic intakes into exposure models by linking inhalation rates to activity information. As mentioned earlier, each cohort of the pNEM-type models, or each (virtual or actual) individual of the SHEDS, MENTOR, APEX, and HAPEM models, is assigned an exposure event sequence derived from activity diary data. Each exposure event is typically defined by a start time, a duration, assignments to a geographic location and microenvironment, and an indication of activity level. The most recent versions of the above models have defined activity levels using the activity classification coding scheme incorporated into CHAD. A probabilistic module within these models converts the activity classification code of each exposure event to an energy expenditure rate, which in turn is converted into an estimate of oxygen uptake rate. The

oxygen uptake rate is then converted into an estimate of total ventilation rate ($\dot{V}_E$) expressed in Liters/min. Johnson (2001) reviewed briefly the physiological principles incorporated into the algorithms used in pNEM to convert each activity classification code to an oxygen uptake rate and describes the additional steps required to convert oxygen uptake to ($\dot{V}_E$).

McCurdy (1997; 2000) has recommended that the ventilation rate should be estimated as a function of energy expenditure rate. The energy expended by an individual during a particular activity can be expressed as EE = (MET)(RMR) in which EE is the average energy expenditure rate (kcal/min) during the activity and RMR is the resting metabolic rate of the individual expressed in terms of number of energy units expended per unit of time (kcal/min). MET (the metabolic equivalent of tasks) is a ratio specific to the activity and is dimensionless. If RMR is specified for an individual, then the above equation requires only an activity-specific estimate of MET to produce an estimate of the energy expenditure rate for a given activity. McCurdy et al. (2000) developed distributions of MET for the activity classifications appearing in the CHAD database.

An issue that should be mentioned in closing is that of evaluating comprehensive prognostic exposure modeling studies, for either individuals or populations, with field data. Although databases that would be adequate for performing a comprehensive evaluation are not expected to be available any time soon, there have been a number of studies, reviewed in earlier sections of this chapter, which can be used to start building the necessary information base. Some of these studies report field observations of personal, indoor, and outdoor levels and have also developed simple semi-empirical personal exposure models that were parameterized using the observational data and regression techniques.

In conclusion, though existing inhalation exposure modeling systems have evolved considerably in recent years, limitations of available modeling methods and data in relation to potential SO_2 studies should be taken into account. Existing prognostic modeling systems for inhalation exposure can in principle be directly applied to, or adapted for, SO_2 studies; APEX, SHEDS, and MENTOR-1A are candidates. However, such applications would be constrained by data limitations such as ambient characterization at the local scale and by lack of quantitative information for indoor sources and sinks.

Annex D. Controlled Human Exposure

This Annex summarizes the findings of human clinical studies that have been published since the previous review. Descriptions of older studies were presented in the 1994 Supplement to the Second Addendum to the 1982 AQCD for Sulfur Oxides (U.S. EPA, 1994a), and are not described in great detail in this document.

Table D-1. Effects of medications on SO_2-induced changes in lung function among human subjects.

Study	Concentration	Duration	Subjects	Exposure Status	Effects
Bigby and Boushey (1993)	0.25 – 8.0 ppm	4 min	10 asthmatics	Increasing concentrations of SO_2 during voluntary eucapnic hyperpnea (20 L/min) preceded by administration of the anti-inflammatory agent nedocromil sodium (baseline, placebo, 2 mg, 4 mg, 8 mg).	Treatment with nedocromil sodium significantly increased the concentration of SO_2 required to produce an 8 unit increase in sRaw. Increasing the dose of nedocromil sodium from 2 mg to 8 mg did not significantly affect the response.
Lazarus et al. (1997)	0.25 – 8.0 ppm	4 min	12 asthmatics	Subjects exposed via mouthpiece to filtered air and increasing concentrations of SO_2 during eucapnic hyperventilation (20 L/min). Exposures occurred following pretreatment with a leukotriene receptor antagonist (zafirlukast 20 mg) or placebo.	Compared with placebo, zafirlukast significantly increased the SO_2 concentration required to produce an 8 unit increase in sRaw. This effect was observed with challenges occurring both at 2 and 10 h following treatment.
Field et al. (1996)	0.25 – 8.0 ppm	3 min	31 asthmatics	Increasing concentrations of SO_2 (including clean air exposure) in an exposure chamber during voluntary eucapnic hyperpnea (35 L/min) preceded by administration of placebo, the anticholinergic bronchodilator ipratropium bromide (15 subjects), morphine (opioid agonist) (15 subjects), or the anti-inflammatory agent indomethacin (16 subjects).	Both ipratropium bromide and morphine reduced the responsiveness to SO_2, significantly increasing the SO_2 concentration required to reduce specific airway conductance by 35%. Similarly, indomethacin was observed to attenuate airway responsiveness to SO_2, however, this effect was smaller than what was observed with either ipratropium bromide or morphine.
Gong et al. (1996)	0.75 ppm	10 min	10 asthmatics	Subjects exposed to SO_2 or clean air in a chamber while performing light exercise (29 L/min) at 1, 12, 18, and 24 h after pretreatment with salmeterol xinafoate (β_2-adrenergic agonist) or placebo (each subject exposed 4 times).	Observed a significant protective effect of salmeterol xinafoate at 1 and 12-h post-dosing. Following exercise/SO_2 exposure at 1, 12, 18, and 24 h, FEV_1 decreased (versus preexposure) by 7, 12, 25, and 26%, respectively. Exercise with SO_2 resulted in an approximate 26% decrease in FEV_1 at all time points with placebo.
Gong et al. (2001)	0.75 ppm	10 min	11 asthmatics	Exposure to SO_2 or clean air following 3 days of treatment with montelukast (leukotriene receptor antagonist) or placebo (each subject exposed 4 times). Exposures conducted in an exposure chamber during moderate levels of exercise (35 L/min).	Reported a statistically significant SO_2-induced increase in eosinophil count in induced sputum. Measures of lung function (FEV_1 and sRaw), as well as respiratory symptoms and eosinophil count all showed significant improvement after pretreatment with montelukast.

Table D-2. Summary of new studies of controlled human exposure to SO_2.

Study	Concentration	Duration	Subjects	Exposure Status	Effects
Trenga et al. (2001)	0.1, 0.25 ppm	10 min	17 asthmatics	SO_2-sensitive asthmatics exposed to SO_2 via mouthpiece while performing mild to moderate levels of exercise. Exposures preceded by 45 min exposures to filtered air or O_3 (0.12 ppm), with or without pretreatment with dietary antioxidants.	Exposure to O_3 slightly increased bronchial responsiveness to SO_2 as measured by FEV_1 and peak expiratory flow. Pretreatment with dietary antioxidants was shown to have a protective effect on respiratory response, particularly among individuals with greater sensitivity to SO_2.
Devalia et al. (1994)	0.2 ppm	6 h	10 asthmatics	Exposures to filtered air, as well as 0.2 ppm SO_2 and 0.4 ppm NO_2, conducted separately and in combination in an exposure chamber (subjects at rest). All subjects sensitive to inhaled house dust mite antigen.	Neither SO_2 nor NO_2, alone or in combination, significantly affected FEV_1. The combination of SO_2 and NO_2 significantly reduced the amount of inhaled allergen (60.5% change, $p = 0.015$) required to produce a 20% decrease in FEV_1 ($PD20FEV_1$). Both SO_2 and NO_2 alone reduced $PD20FEV_1$, but this reduction was not statistically significant (32.2% ($p = 0.506$), and 41.2% ($p = 0.125$), respectively).
Rusznak et al. (1996)	0.2 ppm	6 h	13 asthmatics	Exposures to filtered air and a combination of 0.2 ppm SO_2 and 0.4 ppm NO_2 in an exposure chamber (subjects at rest). All subjects sensitive to inhaled house dust mite antigen.	Confirmed findings of Devalia et al. and further observed that the combination of SO_2 and NO_2 enhanced airway responsiveness to an inhaled allergen up to 48 h post-exposure (maximal response at 24 h).
Tunnicliffe et al. (2001)	0.2 ppm	1 h	12 healthy adults, 12 asthmatics	Exposures (head dome) at rest to filtered air and 0.2 ppm SO_2.	Among healthy subjects, an SO_2-induced increase in heart rate variability (total power) was observed, while a reduction in heart rate variability with SO_2 versus air was observed in asthmatics.
Tunnicliffe et al. (2003)	0.2 ppm	1 h	12 healthy adults, 12 asthmatics	Exposures (head dome) at rest to filtered air and 0.2 ppm SO_2.	Exposures to SO_2 at 0.2 ppm did not have a significant effect on lung function, respiratory symptoms, markers of inflammation, or antioxidant levels in healthy adults or mild asthmatics.
Routledge et al. (2006)	0.2 ppm	1 h	20 older adults with coronary artery disease (age 52-74), 20 healthy older adults (age 56-75)	Exposures (head dome) at rest to filtered air, as well as 0.2 ppm SO_2 and ultra-fine carbon particles (50 $\mu g/m^3$), separately and in combination.	In healthy subjects, exposure to SO_2 alone significantly decreased heart rate variability 4 h post-exposure compared to clean air. No effect was observed in subjects with coronary artery disease. The combination of SO_2 and carbon particles did not affect heart rate variability in either group. SO_2 was not observed to affect markers of inflammation or coagulation.
Nowak et al. (1997)	0.25 – 2.0 ppm	3 min	786 adults	Mouthpiece exposures to filtered air and increasing concentrations of SO_2 during eucapnic hyperventilation (40 L/min).	Among individuals who were not hyperresponsive to methacholine, less than 1% were found to be hyperresponsive to SO_2. However, more than 22% of the individuals who were hyperresponsive to methacholine were also hyperresponsive to SO_2. Individuals were considered hyperresponsive to SO_2 when exposure resulted in a 20% or greater decrease in FEV_1 versus baseline.
Trenga et al. (1999)	0.5 ppm	10 min	47 asthmatics	Subjects exposed to SO_2 via mouthpeice while performing light to moderate levels of exercise.	An SO_2-induced decrease in FEV_1 of at least 8% was observed in 53% of the subjects (range 8-44%). Increases in respiratory symptoms were significantly associated with decreases in FEV_1. Among SO_2-sensitive subjects, severity of asthma (as defined by medication use) was not a significant predictor of the level of response. It is not clear whether the response was adjusted for the effects of exercise in clean air.
Winterton et al. (2001)	0.5 ppm	10 min	62 asthmatics	Subjects exposed to SO_2 via mouthpiece while performing light to moderate levels of exercise.	Subjects who experienced at least at 12% decrease in FEV_1 following exposure were considered to be sensitive to SO_2. Out of 58 subjects who were genotyped for the polymorphism at position -308 in the promoter region of TNF-α, 21% (N: 12) were sensitive to SO_2. Sensitivity to SO_2 was found to be associated with the homozygous wild type allele (GG) (12 of 12 responders vs. 28 of 46 subjects who were not responsive to SO_2).
Gong et al. (1995)	0.5, 1.0 ppm	10 min	14 asthmatics	Exposure to SO_2 and filtered air were conducted in an exposure chamber during low, moderate, and heavy levels of exercise (target ventilation ranges of 20-29, 30-39, and 40-49 L/min).	For the average individual, increasing SO_2 concentration resulted in a significant decrement in lung function (decrease in FEV_1 and increase in sRaw) as well as a significant increase in respiratory symptoms. Increasing SO_2 conc. had a greater effect on lung function and respiratory symptoms than increasing level of exercise.

Annex E. Toxicological Studies

This Annex summarizes the findings of animal toxicology studies that have been published since the previous review. Descriptions of older studies were presented in the 1982 AQCD for Sulfur Oxides (U.S. EPA, 1982), and are not described in great detail in this document.

Table E-1. Respiratory System – Effects of SO_2 on lung function.

Study	Concentration	Duration	Species	Effects
ACUTE AND SUBACUTE				
Lewis and Kirchner (1984)	10 or 30 ppm (26.2 or 78.6 mg/m^3); intratracheal	5 min	Mongrel dog; male and female; age and weight NR; N = 5-15 /group	Initial transient bronchoconstriction approximately 10 min in duration followed by a gradual change in pulmonary mechanics (43% increase in airway resistance and 30% decrease in dynamic compliance) 4 hrs following 30 ppm but not 10 ppm SO_2.
Barthélemy et al. (1988)	0.5 or 5 ppm (1.3 or 13.1 mg/m^3); intratracheal	45 min	Rabbit; sex NR; adult; mean 2.0 kg; N = 5-9/ group; rabbits were mechanically ventilated	Lung resistance increased by 16% and 50% in response to 0.5 and 5 ppm SO_2, respectively. Bivagotomy had no effect on 5 ppm SO_2-induced increases in lung resistance. Reflex bronchoconstrictive response to phenyldiguanide (intravenously administered) was eliminated by exposure to SO_2 but SO_2 had no effect on lung resistance induced by intravenously- administered histamine. Authors concluded that (1) vagal reflex is not responsible for SO_2-induced increase in lung resistance at 45 min; (2) transient alteration in tracheobronchial wall following SO_2 exposure may have reduced accessibility of airway nervous receptors to phenyldiguanide.
Amdur et al. (1983)	~1 ppm (2.62 mg/m^3); head only	1 h	Hartley guinea pig; male; age NR; 200-300 g; N = 8-23/group	An 11% increase in pulmonary resistance and 12% decrease in dynamic compliance were observed. Neither effect persisted into the 1 h period following exposure. No effects were observed for breathing frequency, tidal volume, or min volume.
Conner et al. (1985)	1 ppm (2.62 mg/m^3); nose only	3 h/day for 6 days; animals evaluated up to 48 h post-exposure	Hartley guinea pig; male; age NR; 250-320 g; N = ≤ 18 group/time point	No effect was observed on residual volume, functional reserve capacity, vital capacity, total lung capacity, respiratory frequency, tidal volume, pulmonary resistance, pulmonary compliance, diffusing capacity for CO or alveolar volume at 1 or 48 h after last exposure.
SUBCHRONIC AND CHRONIC				
Douglas et al. (1994)	5 ppm (13.1 mg/m^3); whole body	2 h/day for 13 wks from birth	New Zealand White rabbit; male and female; 1 day old; weight NR; N = 3-4/ group; immunized against *Alternaria tenuis*	No effects on lung resistance, dynamic compliance, transpulmonary pressure, tidal volume, respiration rate, or min volume.
Scanlon et al. (1987)	15 or 50 ppm (39.3 or 131 mg/m^3); intratracheal exposure	2 h/day, 4 or 5 days/wk, for 5 mos (low dose group) or 10-11 mos (high dose group); authors stated that physiological changes were observed within 5 mos; 7-9 mo recovery period	Mongrel dog; adult; sex NR; 10-20 kg; N = 3-4/group (3 hyperresponsive, 3 hyporesponsive, and 1 avg responsive)	At 15 ppm, there was no clinical evidence of bronchitis; pulmonary resistance increased by 35-38% in 2 of 3 dogs, and dynamic lung compliance decreased in 1 of 3 dogs, but physiological changes were not significant for the group as a whole. At 50 ppm, cough and mucus hypersecretion were observed; symptoms ceased during the recovery period. Pulmonary resistance increased by 56% during the treatment period and an additional 28% during the recovery period for a total increase of 99%; dynamic lung compliance decreased in 2 of 4 dogs and increased in 1 of 4 dogs during treatment but there were no significant changes in the group as a whole. Authors considered 15 ppm to be the lower limit of exposure that failed to produce physiological changes.
Smith et al. (1989)	1 ppm (2.62 mg/m^3); whole body	5 h/day, 5 days/wk for 4 mos	Sprague-Dawley rat; male; young adult; initial weight NR; N = 12-15/data point	Physiological tests were conducted in anesthetized animals both during spontaneous breathing and during paralysis. SO_2 exposure resulted in an 11% decrease in residual volume and reduced quasistatic compliance in paralyzed animals. Authors noted that because residual volume was decreased only in paralyzed rats and the magnitude of effect was very small, it may have been due to chance. Quasistatic compliance values were observed to be very high in controls, and may have accounted for effect in the treatment group.

Table E-2. Respiratory System – Inflammatory responses following SO_2 exposure.

Study	Concentration	Duration	Species	Effects
ACUTE/SUBACUTE/SUBCHRONIC				
Clarke et al. (2000)	10 ppm (26.2 mg/m^3); nose only	4 h	Outbred Swiss mouse; female; age, weight NR; N = 10/experimental value	No evidence was seen of inflammatory response in terms of total cell number, lymphocyte/polymorphonuclear leukocytes differentials, or total protein level taken from BAL fluid.
Meng et al. (2005a)	5.35, 10.7, or 21.4 ppm (14, 28, or 56 mg/m^3); whole body	4 h/day for 7 days	Kunming albino mouse; male; age NR; 18-22 g; N = 10/group	In lung tissue, in vivo SO_2 exposure (low, mid concentrations) significantly elevated levels of the pro-inflammatory cytokines interleukin-6 and tumor necrosis factor-α, but did not affect levels of the anti-inflammatory cytokine transforming growth factor-β1. In serum, the only effect observed was a low-dose elevation of tumor necrosis factor-α.
Langley-Evans et al. (1996)	5, 50, or 100 ppm (13.1, 131, or 262 mg/m^3); whole body	5 h/day for 7-28 days	Wistar rat; male; 7 wks old; weight NR; N = 4-5/treatment group, 8 controls	No lung injury was observed and evidence of inflammatory response was only observed in the 100 ppm group. A 4-fold increase in BAL fluid leukocyte numbers was observed in the 100 ppm group at day 14; the increase lessened at days 21 and 28 but remained higher than controls. The number of macrophages in BAL fluid was increased at day 28 in the 100 ppm group. Neutrophil numbers were 120 times higher than controls at day 14 in the 100 ppm group but returned to normal by day 21. Blood neutrophils were depleted in rats exposed to 50 ppm on days 7-21 but were increased in rats exposed to 5 ppm (significant) and 100 ppm (non-significant) at day 14. Lung epithelial permeability was not affected.
Conner et al. (1989)	1 ppm (2.62 mg/m^3); nose only	3 h/day for 1-5 days; bronchoal-veolar lavage per-formed each day	Hartley guinea pig; male; age NR; 250-320 g; N = 4	No change in numbers of total cells and neutrophils, protein levels or enzyme activity in lavage fluid following SO_2 exposure.
Park et al. (2001a)	0.1 ppm (0.26 mg/m^3); whole body; with and without exposure to ovalbumin	5 h/day for 5 days	Dunkin-Hartley guinea pig; male; age NR; 250-350 g; N = 7-12/group	After bronchial challenge, the ovalbumin/SO_2-exposed group had significantly increased eosinophil counts in BAL fluid compared with all other groups, including the SO_2 group. The bronchial and lung tissue of this group showed infiltration of inflammatory cells, bronchiolar epithelial damage, and mucus and cell plug in the lumen.
Li et al. (2007)	2 ppm (5.24 mg/m^3) with and without exposure to ovalbumin	1 h/day for 7 days	Wistar rat; male; age NR	Increased number of inflammatory cells in BAL fluid, increased levels of MUC5AC and ICAM-1 and an enhanced histopathological response compared with those treated with ovalbumin or SO_2 alone.

Table E-3. Respiratory System – Effects of SO_2 exposure on airway responsiveness and allergic sensitization.

Study	Concentration	Duration	Species	Effects
ANTIGEN SENSITIZATION / ALLERGIC REACTIONS – ACUTE / SUBACUTE				
Abraham et al. (1981)	5 ppm (13.1 mg/m³); head only	4 h	Sheep; sex and age NR; mean weight 38 ± 7 kg; N = 7/group	Acute exposure to 5 ppm SO_2 did not produce significant airway changes (pulmonary resistance, static compliance, dynamic compliance, tidal volume, breathing frequency) in either normal or allergic (sensitized to *Ascaris suum* antigen) sheep, nor increase airway reactivity (measured as pulmonary resistance increase after aerosolized carbachol provocation) in normal sheep. However, 5 ppm SO_2 did significantly increased airway reactivity in allergic sheep, which have antigen-induced airway responses similar to humans with allergic airway disease; may model airway responses to SO_2 in a sensitive human subpopulation.
Park et al. (2001a)	0.1 ppm (0.26 mg/m³); whole body; with and without exposure to ovalbumin	5 h/day for 5 days	Dunkin-Hartley guinea pig; male; age NR; 250-350 g; N = 7-12/group	After bronchial challenge, the ovalbumin/SO_2-exposed group had significantly increased enhanced pause (an indicator of airway obstruction) compared with all other groups, including the SO_2 group. Authors concluded that low level SO_2 may enhance the development of ovalbumin-induced asthmatic reactions in guinea pigs.
Riedel et al. (1988)	0.1, 4.3, or 16.6 ppm (0, 0.26, 11.3, or 43.5 mg/m³); whole body; animals were sensitized to ovalbumin on the last 3 days of exposure.	8 h/day for 5 days	Perlbright-White Guinea pig; female; age NR; 300-350 g; N = 5 or 6/group (14 controls)	Bronchial provocation with ovalbumin was conducted every other day for 2 wks, starting at 1 wk after last exposure. Numbers of animals displaying symptoms of bronchial obstruction after ovalbumin provocation increased in all SO_2 groups compared to air-exposed groups. Anti-ovalbumin antibodies (IgG total and IgG1) were increased in BAL fluid and serum of SO_2-exposed animals compared to air-exposed controls; statistical significance attained for IgG total in BAL fluid at ≥ 4.3 ppm SO_2 and in serum at all SO_2 concentrations. Results indicate that subacute exposure to even low concentrations of SO_2 can potentiate allergic sensitization of the airway.
ANTIGEN SENSITIZATION / ALLERGIC REACTIONS – SUBCHRONIC				
Kitabatake et al. (1992; 1995)	5 ppm (13.1 mg/m³); whole body; sensitized with *Candida albicans* on day 1 and wk 4	4 h/day, 5 days/wk, 6 wks	Hartley guinea pig; male; age NR; ~200 g; N = 12/group	Respiratory challenge to *Candida albicans* was conducted 2 wks after last exposure. At 15 h after challenge an increased number of SO_2-exposed animals displayed prolonged expiration, inspiration, or both. Authors concluded that SO_2 exposure increased dyspneic symptoms.
GENERAL BRONCHIAL REACTIVITY STUDIES – ACUTE				
Amdur et al. (1988)	1 ppm	1 h	Guinea pig; N=8	Airway responsiveness to acetylcholine was measured 2 h following SO_2 exposure. No changes were observed.
Douglas et al. (1994)	5 ppm (13.1 mg/m³); whole body	2 h	New Zealand White rabbit; sex NR; apparently 3 mos old; 2.2-3.1 kg; N=6/group	No effect on airway responsiveness to inhaled histamine, as measured by provocation concentrations of histamine required to increase pulmonary resistance by 50% and decrease dynamic compliance by 35%.
Lewis and Kirchner (1984)	10 or 30 ppm (26.2 or 78.6 mg/m³); intratracheal	5 min; a second exposure was conducted 20 days later, after exposure to the antiallergic drug	Mongrel dog; male and female; age and weight NR; N = 5-15/group	No effect was observed at 10 ppm. At 30 ppm hyperresponsiveness and hypersensitivity to aerosolized methacholine and 5-hydroxytryptamine was observed for up to 24 h following exposure. Twenty days later, pretreatment with aerosolized 4% Wy-41,195 or disodium cromoglycate (antiallergic drugs) at high doses lessened the methacholine-induced hypersensitivity observed after exposure to 30 ppm SO_2. Calculations used to determine hyperresponsive and hyperreactivity were not clear.
GENERAL BRONCHIAL REACTIVITY STUDIES – CHRONIC				
Scanlon et al. (1987)	15 or 50 ppm (39.3 or 131 mg/m³); intratracheal	2 h/day, 4 or 5 days/wk for 5 mos (low dose group) or 10-11 mos (high dose group); physiological changes observed within 5 mos; 7-9 mo recovery period.	Mongrel dog; adult; sex NR; 10-20 kg; N = 3-4/ group (3 hyperresponsive, 3 hyporesponsive, and 1 avg responsive)	Bronchial reactivity in response to inhaled histamine or methacholine was not affected in either treatment group, as determined by the concentration of histamine or methacholine required to double pulmonary resistance or the concentrations required to decrease dynamic compliance by 65% (ED_{65}).

Table E-4. Respiratory System – Effects of SO_2 layered on metallic or carbonaceous particles.

Study	SO_2	Metal or Carbon	Effects
Lam et al. (1982) Hartley guinea pig; male; age NR;240-300 g; N = 7-16/group Exposure: 3 h	0 or ~1 ppm (2.6 mg/m³); whole body	Zinc oxide: 0.8, 2.7, 6.0, or 7.8 mg/m³ (0.05 micron projected area diameter, GSD 2.0) (sulfate, sulfite, and sulfur trioxide detected)	Vital capacity: No effect with exposure to 7.8 mg/m³ zinc oxide alone and 2.7 mg/m³ zinc oxide in combination with SO_2, but decreased with exposure to 0.8 and 6.0 mg/m³ zinc oxide in combination with SO_2. Total lung capacity: No effect with exposure to 7.8 mg/m³ zinc oxide alone, but decreased with exposure to 6.0 mg/m³ zinc oxide in combination with SO_2. Diffusion capacity for CO and ratio of diffusion capacity for CO to total lung capacity or alveolar volume: No effect with exposure to 7.8 mg/m³ zinc oxide alone, but decreased with exposure to 2.7 and 6.0 mg/m³ zinc oxide in combination with SO_2. Alveolar volume: No effect with exposure to 7.8 mg/m³ zinc oxide alone, but decreased with exposure to 6.0 mg/m³ zinc oxide in combination with SO_2.
Amdur et al. (1983) Hartley guinea pig; male; age NR; 200-300 g; N = 8-23/group Exposure: 1 h	~1 ppm (2.6 mg/m³); head only	Zinc oxide: 0 mg/m³	Pulmonary function: SO_2 exposure alone resulted in an 11% increase in resistance and 12% decrease in compliance.
	0 ppm	Zinc oxide: ~1-2 mg/m³ (0.05 micron projected area diameter, GSD 2.0); mixed at 24 °C and 30% RH	Pulmonary function: Zinc oxide exposure alone resulted in a 9% decrease in compliance that persisted 1 h after exposure.
	~1 ppm (2.6 mg/m³); head only	Zinc oxide: ~1-2 mg/m³; mixed at 24 °C and 30% RH	Pulmonary function: A 12% decrease in compliance and decreased tidal volume that persisted 1 h after exposure, and decreased min volume. There was no evidence of new compound formation. Authors concluded that effects on tidal volume and min volume most likely represented an additive effect.
		Zinc oxide: ~1-2 mg/m³; mixed at 480 °C and 30% RH	Pulmonary function: A 12% decrease in compliance and decreased tidal volume that persisted 1 h after exposure and a 12% increase in resistance and decreased min volume. There was no evidence of new compound formation.
		Zinc oxide: ~1-2 mg/m³; mixed at 480 °C and 80% RH with addition of water vapor downstream	Pulmonary function: A 13% decrease in compliance that persisted 1 h after exposure and a 29% increase in resistance. Sulfite formation was observed.
		Zinc oxide: ~1-2 mg/m³; mixed at 480 °C and 30% RH with addition of water vapor during mixing.	Pulmonary function: A 19% increase in resistance that persisted 1 h after exposure, decreased tidal volume immediately after exposure, and a 26% decrease in compliance 1 h after exposure. Sulfate, sulfite, and sulfur trioxide formation was observed.
Chen et al. (1991) Hartley guinea pig; male; age NR;275-375 g; N = 8/group Exposure: 1h	1.10-1.25 ppm (2.9-3.3 mg/m³); head only	Copper oxide: 0 or 1.16-2.70 mg/m³ (< 0.1 micron)	Pulmonary resistance: Increased 32-47% during exposure and at 1 and 2 h postexposure when SO_2 and copper oxide were mixed at 37 °C, a condition that resulted in formation of 0.36 µmol/m³ sulfite on the copper oxide particles. No effect was observed when the compounds were mixed at 1411 °C, a condition that led to the formation of sulfate on the copper oxide particles. Dynamic lung compliance: No effect when mixed under conditions that led to the formation of either sulfate or sulfite on particles.
Chen et al. (1992) Hartley guinea pig; male; age NR; 290-410 g; N = 6-9/group Exposure: 1h	1.02 ppm (2.7 mg/m³); head only	Zinc oxide: 0 mg/m³	Baseline pulmonary resistance at 2 h following exposure: No effect in any group. AHR to acetylcholine: No effect with exposure to SO_2 or zinc oxide alone; compared to furnace controls (3% argon). Hyperresponsiveness increased in both groups exposed to SO_2-layered zinc oxide particles.
	0	2.76 mg/m³ (0.05 micron median diameter, GSD 2.0)	
	1.10 ppm (2.9 mg/m³)	0.87 mg/m³	
	1.08 ppm (2.8 mg/m³)	2.34 mg/m³	
Jakab et al. (1996) Swiss mouse;	10 ppm (26.2 mg/m³); nose only	0 mg/m³	AM Fc receptor-mediated phagocytosis of sheep red blood cells at 3 days after exposure: Dose-dependent reductions in AM phagocytosis were observed at each

Study	SO_2	Metal or Carbon	Effects
female; 5 wks old; 20-23 g; N = 5/group Exposure: 4 h	0 ppm	Carbon black: 10 mg/m^3 (0.3 micron, GSD 2.7)	concentration of SO_2 mixed with carbon black aerosol at 85% relative humidity, the only conditions under which SO_2 significantly chemisorbed to carbon black aerosol and oxidized to sulfate. AM phagocytic activity was reduced somewhat immediately after exposure (Day 0) to carbon black and 10 or 20 ppm SO_2, was minimal on Days 1 and 3, began increasing on Day 7, and was fully recovered by Day 14. No effects were observed with exposure to SO_2 or carbon black alone. The data indicate that environmentally relevant respirable carbon particles can act as effective vectors for delivering toxic amounts of acid SO_4^{2-} to distal parts of the lung.
	5 ppm (13.1 mg/m^3)	10 mg/m^3 (formed 6 µg sulfate at 85% humidity)	
	10 ppm (26.2 mg/m^3)	10 mg/m^3 (formed 13.7 µg sulfate at 85% humidity)	
	20 ppm (52.4 mg/m^3)	10 mg/m^3 (formed 48.7 µg sulfate at 85% humidity)	
Clarke et al. (2000) Outbred Swiss mouse; female; age and weight NR; N = 10 or 12/ experimental value. Exposure: 4 h once or for 4, 5, or 6 days	10 ppm (26.2 mg/m^3); nose only	0 mg/m^3	Inflammatory response after a single 4 h exposure: There was no effect on total cell number, lymphocyte/PMN differentials, or total protein levels in BAL fluid in any group.
	0 ppm	Carbon black: 10 mg/m^3 (10% humidity)	AM Fc receptor-mediated phagocytosis after a single 4 h exposure: Suppressed by acid sulfate coated particles (at ~140 µg/m^3) at 1, 3, and 7 days postexposure; values returned to normal by Day 14.
	0 ppm	Carbon black: 10 mg/m^3 in 85% humidity to generate 8 µg/m^3 acid sulfate	
	10 ppm (26.2 mg/m^3)	Carbon black: 10 mg/m^3 in 10% humidity to generate 41 µg/m^3 acid sulfate	Intrapulmonary bactericidal activity toward *Staphylococcus aureus*: Decreased by a single 4 h exposure to sulfate coated particles (at ~140 µg/m^3) at 1 and 3 days postexposure, with recovery by day 7. Suppression was also observed after 5 and 6 days of repeated exposure to ~20 µg/m^3 sulfate-coated particles, a condition more relevant to potential ambient human exposures.
	10 ppm (26.2 mg/m^3)	Carbon black: 10 mg/m^3 in 85% humidity to generate 137 µg/m^3 acid sulfate	
	1 ppm (2.62 mg/m^3)	Carbon black: 1 mg/m^3 in 85% humidity to generate 20 µg/m^3 acid sulfate	
Conner et al. (1985) Hartley guinea pig; male; age NR; 250-320 g; N = 5-18/group/ time point Exposure: 3 h/day for 6 days; Animals evaluated for up to 72 h following exposure	1 ppm (2.6 mg/m^3); nose only	Zinc oxide: 0 or 6 mg/m^3 (0.05 micron projected area diameter, GSD 2.0)	Right lung to body weight ratio: No effect of SO_2 alone. Increased at 48 h in group exposed to zinc oxide/SO_2. Right lung wet to dry weight ratio: No effect of SO_2 alone. Increased at 1 h after exposure in zinc oxide/SO_2 group. Lung morphology: No lesions were observed in SO_2 group. In group exposed to zinc oxide/SO_2 there was an increased incidence of alveolar duct inflammation consisting of interstitial cellular infiltrate, increased numbers of macrophages, and replacement of squamous alveolar epithelium with cuboidal cells. Frequency and severity of lesions were greatest immediately following exposure and by 72 h following exposure, lesions were mild and infrequent. Tracheal secretory cell concentration: No effects with either exposure. Epithelial permeability: No effects with either exposure scenario. DNA synthesis (^{3}H-thymidine uptake) terminal bronchial cells: Unaffected by SO_2. Increased at 24 and 72 h after exposure to zinc oxide/SO_2. Lung volumes: Unaffected by SO_2 exposure. Functional reserve capacity, vital capacity, and total lung capacity were decreased from 1 to 72 h following exposure to zinc oxide/SO_2. Diffusion capacity for CO: Unaffected by SO_2 exposure. Decreased by ~40-50% from 1 to 24 h following zinc oxide/SO_2 exposure. Alveolar volume: Unaffected by SO_2 exposure. Decreased by ~10% from 1 to 24 h following exposure to zinc oxide/SO_2. Pulmonary mechanics: Respiratory frequency, tidal volume, pulmonary resistance, pulmonary compliance were unaffected by either exposure. Author conclusion: Changes were identical to those reported in a previous study in which guinea pigs were exposed to zinc oxide alone. Sulfur compounds deposited on surface are less important than zinc oxide particle.

Study	SO_2	Metal or Carbon	Effects
Amdur et al. (1988) Guinea pig, sex, age, and weight NR; N = 8-9/group Exposure: 3 h/day for 5 days	1 ppm (2.6 mg/m^3); head only	Zinc oxide: 1 or 2.5 mg/m^3 (0.05 micron CMD, GSD 2.0) Sulfate was generated at 7 and 11 µg/m^3 at each respective dose; sulfuric acid level was reported at 21 and 33 µg/m^3 at each respective dose.	Pulmonary diffusing capacity: No effect with exposure to 1 ppm SO_2 or 2.5 mg/m^3 zinc oxide alone (data not shown by authors). Significant and dose related decreases on exposure days 4 and 5 at 7 µg/m^3 sulfate (20% less than control) and days 2-5 at 11 µg/m^3 sulfate (up to 40% less than control).
Exposure: 1 h			Bronchial sensitivity to acetylcholine: No effect of 1 ppm SO_2 or 2.5 mg/m^3 zinc oxide alone. Increased with SO_2 administered in combination with either zinc oxide dose. The authors noted that responses were similar to those produced by 200 µg/m^3 sulfuric acid of similar particle size, thus indicating the importance of surface layer.
Shami et al. (1985) Fischer-344 rat; male and female; 18-19 wks old, weight NR; N = 2/sex/group at each evaluation time period Exposure: 2 h/day for 4 days, followed by 2 days without exposure, followed by 5 more days of exposure; animals were evaluated for up to 28 days following exposure	5 ppm (13 mg/m^3); nose only	22 mg/m^3 gallium oxide (0.2 micron volume median diameter, GSD not reported), with and without addition of 7 mg/m^3 B[c]P	Tracheal and large airways morphology: No effects observed with coexposure to gallium oxide and SO_2. Pulmonary morphology: Increased numbers of non-ciliated cells in terminal bronchial epithelium were observed in the SO_2/gallium oxide/benzo(a)pyrene group. Mild peribronchial and perivascular mononuclear inflammatory cell infiltrate, small hyperplastic epithelial cells in alveoli, and alveolar septal hypertrophy were observed in the SO_2/gallium oxide group, with and without B[c]P; effects were more prominent with B[c]P exposure. Cell proliferation (^{3}H-thymidine uptake) in trachea and large airways: Increased on days 1 and 14 in SO_2/ gallium oxide group; basal cells primarily labeled. Increased on day 8 In the SO_2/gallium oxide/B[c]P group. Cell proliferation (^{3}H-thymidine uptake) in terminal bronchioles: Increased on day 14 in SO_2/gallium oxide group; Clara cells primarily labeled. Increased on day 11 in the SO_2/gallium oxide/B[c]P group. Types of ^{3}H-thymidine-labeled cells in the alveolar region: Type 2 cells were primarily labeled in the alveolar region through 14 days of exposure in the SO_2/gallium oxide group. Labeling was increased in Type II, Type I, and endothelial cells on day 8 in the SO_2/gallium oxide/B[c]P group.
Wolff et al. (1989) F344/Crl rat; male and female; 10-11 wks old; weight NR; N = 6/sex/group Exposure: 2 h/d, 5 d/wk, 4 wks	5 ppm (13 mg/m^3); nose only	Gallium oxide: 0 or 27 mg/m^3 (~0.20 micron MMD, GSD ~1.5-2), with and without 7.5 mg/m^3 of 1-NP and B[c]P	Pulmonary particle clearance: No effect was observed with exposure to SO_2 alone; clearance was slowed only by gallium oxide, with or without coexposure to SO_2 or the other compounds; SO_2 in combination with the PAH had no effect on clearance rate. Authors concluded that toxicity was dominated by gallium oxide.

Table E-5. Respiratory System – Effects of mixtures containing SO_2 and O_3.

Study	SO_2	O_3	Effects
ACUTE/SUBACUTE			
Abraham et al. (1986) Sheep; sex NR; adult; 23-50 kg; N = 6 Exposure: 5 h/day for 3 days	3 ppm (7.9 mg/m^3); head only	0.3 ppm	Tracheal mucus velocity: Decreased by 40% immediately after exposure and 25% at 24 h postexposure to the mixture of the 2 compounds. The effects of either compound alone were NR. Ciliary beat frequency: No effect
CHRONIC/SUBCHRONIC			
Aranyi et al. (1983) CD1 mouse; female; 3-4 wks old; weight NR; N = 360/group total (14-154/group in each assay) Exposure: 5 h/day, 5 days/wk for up to 103 days	5.0 ppm (13.2 mg/m^3) in addition to 1.04 mg/m^3 ammonium sulfate; whole body	0.2 mg/m^3 (0.10 ppm)	Mortality rate after *Streptococcus* aerosol challenge: Increased in groups exposed to O_3 alone and mixture of O_3, SO_2, and ammonium sulfate. Alveolar macrophage bactericidal activity towards inhaled *K. pneumoniae*: Increased trend (non-significant) in O_3 group but significantly increased in mixture group. Counts, viability, and ATP levels in cells obtained by pulmonary lavage: No effect of either treatment.
Raub et al. (1983) Golden hamster; male; age NR; ~105 g; N = 14 or 15/group; mild emphysema was induced in some animals by intratracheal administration of elastase Exposure: 23 h/day, 7 days/wk, for 4 wks	1 ppm (2.62 mg/m^3); whole body	1 ppm in addition to 3 ppm trans-2-butene	Lung volumes: End expiratory volume, residual volume, total lung capacity and vital capacity were unaffected in the mixture versus air exposure group in normal or emphysematous hamsters. Respiratory system compliance: Unaffected in the mixture versus air exposure group in normal or emphysematous hamsters. Distribution of ventilation (N2 washout slope): The N2 slope decreased in the mixture versus air exposure group in both normal and emphysematous hamsters. Diffusion capacity for CO: Significantly increased in the mixture versus air-exposed normal animals. Although the text reported an increase in the mixture versus air-exposed emphysematous animals, Figure 3 of the study indicated that the effect was very small and did not obtain statistical significance. Significantly lower in emphysematous versus normal hamsters exposed to the mixture. The authors noted a significant interaction between exposure to the mixture and emphysema. Histopathology: Inflammatory lesions were found in the lungs of emphysematous hamsters exposed to air or the mixture. Hyperplasia incidence was higher in emphysema hamsters exposed to the mixture versus air. Inflammatory lesions were similar in emphysematous hamsters exposed to air or the mixture. Data were not shown for histopathology data. Overall author conclusion**:** Animals with impaired lung function may have decreased capacity to compensate for the pulmonary insult caused by exposure to a complex pollutant mixture.

Table E-6. Respiratory System – Effects of SO_2 and sulfate mixtures.

Study	SO_2	Sulfate	Effects
ACUTE			
Mannix et al. (1982) Sprague Dawley rat, male, age NR, ~200 g, N = 8/group 4 h exposure	5 ppm (13.1 mg/m^3); nose only	Sulfate aerosol 1.5 (0.5 micron MMAD, GSD 1.6)	Lung clearance of radiolabeled tracer particles: No significant effect was observed with the mixture of the two compounds at 80-85% humidity.
CHRONIC/SUBCHRONIC			
Smith et al. (1989) Sprague-Dawley rat, male, young adult, initial weight NR, N = 12-15/data point Exposure: 5 h/day, 5 days/wk for 4 or 8 mos; half the animals in the 8-mo group were allowed to recover for 3 mos.	1 ppm (2.62 mg/m^3); whole body	0	Morphological observations at 4 mos exposure in "normal" rats: Bronchiolar epithelial hyperplasia and increased numbers of non-ciliated epithelial cells were observed in rats exposed to either compound alone but coexposure to both compounds did not magnify the effects. An increase in alveolar chord length was observed in the $(NH_4)_2SO_4$ group and no further changes were observed with coexposure to SO_2. Morphological observations at 4 mos exposure in rats treated with elastase to induce an emphysema-like condition: Bronchiolar epithelial hyperplasia was decreased in groups exposed to either compound alone or the mixture of the two compounds. A decrease in alveolar chord length was observed in the $(NH_4)_2SO_4$ group and no further changes were observed with coexposure to SO_2. Morphological observations at 8 mos exposure in "normal" rats: An increase in non-ciliated epithelial cells and alveolar birefringence (an indication of alveolar interstitial fibrosis) was observed only in the group exposed to $(NH_4)_2SO_4$. Morphological observations at 8 mos exposure in rats treated with elastase: An increase in lung volume per body weight and emphysema incidence was observed in groups treated with either compound alone or in combination; alveolar chord length was increased only in the group exposed to the mixture of compounds. Morphological observations at 12 mos exposure in normal rats: Increased alveolar chord length was observed only in the $(NH_4)_2SO_4$ group. Morphological observations at 12 mos exposure in rats treated with elastase: An increase in absolute lung volume was observed only in the group treated with the mixture of both compounds. Lung function effects at 4 mos exposure in normal rats: A decrease in residual volume was observed in the SO_2 group and decreased quasistatic compliance was observed in the SO_2 group and in the $(NH_4)_2SO_4$ group, but the effects were not observed with the mixture. Lung function effects at 4 mos exposure in elastase-treated rats: Ratio of residual volume/total lung capacity and N_2 washout was decreased in the SO_2 group and in the $(NH_4)_2SO_4$ group, but the effects were not observed with the mixture. Overall conclusions: In general, pollutant effects were minimal and transient, and appeared obscured or repressed in elastase-treated groups; $(NH_4)_2SO_4$ was more bioactive than SO_2, with little evidence of mixture additivity (in several instances, effects seen with one or both pollutants individually were not seen with the mixture).
	0	$(NH_4)_2SO_4$ 0.5 mg/m^3 (MMAD = 0.42-0.44 ± 0.04 micron, GSD 2.2-2.6)	
	1 ppm (2.62 mg/m^3)	0.5 mg/m^3	

Table E-7. Respiratory System – Effects of actual or simulated air pollution mixtures.

Study	Exposed	Control	Effects
ACUTE / SUBACTUTE			
Mautz et al. (1988) Sprague-Dawley rat, male, age NR, 240-280 g, N = 6-9/group Exposure: 4 h	Air pollutant mixture at full concentration (tested in 2 studies): 0.35 ppm O_3, 1.3 ppm NO_2, 2.5 ppm (6.6 mg/m^3) SO_2, 10 µg/m^3 manganese sulfate, 500 µg/m^3 ferric sulfate, 500 µg/m^3 ammonium sulfate, 500 µg/m^3 carbon aerosol. Mixture also tested ½ and ¼ concentrations. For aerosols: MMAD = 0.3-0.48 micron with GSD: 2.6-4.6. Nose-only exposure. Compounds formed: sulfate, nitrate, hydrogen ion, nitric acid.	Clean air	Breathing pattern: Effect of full concentration mixture in 2 studies – increased breathing frequency, trend or significant decrease in tidal volume, decreased or unaffected O_2 consumption, increased or unaffected ventilation equivalent for O_2. Effect of half concentration mixture – increased min ventilation. Quarter concentration – no significant effects. Histopathology: Full concentration – area of type 1 parenchymal lung lesions increased in 1 of 2 experiments; area of type 2 parenchymal lung lesions were increased in both experiments. Effects were equivalent to those observed with O_3 exposure alone. Half and quarter concentrations – no effects. Mucociliary clearance: No effect on early or late clearance of ^{85}Kr-labeled polystyrene particles. Nasal epithelial injury (measured by tritiated thymidine uptake): No effect at any concentration.
Phalen and Kleinman (1987) Sprague-Dawley rat, male, age NR, 200-225 g, N = 5-13/group/ time period Exposure: 4 h/day for 7 or 21 days	2.55 ppm (6.7 mg/m^3) SO_2, 0.3 ppm O_3, 1.2 ppm NOx, 150 µg/m^3 ferric oxide, 130 µg/m^3 nitric acid, 2.0 µM/m^3 hydrogen ion, and 500 µg/m^3 total Fe^{3+}, Mn^{2+}, and NH_4^{2+} combined; nose only	Purified air	Bronchoalveolar epithelial permeability to ^{99m}Tc-diethylenetriaminepentaacetate: No effect at either time period. Nasal mucosal permeability to ^{99m}Tc-diethylenetriaminepentaacetate: No effect at either time period. Macrophage rosette formation: Decreased (indicating damage to F_c receptors) for up to 4 days after 7- or 21-day exposure; magnitude of effect greater following 21-day exposure. By day 4 post-exposure, numbers began increasing and by day 7 were equivalent to control values. Macrophage phagocytic activity: In rats exposed for 7 days, decreased activity was observed for 2 days post-exposure. No effects observed after 21-day exposure.
SUBCHRONIC / CHRONIC			
Saldiva et al. (1992) Wistar rat, male, 2 mos old, weight NR, N = 14-30/group Exposure: 6 mos	Urban air: São Paulo, mean levels of air pollutants measured 200 m from the police station where rats were kept: 29.05 µg/m^3 (0.011 ppm) SO_2; 1.25 ppm CO, 11.08 ppb O_3, 35.18 µg/m^3 particulates	Rural air: Atibaia, an agricultural town 50 km from São Paulo was considered the control; air pollutant levels were not measured	Death: 37 of 69 São Paulo rats died before study end; autopsy of 10 animals identified pneumonia as the cause of death; 10/56 Atibaia animals died. Respiratory mechanics: Nasal resistance was higher in Atibaia animals. No differences were observed for pulmonary resistance or dynamic lung elastance. Mucus properties: São Paulo animals' tracheal mucus output was lower, relative speed of tracheal mucus was slower, ratio between viscosity and elasticity was higher for nasal mucus, and rigidity of tracheal mucus was increased. Bronchoalveolar lavage: In lavage fluid from São Paulo animals, there were increased numbers of cells, lymphocytes, polymorphonuclear cells. Histochemical evaluation: Hyperplasia was observed in respiratory epithelium of rats housed in São Paulo. Ultrastructural studies: Animals housed in São Paulo had a higher frequency of cilia abnormalities including composite cilia, microtubular defect, vesiculation, and decreased microvelocity of luminal membrane.
Lemos et al. (1994) Rats from the same cohort as Saldiva et al. (1992). N = 15/group Exposure: 6 mos	Urban air: São Paulo, mean levels of pollutants measured 200 m from police station where rats were kept: 29.05 µg/m^3 (0.011 ppm) SO_2; 1.25 ppm CO, 11.08 pb O_3, 35.18 µg/m^3 particulates	Rural air: Atibaia, agricultural town 50 km from São Paulo, considered control; air pollutant levels not measured	Nasal passage pathology: Rats housed in São Paulo had increased nasal epithelium volume, larger amounts of mucosubstances stored in epithelium, and more acidic mucus secretions in lamina propria glands.
Pereira et al. (1995) 4 groups of rats housed: 3 mos in São Paulo, 3 mos in São Paulo followed by 3 mos in Atibaia, 3 mos in Atibaia, or 6 mos at Atibaia. Wistar rats, male, 1.0-1.5 mos old, weight NR, N = 30/group	Urban air: São Paulo, levels of air pollutants measured were: ~8-50 µg/m^3 (0.003-0.019 ppm) SO_2, ~0.1-0.45 ppm nitrogen dioxide, ~4.8-7 ppm carbon monoxide, and ~50-120 µg/m^3 PM	Rural air: Atibaia, an agricultural town 50 km from São Paulo was considered the control; air pollutant levels were not measured	Lung responsiveness to methacholine: Increased respiratory system elastance resulting from increased sensitivity to methacholine in rats housed in São Paulo for 3 mos compared to all the other groups. No exposure-related effects were observed for respiratory system resistance.

Table E-8. Effects of meteorological conditions on SO_2 effects.

Study	SO_2	Condition	Effects
Barthélemy et al. (1988) Rabbit, sex NR, adult, mean 2.0 kg, N = 5-10/group; animals were mechanically ventilated Exposure: 45 min	0.5 or 5 ppm (1.31 or 13.1 mg/m^3); intratracheal	Drop in air temperature from 38 °C to 15 °C	Lung resistance: Exposure to cool air for 20 min resulted in a ~54% mean increase in lung resistance. Exposure to SO_2 for 20 min increased lung resistance by 16% at 0.5 ppm and 50% at 5 ppm. The difference in lung resistance from warm to cold air was halved (27%) by exposure to 0.5 ppm and was not significant at 5 ppm. The authors concluded that transient alteration in tracheobronchial wall following SO_2 exposure may have reduced accessibility of airway nervous receptors to cold air.
Hälinen et al. (2000a) Duncan-Hartley guinea pig, male, age and weight NR, N = 7-12/group, mechanically ventilated; animals were hyperventilated during cold air and SO_2 exposure to simulate exercise. In pre-exposure period: 15-min exposure to warm humid air, 10-min exposure to cold dry air, and 15-min exposure to warm humid air. In the SO_2 exposure period: 10-min exposures to each SO_2 concentration in cold dry air or with cold dry air alone were preceded and followed by 15-min exposures to warm humid air	1.0, 2.5, or 5 ppm (2.62, 6.55, or 13.1 mg/m^3); apparently intratracheal	Drop in intratracheal temperatures from ~35.5 °C to ~27 °C	Peak expiratory flow: Percent decreases were significantly greater with exposures to SO_2 in dry air at concentrations of 1.0 ppm (~32.7%) and 2.5 ppm (~35.6%) than with exposure to cold dry air (~27%); decrease at 5 ppm SO_2 in cold dry air (~25.3%) was similar to that with cold dry air. The effects did not persist following exposures. Tidal volume: Percent decreases were significantly greater with exposure to SO_2 in cold dry air at concentrations of 1.0 ppm (~22.4%) and 2.5 ppm (~28.3%) than with exposure to cold dry air (~18.1%); decrease at 5 ppm SO_2 in cold dry air (~17.8%) was similar to that of cold dry air. The effects did not persist following exposures. Bronchoalveolar lavage: The clean dry air group had significantly more macrophages, lymphocytes, and increased protein concentration in lavage than the warm humid air control. The cold dry air + SO_2 group had fewer macrophages than the clean dry air group and higher protein concentration than controls. Histopathology: Increased incidence of eosinophilic infiltration within and below tracheal epithelium with exposure to cold dry air or SO_2 in cold dry air.
Hälinen et al. (2000b) Duncan-Hartley guinea pig, male, age and weight NR, N = 8-9/group, mechanically ventilated; animals were hyperventilated during cold air and SO_2 exposure to simulate exercise Exposure: 60 min	1 ppm (2.62 mg/m^3); apparently intratracheal	Drop in intratracheal temperatures from ~37 °C to ~26 °C	Peak expiratory flow: Non-significant decreases compared to baseline (4.5-10.8%) at 10 and 20 min of exposure to cold dry air. With exposure to SO_2 in cold dry air: decreased significantly (11.4%, i.e., bronchoconstriction) compared to baseline at 10 min of exposure but recovered from 20 to 60 min of exposure. The effect with SO_2 exposure was not statistically significant compared to that of cold dry air alone. Tidal volume: Decreased from baseline throughout most of the exposure period with cold dry air or SO_2 in cold dry air; response with SO_2 was more shallow than that of cold dry air alone, but statistical significance compared to cold dry air was obtained only at 60 min of exposure. Bronchoalveolar lavage: Decreased neutrophil numbers in the SO_2 group compared to the warm humid air group but no significant difference compared to the cold dry air group. Histopathology: No effect in lung or tracheobronchial airway. General conclusions: Functional effects on the lower respiratory tract were weaker than in the previous study with 10-min exposures (Hälinen et al., 2000a).

Table E-9. Cardiovascular effects of SO_2 and metabolites.

Study	Conc.	Duration	Species	Effects
IN VITRO EXPOSURE				
Nie and Meng (2005)	Bisulfite/sulfite, 1:3 molar/molar, 10 µM	NR	Ventricular myocytes isolated from Wistar rat; adult; 200-300 g; N = 8	Effects of the 10 µM bisulfite/sulfite mixture on sodium current included a shift of steady state inactivation curve to a more positive potential, a shift of the time-dependent recovery from inactivation curve to the left, accelerated recovery, and shortened inactivation and activation time constants. It was concluded the bisulfite/sulfite mixture stimulated cardiac sodium channels.
Nie and Meng (2006)	Bisulfite/sulfite, 1:3 molar/molar, 10 µM	NR	Ventricular myocytes isolated from 200-300 g; N = 8	Effects of the 10 µM bisulfite/sulfite mixture on voltage-dependent L-type calcium currents included a shift of steady-state activation and inactivation to more positive potentials, accelerated recovery from inactivation, and shortened fast and slow time inactivation constants. Authors stated that their results suggested the possibility of cardiac injury following SO_2 inhalation.
ACUTE / SUBACUTE				
Hälinen et al. (2000a)	1.0, 2.5, or 5 ppm (2.62, 6.55, or 13.1 mg/m^3) in cold dry air; apparently intra-tracheal	In pre-exposure period: 15 min exposure to warm humid air, 10 min to cold dry air, and 15 min to warm humid air. In exposure period: 10 min exposures to each SO_2 concentration or cold dry air were preceded and followed by 15 min exposures to warm, humid air.	Duncan-Hartley guinea pig; male; age and weight NR; N = 7-12/ group, mechanically ventilated; animals were hyperventilated during cold air and SO_2 exposure to simulate exercise	Arterial blood pressure increased transiently during exposure to 5 ppm SO_2 in cold dry air. No analyses were done to determine if the effects on blood pressure were caused by exposure to cold air or SO_2.
Hälinen et al. (2000b)	1 ppm (2.62 mg/m^3) in cold dry air; apparently intratracheal	60 min	Duncan-Hartley guinea pig; male; age and weight NR; N = 8-9/group, mechanically ventilated; animals were hyperventilated during cold air and SO_2 exposure to simulate exercise	Blood pressure and heart rate increased similarly with exposure to cold dry air or SO_2 in cold dry air. Blood pressure generally increased during the first 10-20 min of exposure and remained steady from that point forward. The increase in heart rate was gradual. No analyses were done to determine if the effects on blood pressure were caused by exposure to cold air or SO_2.
Nadziejko et al. (2004)	1 ppm (2.62 mg/m^3); nose only	4 h	F344 rat, male, 18 mos old, weight NR, N = 20 (crossover design)	SO_2 exposure had no effect on spontaneous arrythmia frequency in aged rats. Authors urged caution in the interpretation of effects because occurrence of arrhythmias in aged rats was sporadic and variable from day to day.
Meng et al. (2003a)	10, 20, or 40 ppm (26.2, 52.4 or 105 mg/m^3); whole body	6 h	Wistar rat; male; 7-8 wks old; 180-200 g; N = 10/group	A dose-related decrease in blood pressure was observed at ≥ 20 ppm.
Meng et al. (2003a)	10, 20, or 40 ppm (26.2, 52.4, or 104.8 mg/m^3); whole body	6 h/day for 7 days	Wistar rat, male; 7-8 wks old; 180-200 g; N = 10/group	Dose-related decreases in blood pressure were observed on exposure day 3 in the 10 ppm group, exposure days 2-6 in the 20 ppm group, and all exposure days in the 40 ppm group. The authors noted possible adaptive mechanism in the low but not the high dose group.
Langley-Evans et al. (1996)	5, 50, or 100 ppm (13.1, 131, or 262 mg/m^3); whole body	5 h/day for 7-28 days	Wistar rat; male; 7 wks old; weight NR; N = 4-5/treatment group, 8 controls	GSH was depleted in the heart at 5 and 100 ppm. At 50 ppm, GSH level decreased in heart at 7 days and returned to normal by 14 days. No effects were observed for other GSH-related enzymes. Injury and inflammation were not assessed in heart, but assessment in lung revealed no effect.
Meng et al. (2003b)	8.4, 21, or 43 ppm (22, 56, or 112 mg/m^3); whole body	6 h/day for 7 days	Kunming albino mouse; male and female; 5 wks old; 19 ± 2 g; N = 10/sex/group	Changes observed in heart (concentrations of effect) included: lower SOD activity in males and females (≥ 8.4 ppm), higher TBARS level in males and females (≥ 8.4 ppm), lower GPx activity in males (8.4 and 21 ppm; also 43 ppm according to text) and lower GSH level in males (43 ppm). Authors concluded that SO_2 induced oxidative damage in hearts of mice.
Wu and Meng (2003)	8.4, 24.4, or 56.5 ppm (22, 64, or 148 mg/m^3); whole body	6 h/day for 7 days	Kunming-strain mouse; male; age NR; 18-20 g; N = 10/group	GSH, GST, and G6PD activities were decreased in the heart at 56.5 ppm.

Table E-10. Hematological effects of SO_2.

Study	Concentration	Duration	Species	Effects
ACUTE/SUBACUTE				
Baskurt (1988)	0.87 ppm (2.36 mg/m^3); whole body	24 h	Swiss Albino rat; male; age NR; 250-300 g; N = 51, 50	Effects of SO_2 exposure included increased hematocrit, sulfhemoglobin and osmotic fragility and decreased whole blood and packed cell viscosities. RBC number, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration, and plasma viscosity were not significantly altered.
SUBCHRONIC				
Gümüşlü et al. (1998)	10 ppm (26.2 mg/m^3); whole body	1 h/day, 7 days/wk for 8 wks	Swiss-Albino rat; male; 2.5-3.0 mos old; weight NR; N = 30 (14 controls, 16 treated)	Decreased CuZn SOD activity, increased GPx and GST activity, and increased TBARS formation were observed in RBC of treated rats. No significant effect on G6PD or catalase levels was observed.
Yargiçoğlu et al. (2001)	10 ppm (26.2 mg/m^3); whole body	1 h/day, 7 days/wk for 6 wks	Albino rat, male; 3, 12, and 24 mos old; mean weight 213-448 g; N = 10/group	Enzyme and GSH activity (GPx, catalase, GSH, and GST) were increased and CuZn SOD activity was decreased in RBCs of all experimental groups compared to controls. RBCs in older rats had lower levels of all antioxidant enzymes and increased TBARS activity compared to younger rats.
Langley-Evans et al. (1997; 2007)	100 ppm (286 mg/m^3); whole body. Units were initially reported as µg/m^3 but were corrected per correspondence w/author.	5 h/day for 28 days	Wistar rat, male; 7 wks old; weight NR; N = 4-16	Dams were fed diets containing casein at 180 [control], 120, 90, or 60 g/kg during pregnancy and their offspring were exposed to air or SO_2 as adults. In blood of offspring, SO_2 exposure significantly reduced the numbers of circulating total leukocytes and lymphocytes in the 180 and 120 g/kg dietary groups; neutrophils numbers were not affected in any group. GSH levels in the 180 and 60 g/kg (but not the two intermediate) dietary groups were reduced by SO_2 exposure.
Etlik et al. (1995)	10 ppm (26.2 mg/m^3); whole body	1 h/day for 30 days	Guinea pig; sex and age NR; 250-450 g; N = 12/group	SO_2 exposure resulted in RBC membrane lipoperoxidation (elevated levels of malonyldialdehyde) and other oxidative damage (elevated osmotic fragility ratios and levels of methemoglobin and sulfhemoglobin). All effects significantly ($p < 0.05$) mitigated by injections of Vitamin E+C three times per wk.
Ağar et al. (2000)	10 ppm (26.2 mg/m^3); whole body	1 h/day, 7 days/wk for 6 wks	Swiss Albino rat; male; 3 mos old; weight NR; N = 10/group in 4 groups	RBC parameters were monitored in non-diabetic rats, non-diabetic rats exposed to SO_2, alloxan-induced diabetic rats, and diabetic rats exposed to SO_2. In both non-diabetic and diabetic rats exposed to SO_2, levels of GPx, catalase, GSH, GST, and TBARS were elevated in RBC while those of SOD were reduced.
Etlik et al. (1997)	10 ppm (26.2 mg/m^3); whole body	1 h/day for 45 days	Rat; sex and age NR; 214-222 g; N = 6-8/group	SO_2 exposure significantly elevated levels of methemoglobin, sulfhemoglobin and malonyldialdehyde, the latter of which was substantially reversed by Vitamin E+C treatment. RBC osmotic fragility was increased by SO_2, and again partially mitigated by Vitamin E+C. SO_2 elevated RBC, white blood cell, hemoglobin and hematocrit values, but not mean corpuscular volume, mean corpuscular hemoglobin or mean corpuscular hemoglobin concentration. Vitamin E+C exposure did not affect these parameters.

Table E-11. Carcinogenic effects of SO_2.

Study	Concentration	Duration	Species	Effects
PULMONARY EFFECTS				
Gunnison et al. (1988)	0, 10, or 30 ppm (0, 26.2, or 78.6 mg/m³) SO_2 (whole body) ± 1 mg B[a]P 0, 100 or 400 ppm W, or [400 ppm W + 40 ppm Mo] in a low-Mo diet, ± B[a]P (See Effects column) ± B[a]P	SO_2: 21 wk, 5 day/wk (minus holidays), 6 h/day High W, low Mo diet: 21 wk, 7 day/wk B[a]P: 15 wk, once per wk starting wk 4	Rat, Sprague-Dawley; male; 9 wk old; ~315- 340 g; N = 20-74/group	Purpose was to investigate carcinogenic/cocarcinogenic effects of SO_2 inhalation or dietary-induced high levels of systemic sulfite/bisulfite in conjunction with tracheal installation of B[a]P. High drinking water levels of W in conjunction with low-Mo feed induce sulfite oxidase deficiency in rats, and thus high systemic levels of sulfite and bisulfite (at 0, 100 or 400 ppm W, mean plasma sulfite was 0, 0 or 44 μM, while mean tracheal sulfite + bisulfite was 33, 69 or 550 nmol/g wet wt). Mortality in B[a]P groups (~50% after ~380-430 d) was due almost exclusively to SQCA of the respiratory tract; survival rate was excellent for other groups (~50% mortality after ~620-700 d). Results indicate no SQCA was induced in any of the SO_2 inhalation or systemic sulfite + bisulfite groups, nor were incidences in the B[a]P groups enhanced by such coexposures. This lack of cocarcinogenicity does not support the hypothesis that SO_2 exposure could elevate systemic sulfite/bisulfite, generating $GSSO_3H$, which would inhibit GST and reduce intracellular GSH, thus interfering with a major detoxication pathway for B[a]P and enhancing its carcinogenicity. Authors note that due to the high incidence of animals with tumors in the two B[a]P only groups (65/72 and 63/72), cocarcinogenicity of SO_2 or sulfite + bisulfite could only have been demonstrated by shortening of tumor induction time and/or increased rate of SQCA appearance—neither were observed.
Ohyama et al. (1999)	0, 0.2 mL C, or (0.2 mL DEP+C ± [4 ppm (10.48 mg/m³) SO_2 or 6 ppm (11.28 mg/m³) NO_2 or 4 ppm SO_2 + 6 ppm NO_2]; whole body) [Note: 0.2 mL CBP = 1mg; 0.2 mL DEcCBP =1 mg CBP + 2.5 mg DEP]	SO_2 and/or NO_2: 10 mo, 16 h/day CBP or DEcCBP: 4 wk, once/wk by intratracheal infusion	Rat, SPF F344/Jcl; male; 6 wk old; wt NR; N = 23-30/group in 6 groups	Purpose was to study effects of DEP on rat lung tumorigenesis and possible tumor promoting effects of SO_2 or NO_2 singly or together. Alveolar hyperplasia and adenoma were significantly ($p < 0.01$-0.05) increased over controls in the CBP group, but not the DEcCBP group. This was ascribed to induction of alveolitis and AM infiltration (a tumor response specific to rat and of questionable relevance to humans) in the former group, but apparently prevented by DEP in the latter. Alveolar bronchiolization near small hyaline masses of deposited DEcCBP was observed in all DEcCBP groups, the masses presumably allowing long-term exposure to DEP extracts by contacted alveolar epithelium. DNA adducts were found only in the three gas-exposed groups. Discounting the CBA group, elevated alveolar hyperplasia was seen only in the DEcCBP + NO_2 group, and elevated incidences of alveolar adenoma in the DEcCBP + SO_2 and particularly the DEcCBP + NO_2 groups; neither effect was observed with coexposure to both gases—speculated by the authors to perhaps result from inhibition of the stronger NO_2 promotion by HSO_3^-. Thus, SO_2 appears to have weaker capacity than NO_2 for promoting tumor induction (and perhaps genotoxicity) by DEP extract, and may antagonize such effects by NO_2 during coexposure of the gases.
Ito et al. (1997)	0, C, or (25 mg SPM+C ± [4 ppm (10.48 mg/m³) SO_2 or 6 ppm (11.28 mg/m³) NO_2 or 4 ppm SO_2 + 6 ppm NO_2]); whole body	SO_2 and/or NO_2: 11 mo, 16 h/day C ± SPM: 4 wk, once/wk by intratracheal injection	Rat, SPF Fisher 344; male; 5 wk old; wt NR; N = 5/group in 6 groups	Purpose was to study effects of Tokyo air SPM, with or without coexposure to SO_2 or NO_2 or their combination, on the development of proliferative lesions of PEC. PEC hyperplasia was significantly ($p < 05$) increased by exposure to SPM, but coexposure to either gas or their mixture was without additional effect. No PEC papillomas were observed in control groups, while a few were seen in the SPM groups, irrespective of gas coexposures. Thus, SO_2 demonstrated no tumor promotion or cocarcinogenic properties. [Study did not describe the nature of the carbon (C) used.]
Heinrich et al. (1989)	0 or [10 ppm (26.2 mg/m³) SO_2 + 5 ppm (9.4 mg/m³) NO_2] ± [3 or 6 mg/kg bw of DEN]; exposure to gases whole body	SO_2 + NO_2: 6, 10.5, 15, or 18 mo, 5 day/wk, 19 h/day DEN: once by s.c. injection, ~2 wk after the start of inhalation exposure	Hamster, Syrian golden; both sexes; 10 wk old; bw NR; N = 40/sex per each of 12 exposure groups	The principle focus of this large study was to examine whether two inhaled diesel-exhaust emission preparations (± particulates) could enhance the tumorigenesis of injected DEN. Ancillary aim was to see whether inhalation of the irritant SO_2+NO_2 mixture could cause similar enhancement of DEN tumorigenicity. Gas mixture exposure did not affect bw gain, but slightly shortened survival times (although significantly only for females). Apart from effects attributed to DEN, serial sacrifices showed progressive increases in ciliated tracheal cell aberrations and in number of tracheal mucosal cells. In the lung, gas mixture-related effects were limited to a progressing alveolar lesion involving lining with bronchiolar epithelium and the presence of some pigment-containing AM, and to a mild, diffuse thickening of the alveolar septa. SO_2+NO_2 exposure did not by itself elevate tumor rate in the upper respiratory tract, nor did it enhance increases induced by DEN. Thus the mixture appeared to have no tumor inducing or promoting effects.
NONPULMONARY EFFECTS				
Klein et al. (1989)	0 or 6 ppm (0 or 15.72 mg/m³) SO_2, ± 0.2 ppm (600 μg/m³); whole body; NDMA	20 mo, 5 day/wk, 4 h/day	Rat, Sprague-Dawley; female; age and wt NR; N = 36/group in 4 relevant groups	This is a preliminary report for observations after 20 mo (800 h inhalation in 200 exposures, with calculated inhaled cumulative doses of 77 mg SO_2 and 2-3 mg NDMA per rat). The effects of NDMA ± SO_2 inhalation were studied. Group mortality was as follows: control (3/36), SO_2 (5/36), NDMA (4/36), NDMA + SO_2 (7/36). The only tumors observed were nasal: control (0), SO_2 (0), NDMA (1), NDMA + SO_2 (3). No observable parameters, including body wt gain, were affected by the additional SO_2 exposure; assessment of tumor incidence effects could not yet be performed.

Table E-12. Nervous system effects of SO_2 and metabolites.

Study	Concentration	Duration	Species	Effects
IN VITRO / EX VIVO				
Du and Meng (2004a)	1, 10, 50, or 100 µM SO_2 derivatives (1:3, $NaHSO_3$ to Na_2SO_3)	Not specified	Wistar rat; sex NR; 6-12 days old; weight and number NR; typical observations made on 60 isolated hippocampal neurons per concentration	Exposure to SO_2 derivatives (sulfite, bisulfite) reversibly increased the amplitude of potassium channel TOCs in a dose-dependent and volt-age-dependent manner. Compared to controls, 10 µM SO_2 shifted inactivation of depolarization toward more positive potentials without significantly affecting the activation process. By increasing maximal TOC conductance and delaying TOC inactivation, micromolar concentrations of SO_2 derivatives may increase the excitability of hippocampal neurons and thus contribute to the enhanced neuronal activity associated with SO_2 intoxication.
Du and Meng (2004b)	1 or 10 µM SO_2 derivatives (1:3, $NaHSO_3$ to Na_2SO_3)	2-4 min	Wistar rat; both sexes; 10-15 days old; weight and number NR; N = 6-13 isolated dorsal root ganglion neurons averaged per endpoint	Maximum sodium current amplitudes for both TTX-S and TTX-R channels were increased by exposure to SO_2 derivatives (10 or 1 µM, respectively), with amplitudes diminished at more negative evoking potentials and enhanced at less negative or positive potentials. SO_2 derivatives (a) slowed both current activation and inactivation for both types of sodium channels; (b) shifted activation currents to more positive potentials, increasing threshold voltages for action potential generation and contributing to reduced neuron excitability; and (c) caused even larger counteracting positive shifts in inactivation voltages tending to increase dorsal root ganglion neuron excitability. On balance, the data suggest micromolar concentrations of sulfite/bisulfite can increase the excitability of dorsal root ganglion neurons, providing a basis for SO_2-associated neurotoxicity.
Du and Meng (2006)	0.01, 0.1, 0.5, or 1 µM SO_2 derivatives (1:3, $NaHSO_3$ to Na_2SO_3)	Not specified, but brief ("added to the external solution just before each experiment")	Wistar rat; both sexes; 10-15 days old; weight and number NR; N = 6-15 isolated dorsal root ganglion neurons averaged per endpoint	In isolated dorsal root ganglion neurons, SO_2 derivatives increased HVA-I_{Ca} amplitudes in a concentration- and depolarizing voltage-dependent manner (EC_{50} was ~0.4 µM) by altering Ca channel properties. This effect was partially reversible by SO_2 derivative washout, and was PKI-inhibitable, indicating involvement of PKA and secondary messengers. Additionally, exposure caused a positive shift in reversal potential. SO_2 derivatives also delayed activation and inactivation of Ca channels, but the latter was more pronounced, thus overall prolonging action potential duration and increasing HVA-I_{Ca}. Exposure also slowed the fast component and accelerated the slow component of recovery from Ca channel inactivation. Thus, ≤ 1 µM sulfite/bisulfite caused prolonged opening and altered properties of Ca channels, elevated HVA-I_{Ca}, and abnormal Ca signaling with neuronal cell injury. Authors speculate these effects may correlate with SO_2 inhalation toxicity, perhaps leading to abnormal regulation via peripheral neuron Ca channels of nociceptive impulse transmission.
ACUTE / SUBACUTE / SUBCHRONIC				
Wu and Meng (2003)	8.4, 24.4, or 56.5 ppm (22, 64, or 148 mg/m³); whole body	6 h/day for 7 days	Kunming-strain mouse; male; age NR; 18-20 g; N = 10/group	Decreased glutathione, G6PD, and GST activities were observed in the brain at 24.4 and 56.5 ppm.
Haider et al. (1981)	10 ppm (26.2 mg/m³); whole body	1 h/day for 21 or 24 days	Guinea pig; sex NR; adult; 250-500 g; N = 12/group (6/subgroup)	The effects of SO_2 exposure on lipid profiles, lipid peroxidation and lipase activity in three regions of the brain (cerebral hemisphere, CH; cerebellum, CB; brain stem, BS) were examined. Significant ($p < 0.001$-0.05) findings include reductions in total lipids (CH, BS; also CB, but nonsignificant) and free fatty acids (CH, CB, BS). PL were elevated in CH, but reduced in CB; Chol was elevated in CH, but reduced in CB and BS; and esterified fatty acids were elevated in CB, but reduced in CH and BS. Levels of malonaldehyde and lipase activity were elevated in all regions. Results indicate that subacute brief exposures to SO_2 can lead to degradation of brain lipids, with the exact nature of the lipid alterations dependent upon brain region.

Study	Concentration	Duration	Species	Effects
Haider et al. (1982)	10 ppm (26.2 mg/m^3); whole body	1 h/day for 30 days	Charles Foster rat; male; adult; 150-200 g; N = 12/group (6/subgroup)	The effects of SO_2 exposure on lipid profiles, lipid peroxidation and lipase activity in three regions of the brain (cerebral hemisphere, CH; cerebellum, CB; brain stem, BS) were examined. Significant ($p < 0.001$-0.05) findings include reductions in total lipids (CH, BS, CB), while PL were elevated only in CB. Chol was elevated in CH and CB, but not BS; and gangliosides were elevated in CB and BS, but reduced in CH. Lipid peroxidation (malonaldehyde formation) was elevated in whole brain and all regions (although nonsignificantly in BS), as was lipase activity in CH, the only tissue examined. Despite regional differences in PL and Chol changes, Chol/PL ratios were elevated in all three brain regions (again nonsignificantly in BS). Results are somewhat different than those seen in guinea pig (Haider et al., 1981), but again suggest that subacute brief exposures to SO_2 can lead to degradation of brain lipids, with the exact nature of the lipid alterations dependent upon brain region.
Haider and Hasan (1984)	10 ppm (26.2 mg/m^3) SO_2 alternated with 20 ppm (14.7 mg/m^3) H_2S; whole body	1 h/day for 30 days (alternating SO_2 or H_2S)	Guinea pig; sex and age NR; 250-400 g; N = 18/group in 2 groups (6/group in some subgroups)	The effects of alternating SO_2 + H_2S exposure on lipid profiles, lipid peroxidation and lipase activity in four regions of the brain (cerebral hemisphere, CH; basal ganglia, BG; cerebellum, CB; brain stem, BS) and in the spinal cord (SC) were examined. Significant ($p < 0.001$-0.05) findings include reductions in total lipids and Chol, and elevated lipid peroxidation (malonaldehyde formation) and lipase activity, in all brain regions and SC. Chol/PL ratios were also reduced in all tissues (but nonsignificantly in BG and CB). For other parameters (PL, free fatty acids, esterified fatty acids, and gangliosides), changes were observed in most tissues but were region-specific. Results indicate that subacute brief, alternating exposures to SO_2 or H_2S lead to degradation of brain lipids, again with the exact nature of the lipid alterations dependent upon brain/spinal cord region. Additionally, some of the effects observed for this mixture vary from those seen with SO_2 alone (Haider et al., 1981; 1982).
Ağar et al. (2000)	10 ppm (26.2 mg/m^3) (± iv alloxan to induce experimental type 1 diabetes); whole body	1 h/day, 7 days/wk for 6 wks	Swiss albino rat; male; 3 mos old; weight NR; N = 10/group in 4 groups	In retina tissue, exposure elevated SOD activity and reduced GPx and catalase activities. TBARS were elevated only in non-diabetic rats exposed to SO_2. In brain tissue, exposure elevated SOD and reduced GPx activities in both non-diabetics and diabetics, while catalase activities were not affected; TBARS were elevated in both non-diabetics and diabetics. With respect to VEPs, exposure prolonged latencies in 4 of 5 VEP components in non-diabetics and 5 of 5 in diabetics, while reducing virtually all peak-to-peak amplitudes in non-diabetics and diabetics. For many endpoints, SO_2 effects were additive to those resulting from the induced diabetic condition. In summary, brain and retinal anti-oxidant and lipid peroxidation status, as well as neuro-visual performance were affected by subchronic exposure to brief periods of 10 ppm SO_2, and these effects were exacerbated by a diabetic condition.
SUBCHRONIC / CHRONIC				
Küçükatay et al. (2003)	10 ppm (26.2 mg/m^3) (± iv alloxan to induce experimental type 1 diabetes); whole body	1 h/day, 7 days/wk for 6 wks	Rat; male; 3 mos old; weight not reported; N = 10/group in 4 groups	In brain tissue, SO_2 exposure elevated SOD and reduced GPx activities in both non-diabetics and diabetics, while catalase activities were not affected; TBARS were elevated in both non-diabetics and diabetics. With respect to afferent peripheral nerve pathways (SEPs), exposure prolonged latencies in 4 of 4 SEP components in both non-diabetics and diabetics; also altered were some inter-peak latencies (non-diabetics and diabetics) and some peak-to-peak amplitudes (non-diabetics only). In some cases, SO_2 effects were additive to those resulting from the induced diabetic condition. In summary, brain anti-oxidant and lipid peroxidation status, as well as afferent peripheral nerve pathways, were affected by subchronic exposure to 10 ppm SO_2, and these effects were exacerbated by a diabetic condition. Authors suggest that SO_2 exposure could potentiate the incidence and/or severity of diabetes.

Study	Concentration	Duration	Species	Effects
Yargiçoğlu et al. (1999)	10 ppm (26.2 mg/m^3); whole body	1 h/day, 7 days/wk for 6 wks	Swiss albino rat; male; 3, 12, or 24 mos old; weight NR; N = 10/group in 6 groups	Effects of aging ± SO_2 exposure on levels of lipid peroxidation (TBARS), antioxidant enzyme status (catalase, GPx, SOD), and afferent peripheral nerve pathways (SEPs) were monitored in the brain of young (Y, 3 mo), middle-aged (M, 12 mo) and old (O, 24 mo) rats. In addition to age-related changes, SO_2 exposure significantly ($p < 0.0001$-0.02) elevated TBARS and SOD, while reducing GPx (Y, M, O); catalase levels were not affected. Of 4 monitored SEP component peaks, SO_2 significantly ($p < 0.01$-0.05) prolonged latencies in groups Y (4/4) and M (1/4), but not in O (0/4). Peak-to-peak amplitudes were decreased in Y, (2/3) and increased in M (1/3), but not affected in O (0/3). Taken together, these data indicate that subchronic exposure to brief periods of 10 ppm SO_2 can impact afferent peripheral nerve pathways and the lipid peroxidation and antioxidant enzyme status of the brain.
Kilic (2003)	10 ppm (26.2 mg/m^3); whole body	1 h/day, 7 days/wk for 6 wks	Swiss albino rat; male; 3, 12, or 24 mos old; weight NR; N = 10/group in 6 groups	Effects of aging ± SO_2 exposure on levels of lipid peroxidation (TBARS), antioxidant enzyme status (catalase, GPx, SOD), and visual system function (VEPs) were monitored in the brain and eye (retina and lens) of young (Y, 3 mo), middle-aged (M, 12 mo) and old (O, 24 mo) rats. In addition to age-related changes, SO_2 exposure significantly ($p < 0.0001$-0.04) elevated TBARS in brain and lens (Y, M, O), and in retina (Y); reduced GPx in brain (Y) and lens (Y, M, O); reduced catalase in retina (Y, M, O); and elevated SOD in brain (Y, M), retina (Y, M, O) and lens (M, O). Of 5 monitored VEP component peaks, SO_2 prolonged latencies in groups Y (4/5), M (3/5) and O (1/5). Taken together, these data indicate that subchronic exposure to brief periods of 10 ppm SO_2 can impact the visual system and the lipid peroxidation and antioxidant enzyme status of the brain and eye.
NEUROBEHAVIOR				
Petruzzi et al. (1996)	5, 12, or 30 ppm (13.1, 31.4, or 78.6 mg/m^3); whole body	Near continuous (80% of time) exposure from 9 days before mating through the 12-14th day of pregnancy	CD-1 mouse, adult male and female parental animals were exposed (N = 10/group/sex) (N = 8 litters/group, fostered by unexposed dams at birth) were evaluated at 2-18 days of age; adult male offspring also evaluated (N = 8/group)	Adults: Observation of behavior outside the exposure chamber on exposure days 3, 6, and 9 revealed dose-related increases in digging and decreases in grooming by females in the 30 ppm group on exposure day 9; non-dose related increases were observed for crossing and wall rearing by females in the 30 ppm group on exposure day 9. Observance of behaviors in 2 breeding pairs/group in the 12 and 30 ppm groups revealed increased rearing and social interaction in the 30 ppm group shortly after the start of exposure, followed by return to baseline levels; effects were generally of greater magnitude in males.

Table E-13. Reproductive and developmental effects of SO_2.

Study	Concentration	Duration	Species	Effects
Meng and Bai (2004)	8.4, 21, or 43 ppm (22, 56, or 112 mg/m^3); whole body	6 h/day for 7 days	Kunming albino mouse; male; 5 wks old; 19 ± 2 g; N = 10/group	Changes observed in mouse testes (concentrations of effects) included decreased activities of SOD (43 ppm, possibly at 21 ppm according to text) and GPx (≥ 21 ppm), increased catalase activity (8.4 and 21 ppm), decreased GSH level (≥ 21 ppm), and increased TBARS levels (≥ 8.4 ppm). The authors concluded that SO_2 can induce oxidative damage in testes of mice.
Gunnison et al. (1987)	10 or 30 ppm (26.2 or 78.6 mg/m^3); whole body	6 h/day, ~5 days/wk for 21 wks (total of 99 days)	Sprague-Dawley CD rat; male; 8 wks old; weight NR; N = 70/group in 3 groups (inhalation series)	No significant ($p < 0.05$) effect on testes histopathology was found, although there was a very slight and probably biologically insignificant increase in relative testes weight. (0.61 ± 0.02 vs. 0.56 ± 0.02, % body weight).
Singh (1989)	32 or 65 ppm (83.8 or 170 mg/m^3); whole body	Gestation day 7-18	CD-1 mouse dams were exposed; numbers of dams exposed and offspring evaluated not indicated	No significant effects were observed for number of live pups born/litter. Pup birth weight was lower at 65 ppm. Righting and negative geotaxis reflexes were delayed at both concentrations.
Petruzzi et al. (1996)	5, 12, or 30 ppm (13.1, 31.4, or 78.6 mg/m^3); whole body	Near continuous (80% of time) exposure from 9 days before mating through the 12-14th day of pregnancy	CD-1 mouse; adult male and female parental animals were exposed (N = 10/group/sex) and male and female offspring (N = 8 litters/group, fostered by unexposed dams at birth) were evaluated at 2-18 days of age; adult male offspring also evaluated (N = 8/group)	Decreased food and water intake were observed in parental males and females of the 12 and 30 ppm groups at the start of mating (exposure days 9-13). No effects observed for mating or successful pregnancies. There were no effects on litter sizes, sex ratio, or neonatal mortality (data not shown by authors). No effects observed for birth weight, postnatal body weight gain, somatic and neurobehavioral development (e.g., eyelid and ear opening, incisor eruption, and reflex development); no postnatal developmental data were shown by authors. No effects observed in passive avoidance testing of adult males.
Fiore et al. (1998)	5, 12, or 30 ppm (13.1, 31.4, or 78.6 mg/m^3); whole body	Near continuous (90% of time) exposure from 9 days before mating through the 14th day of pregnancy	CD-1 mouse; adult male and female parental animals were exposed and adult male offspring (fostered by unexposed dams at birth) were evaluated at ~120 days of age, N = 11-12 offspring/group	In 20-min encounters with unexposed males, prenatally-exposed males compared to controls displayed (dose(s) of effect, time of testing effect observed) increased duration of self grooming (5 ppm, 15-20 min), decreased frequency and duration of tail rattling (≥ 5 ppm at 5-10 min and 12 ppm at 10-15 min), and decreased duration of defensive postures (≥ 12 ppm, 0-5 min). Authors also noted a non-significant decrease in freezing (apparently at all dose levels) and non-significant increases in social exploration (apparently at all doses) and rearing (apparently at ≥ 12 ppm).
Douglas et al. (1994)	5 ppm (13.1 mg/m^3); whole body	2 h/day for 13 wks	New Zealand White rabbit; male and female; N = 3-4/group; 1-day-old; immunized against *Alternaria tenuis*	Following subchronic exposure beginning in the neonatal period, there were no effects on lung resistance, dynamic compliance, transpulmonary pressure, tidal volume, respiration rate, or min volume.

Table E-14. Endocrine system effects of SO_2.

Study	Concentration	Duration	Species	Effects
Lovati et al. (1996)	5 or 10 ppm (13.1 or 26.2 mg/m^3); whole body	24 h/day for 15 days	Sprague-Dawley CD rat; male; age NR; 250-275 g; N = 9/subgroup in 9 subgroups	Subjects were rats fed standard diet (normal) or high cholesterol diet, and rats with streptozotocin-induced diabetes fed standard diet. In diabetic rats, there was no effect on glucose levels. Exposure to ≥ 5 ppm lowered plasma insulin level in normal and hypercholesterolemic diet groups, but elevated it (non-significantly) in diabetic rats. In each rat model, inhalation of SO_2 at levels without overt effects affected insulin levels. Specific effects varied according to diet or diabetes.
Ağar et al. (2000)	10 ppm (26.2 mg/m^3); whole body	1 h/day, 7 days/wk for 6 wks	Swiss Albino rat; male; 3 mos old; weight NR; N = 10/group	Effects were compared in non-diabetic rats and rats with alloxan-induced diabetes. SO_2 increased blood glucose in diabetic and non-diabetic rats.
Küçükatay et al. (2003)	10 ppm (26.2 mg/m^3); whole body	1 h/day, 7 days/wk for 6 wks	Rat, male; 3 mos old; weight NR; N = 10/group in 4 groups	Effects were compared in normal rats and rats with alloxan-induced diabetes. SO_2 elevated blood glucose levels in both non-diabetics and diabetics.

Table E-15. Liver and gastrointestinal effects of SO_2.

Study	Concentration	Duration	Species	Effects
SUBACUTE / SUBCHRONIC				
Meng et al. (2003c)	7.86, 20, or 40 ppm (22, 56, or 112 mg/m^3) per author conversion; whole body	6 h/day for 7 days	Kunming albino mouse, male and female; 5 wks old; 19 ± 2 g; N = 6/sex/subgroup	Effects observed in stomach (concentration of effect) included: increase in SOD activity (7.86 ppm, males only) and TBARS level (≥ 7.86 ppm) and decreases in SOD (≥ 20 ppm, males only) and GPx activities (≥ 20 ppm, males only) and GSH level (40 ppm). Effects observed in intestine were increases in catalase activity (≥ 20 ppm in males, 40 ppm in females) and TBARS level (≥ 20 ppm) and decreases in SOD (≥ 7.86 ppm) and GPx (≥ 20 ppm) activities and GSH level (≥ 7.86 ppm).
Wu and Meng (2003)	8.4, 24.4, or 56.5 ppm (22, 64, or 148 mg/m^3); whole body	6 h/day for 7 days	Kunming-strain mouse; male; age NR; 18-20 g; N = 10/group	No effects were observed in the liver at 8.4 or 24.4 ppm. GST and G6PD activities and GSH level were decreased at 56.5 ppm.
Bai and Meng (2005b)	5.35, 10.70, or 21.40 ppm (14, 28, or 56 mg/m^3); whole body	6 h/day for 7 days	Wistar rat; male; age NR; 180-200 g; N = 6/group in 4 groups	Significant and concentration-dependent changes in mRNA (mid and high concentrations) and protein expression (all concentrations) included increases for *bax* and p53 apoptosis-promoting genes, and decrease for *bcl-2* apoptosis-repressing gene. Authors speculated potential impact on human apoptosis-deficient diseases.
Qin and Meng (2005)	5.35, 10.70, or 21.40 ppm (14, 28, or 56 mg/m^3); whole body	6 h/day for 7 days	Wistar rat; male; age NR; 180-200 g; N = 6/group in 4 groups	SO_2 caused significant concentration-dependent reductions in liver enzyme activities and gene expression for CYP1A1 and CYP1A2. Effects were seen at the mid and high concentrations (only high for CYP1A1 enzyme activity), but not the low. Authors speculate that underlying mechanisms may involve oxidative stress and/or cytokine release, and may represent an adaptive response to minimize cell damage.

Study	Concentration	Duration	Species	Effects
Lovati et al. (1996)	5 or 10 ppm (13.1 or 26.2 mg/m^3); whole body	24 h/day for 15 days	Sprague-Dawley CD rat; male; age NR; 250-275 g; N = 9/subgroup	Subjects were rats fed standard diet (normal) or high cholesterol diet, and rats with streptozotocin-induced diabetes fed standard diet. SO_2 (≥ 5 ppm) elevated plasma triglycerides in normal and hypercholesterolemic groups, while 10 ppm lowered plasma high density lipoprotein cholesterol in hypercholesterolemic rats. In diabetic rats, 10 ppm SO_2 lowered triglycerides and free fatty acids without affecting high density lipoprotein cholesterol or total cholesterol. In the liver, SO_2 elevated triglycerides in normal and hypercholesterolemic groups (at 10 ppm), but lowered it in diabetic rats (at ≥ 5 ppm); esterified cholesterol was elevated in normal rats (at 10 ppm), but lowered in diabetic rats (at ≥ 5ppm), and free cholesterol was unchanged in all groups. In normal rats, triglycerides secretion rate was inhibited by 10 ppm SO_2. SO_2 caused several changes in plasma apolipoprotein composition in normal and hypercholesterolemic groups, but not in diabetic rats. Leukotriene parameters were not affected. Thus, in each rat model, inhalation of SO_2 at levels without overt effects affected plasma and tissue lipid content. Specific effects varied according to diet or diabetes.
Langley-Evans et al. (1996)	5, 50, or 100 ppm (13.1, 131, or 262 mg/m^3); whole body	5 h/day for 7-28 days	Wistar rat; male; 7 wks old; weight NR; N = 4-5/treatment group, 8 controls	GSH was depleted in the liver at 5 and 100 ppm but not at 50 ppm. With respect to GSH-related enzymes, exposure to 5 ppm decreased GRed and GST activity in the liver. Exposure to 50 ppm did not affect liver GST, but decreased liver GRed and GPx.
Langley-Evans et al. (1997); Langley-Evans (2007)	100 ppm (286 mg/m^3); whole body Units were incorrectly reported as µg/m^3 in the study but were corrected according to information provided by study author	5 h/day for 28 days	Wistar rat; male; 7 wks old; weight NR; N = 4-16	Adult rats exposed to air or SO_2 were born to dams fed diets with varying casein contents (180 [control], 120, 90 or 60 g/kg) during gestation. In the liver, SO_2 exposure elevated GSH level in the 120 g/kg dietary group but lowered it in the 60 g/kg dietary group. SO_2 did not affect liver GST in any group. SO_2 increased GCS levels in the 180 and 90 g/kg groups, GPx in the 60 g/kg group, and GRed in the 120 and 90 g/kg groups. This study provides information for an extremely high concentration level but is being acknowledged here with the unit corrected to verify that a low-concentration level study was not missed.
Gunnison et al. (1987)	10 or 30 ppm (26.2 or 78.6 mg/m^3); whole body	6 h/day, ~5 days/wk for 21 wks (total of 99 days)	Sprague-Dawley CD rat; male; 8 wks old; weight NR; N = 70/group in 3 groups (inhalation series)	No effects on relative liver weight or histopathology were found.
Ağar et al. (2000)	10 ppm (26.2 mg/m^3); whole body	1 h/day, 7 days/wk for 6 wks	Swiss Albino rat; male; 3 mos old; weight NR; N = 10/group	Effects were compared in non-diabetic rats, non-diabetic rats exposed to SO_2, alloxan-induced diabetic rats, and diabetic rats exposed to SO_2. SO_2 increased blood glucose in all groups, but did not affect total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, very low density lipoprotein cholesterol, or triglyceride levels in either normal or diabetic rats.
Küçükatay et al. (2003)	10 ppm (26.2 mg/m^3); whole body	1 h/day, 7 days/wk for 6 wks	Rat; male; 3 mos old; weight NR; N = 10/group in 4 groups	Effects compared in normal rats and rats with alloxan-induced diabetes. Among the significant effects observed, SO_2 exposure enhanced the body weight loss seen in the diabetic group, but did not affect body weight gain in the control group. SO_2 elevated blood glucose levels in both controls and diabetics, but lowered triglycerides only in diabetics. Cholesterol parameters were not affected.

Table E-16. Renal effects of SO_2.

Study	Concentration	Duration	Species	Effects
Wu and Meng (2003)	8.4, 24.4, or 56.5 ppm (22, 64, or 148 mg/m^3)	6 h/day for 7 days	Kunming-strain mouse; male; age NR; 18-20 g; N = 10/group	GST was decreased in the kidney at 24.4, or 56.5 ppm (64 and 148 mg/m^3) and G6PD activity was decreased at 56.5 ppm (148 mg/m^3). Kidney GSH levels were reduced at all exposure levels.
Langley-Evans et al. (1996)	5, 50, or 100 ppm (13.1, 131, or 262 mg/m^3)	5 h/day for 7-28 days	Wistar rat; male; 7 wks old; weight NR; N = 4-5/treatment group, 8 controls	GSH was depleted in the kidney in the 5 and 100 ppm groups but not in the 50 ppm group. No effects were observed for other GSH-related enzymes.

Table E-17. Respiratory System – Effect of SO_2 on morphology.

Study	Concentration	Duration	Species	Effects
ACUTE / SUBACUTE				
Conner et al. (1985)	1 ppm (2.6 mg/m^3); nose only	3 h/day for 6 days; animals evaluated for up to 72 h following exposure	Hartley guinea pig; male; age NR; 250-320 g; N = 14/group/time point	In combined group of SO_2-exposed animals and furnace gas controls, no alveolar lesions were observed.
SUBCHRONIC / CHRONIC				
Wolff et al. (1989)	5 ppm (13 mg/m^3); nose only	2 h/day, 5 days/wk for 4 wks	F344/Crl rat; male and female; 10-11 wks old; weight NR; N = 3/sex/ group	No nasal or pulmonary lesions.
Smith et al. (1989)	1 ppm (2.62 mg/m^3); whole body	5 h/day, 5 days/wk for 4 or 8 mos; half the animals in the 8-mo group were allowed to recover for 3 mos.	Sprague-Dawley rat; male; young adult; initial weight NR; N = 12-15/data point	At 4 mos of SO_2 exposure, increases were observed for incidence of bronchial epithelial hyperplasia (80 vs. 40% in controls) and numbers of nonciliated epithelial cells (31.1 vs. 27.7% in controls); neither effect persisted past 4 mos of exposure.
Gunnison et al., (1987)	10 and 30 ppm	6 h/day and 5 day/wk for 21 wks	Sprague-Dawley CD rat; 8 week of age	Mild epithelial hyperplasia in the trachea and larger bronchi, mucoid degeneration and desquamation of epithelium of the larger bronchi.

Table E-18. Respiratory System – Effects of SO_2 exposure on host lung defenses.

Study	Concentration	Duration	Species	Effects
CLEARANCE – SUBCHRONIC				
Wolff et al. (1989)	5 ppm (13.1 mg/m^3); nose only	2 h/day, 5 days/wk for 4 wks	F344/Crl rat; male and female; 10-11 wks old; weight NR; N = 6/sex/group	There was no effect on pulmonary clearance of radiolabeled aluminosilicate particles (MMAD 1.0 micron).
IMMUNE RESPONSES – ACUTE / SUBACUTE				
Jakab et al. (1996)	10 ppm (26.2 mg/m^3); nose only	4 h	Specific pathogen-free white Swiss mouse; female; 5 wks old; 20-23 g; N = 5/ group	No effect was observed on in situ Fc receptor-mediated phagocytosis of sheep red blood cells by AM, which was assessed 3 days after exposure to SO_2.
Clarke et al. (2000)	10 ppm (26.2 mg/m^3) SO_2; nose only	4 h	Outbred Swiss mouse; female; age and weight NR; N = 10/experimental value	No effect on in situ AM phagocytosis (data not shown) or on intrapulmonary bactericidal activity toward *Staphylococcus aureus*.
Azoulay-Dupuis et al. (1982)	10 ppm (26.2 mg/m^3); whole body	24 h, 1 wk, 2 wks, or 3 wks	OF_1 mouse; female; age NR; mean 20.6 g; N = 768 (32/group)	Respiratory challenge with *Klebsiella pneumoniae* resulted in increased mortality and decreased survival time in the 1, 2, and 3 wk SO_2 exposure groups compared to controls. Differences did not correlate with exposure length.
EX VIVO				
Blanquart et al. (1995)	0, 5,10, 20, 30, or 50 ppm (0, 13.1, 26.2, 52.4, or 131 mg/m^3) SO_2	[illegible]	Fauve de Bourgogne rabbit; 1 mo old; tracheal epithelium explants	Relative to control cultures, cell viability was not reduced at 5 and 10 ppm, but was at 30 ppm (~70%) and 50 ppm (~60%). Ciliary beat frequency was significantly reduced ($p < 0.05$) at 10-30 ppm, and was correlated with swollen mitochondria and depletion of cellular ATP, as well as with blebbing of ciliated or microvilli-covered cells and with aggregation and flattening of cilia.
Riechelmann et al. (1995)	2.9, 5.7, 8.6, 11.5, or 14.3 ppm (7.5, 15, 22.5, 30, or 37.5 mg/m^3); ex vivo exposure of trachea	30 min	Guinea pig; sex, age, and weight NR; N = 4-8/group	No remarkable morphologic abnormalities in the tracheal mucociliary system of the 2.9 ppm group, though slight vacuolization, rare membrane blebs, and slightly widened intercellular spaces were observed. Abnormalities in the 5.7 and 8.6 ppm groups were similar and included loosened contact to the basal membrane, extensive intracellular edema and vacuolization, swollen mitochondria, polypoid extrusions and huge blebs in the cell membrane and ciliary membrane, widened intercellular space, and disrupted tight junctions. Additional abnormalities in the 11.5 and 14.3 ppm groups included marked epithelial sloughing, occasionally disrupted cell membranes and microtubules, and frequently disrupted ciliary membranes. Tracheal mucociliary activity was significantly decreased in all exposure groups (from 8.7 ± 1.0 Hz [controls] to 4.0 ± 1.1, 3.4 ± 2.7, 1.8 ± 2.2, 1.5 ± 1.8, and 2.0 ± 1.2 Hz in the 7.5, 15, 22.5, 30, and 37.5 mg/m^3 groups, respectively).
Knorst et al. (1994)	2.5, 5.0, 7.5, 10.0, or 12.5 ppm (6.6, 13.1, 19.7, 26.2, or 32.8 mg/m^3); ex vivo exposure of trachea	30 min	Guinea pig; sex, age, and weight NR; N = 4-7/group	63% decrease in tracheal mucociliary activity at 2.5 ppm with dose-dependent decrease to 81% at 7.5 ppm; higher concentrations did not further decrease mucociliary activity. Ciliary beat frequency decreased by 45% at 5.0 ppm with dose-dependent decrease to 72% at 12.5 ppm. All reductions are relative to baseline values; no effect on controls for either parameter.

Table E-19. Genotoxic effects of SO_2 and metabolites.

Study	Concentration	Duration	Species/System	Effects
"POINT MUTATION" [1] IN VITRO				
Pool-Zobel et al. (1990)	0 or 50 ppm (131 mg/m^3) SO_2 or the equivalent agar concentration of SO_3^{2-}, 15 µg/ml)	48 h	Rat, Sprague-Dawley, female, liver enzyme preparations	In vitro induction of reverse mutation in cultures of *S. typhimurium* strain TA98 was not affected by incubating the bacterial-B[a]P-liver S9 enzyme activation system in the presence of SO_2/sulfite. An ancillary finding from the 0 µg B[a]P control exposures is that SO_2/sulfite itself did not appear mutagenic.
CYTOGENETIC AND DNA DAMAGE[2] IN VITRO				
Pool et al. (1988b)	0, 20, 50 or 200 ppm (0, 52.4, 131 or 524 mg/m^3) SO_2 0, 0.1, 0.2 or 0.4 mM SO_3^{2-} 0 or 2.5 µmol HSO_3^- per microtiter plate well 0, 0.1, 0.2 or 0.4 mM SO_4^{2-} 0 or 10 µmol $MgSO_4$ per tube	1-24 h	Hamster, Syrian golden; fetal lung cells (FHLC, gestational day 15) Rat, Sprague- Dawley; male; age NR; ~200g, hepatocytes Chinese hamster ovary cell line transformed by SV40, CO60 cells Precinorm U (human serum standard)	Toxicity and genotoxicity of SO_2, sulfite/bisulfite and sulfate (also NO_2/NO_x) were variously assessed in several in vitro test systems. It was noted that medium pH remained stable at $[SO_2] \leq 200$ ppm. Precinorm LDH activity was substantially inhibited by 50 ppm SO_2 after 1-3 h, and by 0.1 mM sulfite ion almost immediately, but not by 0.1 mM sulfate ion; AST was modestly inhibited after 5 h by 200 ppm SO_2; other monitored enzymes were not affected. While trypan blue exclusion was not affected, SO_2 cytotoxicity to FHLC was demonstrated at 20 ppm by reduced plating efficiency; at 50 ppm, enzyme activity leaked into culture medium was reduced only for AP and especially LDH (not other enzymes). 200 ppm SO_2 did not induce DNA damage (single-strand breaks) by itself in either FHLC or rat hepatocytes, but did somewhat reduce that induced by AMMN. In hepatocytes, incubation with $MgSO_4$ also caused a small reduction in AMMN-induced DNA damage. A 1 h exposure to 200 ppm SO_2 did not induce selective amplification of SV40 DNA in CO60 cells, nor affect that induced by DMBA or B[a]P. However, while also not affecting induction by DMBA or B[a]P, HSO_3^- added directly to the medium for 24 h did induce SV40 DNA amplification on its own. Authors appear to suggest this might result from arrest of cells in mid-S phase, which leads to DNA amplification. Thus, principal findings include inhibition of LDH by SO_2 or sulfite that could impair the cellular energy system; such an impairment could be responsible (possibly along with SO_4^{2-} conjugation of reactive intermediates) for the observed inhibition of AMMN-induced DNA damage by SO_2. Further, SO_2 does not appear by itself to induce DNA damage.
Shi and Mao (1994)	3 mM SO_3^{2-}	40 min (test tube reactions)	dG or DNA	Test tube reaction mixtures that caused sulfite to oxidize to sulfur trioxide radical resulted in the hydroxylation of dG (8-OHdG) and the generation of DNA double strand breaks.
Shi (1994)	5 mM SO_3^{2-} (as Na_2SO_3)	1.5 h (test tube reaction)	Dg	Test tube reaction of sulfite ion with H_2O_2 shown to generate hydroxyl radicals capable of hydroxylating dG to the DNA damage marker, 8-OHdG. Furthermore, incubation of sulfite with nitrite or various transition metal ions was shown to generate sulfur trioxide anion radical.
CYTOGENETIC AND DNA DAMAGE[2] ACUTE / SUBACUTE				
Ruan et al. (2003)	0 ppm SO_2 (+ 0 or 8 mg/kg bw SSO) or 10.7 ppm (28 mg/m^3) SO_2 (+ 0, 2, 4, 6 or 8 mg/kg bw SSO); whole body	± SSO ip on days 1-3; then SO_2 for 5 day (Days 4-8), 6 h/day	Kunming mouse; male and female; ~6 wk old; 20-25 g; N = 6/sex/conc.	Subacute inhalation of 10.7 ppm (28 mg/m^3) SO_2 induced a significant ($p < 0.001$) 10-fold increase in mouse bone marrow MNPCE, which was partially mitigated in dose-dependent fashion by pretreatment with SSO, a complex natural anti-oxidant substance. SO_2 exposure also resulted in organ:bw ratios that increased for liver and kidney, decreased for lung and spleen, and remained unchanged for heart. Such ratio changes were largely mitigated by SSO pretreatment.
Meng et al. (2002)	0, 5.35, 10.7, 21.4, or 32.1 ppm (0, 14, 28, 56, or 84 mg/m^3) SO_2; whole body	4 h/day for 7 days	Kunming mouse; male and female; ~6 wk old; 20-25 g; N = 10/sex/conc.	In vivo exposure caused significantly ($p < 0.01$-0.001) increased frequencies of bone marrow MNPCE similarly in both sexes at all concentrations in a dose-dependent manner, and with only minimal cytotoxicity at the 3 highest concentrations. The level of MNPCE (%) even at the low SO_2 conc. was triple that of the control value. Thus, subacute inhalation of SO_2 at noncytotoxic concentrations (though still notably higher than most human exposures) was clastogenic in mice.

Study	Concentration	Duration	Species/System	Effects
Meng et al. (2005b)	0, 5.35, 10.7, 21.4, or 32.1 ppm (0, 14, 28, 56, or 84 mg/m^3) SO_2; whole body	6 h/day for 7 days	Kunming mouse; male and female; ~5 wk old; 18-20 g; N = 6/sex/conc.	Following in vivo exposure to SO_2, it was shown by the single cell gel electrophoresis (comet) assay that such exposure induced significant ($p < .001$-.05) dose-dependent DNA damage (presumed mostly to be single-strand breaks and alkali-labile sites) in cells isolated from brain, lung, liver, intestine, kidney, spleen, and testicle, as well as in lymphocytes, and beginning at the lowest concentration (except male intestine—lowest response at 10.7 ppm [28 mg/m^3]). Results demonstrate that SO_2 can cause systemic DNA damage in many organs, not just the lung. Authors note that potential occupational exposures and the fact that the obligate nose-breathing mouse removes ~95% of inhaled SO_2 in its nasal passages make this experimental concentration range relevant to possible human exposures.
Pool et al. (1988a)	0 or 50 ppm (131 mg/m^3) SO_2	24 h/day, 7 day/wk, for 2 wks	Rat, Sprague-Dawley; female; 4 mo old; wt NR; N = 5/group	Assessments were conducted on isolated primary lung and liver cells, or on blood serum. In vivo SO_2 exposure did not affect viability (trypan blue exclusion) of cells either immediately after isolation or after 1 h incubation with 1% DMSO (used for enzyme leakage assays). In contrast to controls, hepatocytes from SO_2-exposed rats released no LDH activity into DMSO-medium after 1 h, and AST activity was reduced. Other enzyme (AP, ALT, GT) activity releases were not affected in lung cells, and none were in hepatocytes. In blood serum, the only effect was a marked increase in LDH activity. The only significant ($p < 0.001$- 0.01) exposure effects on lung or liver activities (in x 9000 g supernatants of cell homogenates) of xenobiotic metabolizing enzymes (AHH, NDMA-D, GST) were elevated NDMA-D in the liver and reduced GST in the lung. Single-strand DNA breakage induced by three nitroso compounds (AMMN, NDMA, NMBzA) was reduced in hepatocytes from SO_2-exposed rats. Authors discuss possible mechanisms for the observed effects, and note they are similar to in vitro effects reported elsewhere (Pool et al., 1988).
CYTOGENETIC AND DNA DAMAGE[2] SUBCHRONIC / CHRONIC				
Ohyama et al. (1999)	0, 0.2 mL C, or (0.2 mL DEP+C ±[4 ppm (10.48 mg/m^3) SO_2 or 6 ppm (11.28 mg/m^3) NO_2 or 4 ppm SO_2+ 6 ppm NO_2]); whole body [Note: 0.2 mL C=1 mg; 0.2 mL DEcCBP =1 mg C + 2.5 mg DEP]	SO_2 and/or NO_2: 16 h/day for 10 mos C or DEP+C: 4 wk, once/wk by intratracheal infusion	Rat, SPF F344/Jcl; male; 6 wk old; wt NR; N = 23-30/group in 6 groups	Purpose was to study effects of DEP on rat lung tumorigenesis and possible tumor promoting effects of SO_2 or NO_2 singly or together. (See Table E-11 for tumor-related effects.) DEP extract-DNA adducts were found only in the three gas-exposed groups. Chromatograms revealed two different adducts, one of which appears somewhat more abundant with SO_2 coexposure, the other substantially more so with NO_2; combined coexposure of both gases with DEP+C produced an adduct chromatogram appearing to be a composite of those for the individual gases. Thus, SO_2 and NO_2 appear capable of promoting the genotoxicity of DEP extract, though perhaps not in identical fashion.

[1]Encompasses classical mutant selection assays based upon growth conditions under which mutants (or prototrophic revertants), but not the wild type (or auxotrophic) population treated with the test agent, can successfully grow (e.g., "Ames test," CHO/HGRPT or mouse lymphoma L5178Y/TK mammalian cell systems, various yeast and Drosophila systems, etc.); while most viable mutation events detected in these assays are typically "point" mutations (DNA base substitutions, small deletions or frameshifts, etc.), some may involve larger losses/rearrangements of genetic material.

[2]Encompasses CA, induction of MN or SCE, aneuploidy/polyploidy, DNA adduct and crosslink formation, DNA strand breakage, etc.

Table E-20. Respiratory System – Effects of SO_2 and metabolites on biochemistry.

Study	Concentration	Duration	Species	Effects
IN VITRO—PRIMARY / NONPRIMARY				
Li and Meng. (2007)	0.1 µM-1mM $NaHSO_3$ and Na_2SO_3 1:3	4 h, followed by harvest at 0-24 h	BEP2D cell line of human bronchial epithelial cells	Increased mRNA and protein levels of MUC5AC and IL-13
Menzel et al. (1986)	0, 0.1, 2, 20, or 40 mM (0, 4, 80, 800, or 1600 µg/mL) SO_3^{2-}	~1 min - 96 h	Rat, Sprague-Dawley; 200-250g; sex, age, and n NR; lung cells and liver cells. Human lung-derived cell line, A549	This study focused on intracellular covalent reactions of sulfite with primarily proteinaceous sulfhydryl compounds in cells isolated from rat lung and rat liver (for some comparative purposes), as well as in the human lung-derived cell line, A549. Sulfitolysis of protein disulfide bonds results in formation of cysteine S-sulfonate, and sulfitolysis of GSSG in formation of $GSSO_3H$. The latter was formed in dose-dependent fashion upon the addition of sulfite to A549 cells. In addition to fibronectin and albumin, this study identified a third sulfite-binding protein in rat lung cytosol. $GSSO_3H$ was shown to be a potent competitive inhibitor of GST in rat lung, liver and A549 cells. Results suggest that SO_2 could affect the detoxication of PAHs and other xenobiotics via formation of $GSSO_3H$ and subsequent inhibition of GST and enzymatic conjugation of GSH with reactive electrophiles.
OXIDATION AND ANTIOXIDANT DEFENSES – (SUBACUTE / SUBCHRONIC)				
Meng et al. (2003b)	8.4, 21, or 43 ppm (22, 56, or 112 mg/m^3); whole body	6 h per day for 7 days	Kunming albino mouse; male and female; 5 wks old; 19 ± 2 g; N = 10/sex/group	Changes observed in lung tissue (concentrations of effect) included higher SOD activity in males (8.4 ppm) and females (8.4 and 21 ppm), lower SOD activity in males (21 and 43 ppm) and females (43 ppm), increased GPx activity in males and females (8.4 ppm), decreased GPx activity in males and females (≥ 21 ppm), decreased catalase activity in males (43 ppm), decreased reduced GSH level in males and females (≥ 8.4 ppm), increased TBARS level in males (≥ 8.4 ppm) and females ≥ 21 ppm). Authors concluded that SO_2 induced oxidative damage in lungs of mice.
Wu and Meng (2003)	8.4, 24.4, or 56.5 ppm (22, 64, or 148 mg/m^3); whole body	6 h/day for 7 days	Kunming-strain mouse; male; age NR; 18-20 g; N = 10/group	Glucose-6-phosphate dehydrogenase and GST activity were decreased in lung at 24.4 and 56.5 ppm. Lung GSH levels were reduced in the 8.44 and 56.5 ppm exposure groups. Administration of buckthorn seed oil increased GST and decreased TBARS activity compared to mice exposed to SO_2 alone.
Langley-Evans et al. (1996)	5, 50, or 100 ppm (13.1, 131, or 262 mg/m^3); whole body	5 h/day for 7-28 days	Wistar rat; male; 7 wks old; weight NR; N = 4-5/treatment group, 8 controls	In the 5 and 100 ppm groups, GSH in BAL fluid decreased at 7 days and increased at 21 days; at 28 days GSH returned to normal in the 5 ppm group and further increased in the 100 ppm group. GSH was depleted in the lung, at 5 and 100 ppm but not at 50 ppm. With respect to GSH-related enzymes, exposure to 5 ppm lowered GCS, GPx, GST, and GRed activity in the lung. Effects in the 100 ppm group were similar to the 5 ppm group, except that lung GPx was not reduced. Exposure to 50 ppm did not affect lung GST, but reduced the number of inflammatory cells in circulation and decreased GCS, GPx, GRed, and GT in the lung. Authors concluded that sulfitolysis of glutathione disulphide occurs in vivo during SO_2 exposure and that SO_2 is a potent glutathione depleting agent, even in the absence of pulmonary injury.

Study	Concentration	Duration	Species	Effects
Gümüşlü et al. (2001)	10 ppm (26.2 mg/m^3); whole body	1 h/day, 7 days/wk for 6 wks	Swiss albino rat; male; 3, 12, or 24 mos old; 210-450 g; N = 9-11/group in 6 groups	Effects of age on SO_2-induced oxidative effects in lung tissue were observed in young (3-mo-old), middle aged (12-mo-old), and old (24-mo old) rats. SO_2 exposure significantly elevated TBARS, SOD, GPx, and GST in all age groups; reduced catalase in young and middle-aged rats, but did not affect catalase in old rats. In rats not exposed to SO_2, SOD, GPx and GST increased with age and catalase decreased with age. General observations in SO_2-exposed animals were increases in SOD, GPx, and TBARS with age. The authors noted that while lipid peroxidation increased with age, relative TBARS increases in response to SO_2 were inversely correlated with age (i.e., largest percent increase seen in young rats).
Langley-Evans et al. (1997; 2007)	~101 ppm (by study author calculations 286 mg/m^3); whole body Note: The study mistakenly listed units of µg/m^3 and it was verified with the authors that the units should have been listed as mg/m^3.	5 h/day for 28 days	Wistar rat, male, 7 wks old, weight NR, N = 4-16	This study explored the effects of maternal diet protein restriction during gestation on offspring lung enzyme responses after SO_2 exposure in adulthood. Adult offspring representing different maternal dietary concentrations of casein (180 [control], 120, 90 or 60 g/kg) were exposed either to air or SO_2. GSH levels in BAL fluid and the lung were not affected either by maternal diet or SO_2 exposure. In the lung GRed and GT were not affected by SO_2 in any maternal diet group; GPx was reduced only in the 120 g/kg maternal diet group; GCS was elevated in the 180 and 60 g/kg groups; and GST was reduced in the 180, 120 and 90 g/kg groups (to the level seen in both the air- and SO_2-exposed 60 g/kg maternal diet groups). This study does not provide information relevant to ambient exposures, but is being mentioned in this table to record that a low-concentration level study was not overlooked.
DIFFERENTIAL GENE EXPRESSION - SUBACUTE				
Qin and Meng (2005)	5.35, 10.70, or 21.40 ppm (14, 28, or 56 mg/m^3); whole body	6 h/day for 7 days	Wistar rat; male; age NR; 180-200 g; N = 6/group in 4 groups	Repeated acute exposure caused significant ($p < 0.001$-0.05) concentration-dependent reductions in enzyme activities and gene expression in the lung for both CYP1A1 and CYP1A2. Effects were seen at the mid and high concentrations, but not the low. Authors speculate that underlying mechanisms may involve oxidative stress and/or cytokine release, and may represent an adaptive response to minimize cell damage.
Bai and Meng (2005a)	5.35, 10.70, or 21.40 ppm (14, 28, or 56 mg/m^3); whole body	6 h/day for 7 days	Wistar rat; male; age NR; 180-200 g; N = 6/group in 4 groups	SO_2 exposure caused significant concentration-dependent changes in the mRNA (mid and high concentrations) and protein expression (all concentrations in lung, but statistical significance not indicated) of apoptosis-related genes: increases for *bax* and *p53* apoptosis-promoting genes, and decreases for the apoptosis-repressing gene *bcl-2*. Caspase-3 activity (occurring early in apoptosis process) was also increased at the mid and high concentration.

Table E-21. Lymphatic system effects of SO2 and SO_2 mixtures.

Study	Concentration	Duration	Species	Effects
SUBCHRONIC / CHRONIC				
Smith et al. (1989)	1 ppm (2.62 mg/m3); whole body	5 h/day, 5 days/wk for 4 mos	Sprague- Dawley rat; male; young adult; initial weight NR; N=12-15/data point	No significant effects were reported for spleen weight or mitogen-induced activation of peripheral blood lymphocytes or spleen cells (data not shown by authors).
Aranyi et al. (1983)	5.0 ppm (13.2 mg/m^3) SO_2 + 1.04 mg/m^3 ammonium sulfate + 0.10 ppm (0.2 mg/m^3) O_3; whole body	5 h/day, 5 days/wk for up to 103 days	CD1 mouse; female; 3-4 wks old; weight NR; N = 360/group total (14-154/group in each assay)	Cytostasis of MBL-2 leukemia target cells by peritoneal macrophage was increased in groups exposed to O_3 alone or a mixture of the three compounds but was significantly higher with the mixture than with O_3 alone at a macrophage:target cell ratio of 10:1; no significant effects were observed with macrophage:target cell ratio of 20:1. Reduction in splenic lymphocyte blastogenesis in response to phytohemagglutinin and concanavalin A occurred after exposure to O_3 alone, but increased response occurred after exposure to the mixture; no response to alloantigen occurred after exposure to O_3 alone but increased response occurred after exposure to mixture; there were no effects on *S. typhosa* lipopolysaccharide with either exposure scenario.

Annex F. Epidemiologic Studies

This Annex summarizes the findings of epidemiologic studies that have been published since the previous review. Descriptions of older studies were presented in the 1982 AQCD for Sulfur Oxides (U.S. EPA, 1982), and are not described in great detail in this document.

Table F-1. Short-term exposure to SO_2 and respiratory morbidity in field/panel studies.

Study	Method	Pollutant Data	Findings
UNITED STATES			
Adamkiewicz et al. (2004) Steubenville, OH Period of Study: Sep 2000-Dec 2000	Panel study of 29 non-smoking adults (median age 70.7 yrs) in Steubenville, OH. Participants provided breath samples weekly to determine the association between air pollution levels and eNO. ANOVA and GLM used in analysis.	24-h avg SO_2: 12.5 ppb Max: 50.9; 25th: 5.4 75th: 16.9; IQR: 11.5 1-h max SO_2: 14.8 ppb Max: 233.9; 25th: 3.7 75th: 15.2; IQR: 11.5 Copollutants: NO_2 NO O_3 $PM_{2.5}$	No associations were observed with SO_2. Single pollutant models Effect (95% CI) per IQR increase in SO_2: Current hour: 0.09 (-0.22, 0.41) 24-h moving avg: 0.24 (-0.61, 1.10)
Delfino et al. (2003a) Los Angeles, CA Period of Study: Nov 1999-Jan 2000	Panel study of 22 Hispanic children with asthma aged 10 to 16 yrs. Participants performed twice-daily PEF measurements and filled out symptom diaries. Analyses of symptoms conducted using GEE with exchangeable correlation. Linear mixed model used for PEF analyses. GEE models controlled for respiratory infections (data available for 20 subjects) and temperature.	1-h max SO_2: 7.0 ppb (SD 4.0); IQR: 4.0 8-h max SO_2: 4.6 ppb (SD 3.0); IQR: 2.5 Copollutants: O_3 (r = −0.19) NO_2 (r = 0.89) CO (r = 0.69) PM_{10} (r = 0.73) EC (r = 0.87) OC (r = 0.83) VOCs	None of the VOCs or gaseous pollutants associated with PEF. Current-day, but not previous-day, SO_2 concentrations associated with symptom score >1 and >2. OR for symptom score >1 per IQR increase in SO_2: 1-h max SO_2: Lag 0: 1.31 (1.10, 1.55); Lag 1: 1.11 (0.91, 1.36) 8-h max SO_2: Lag 0: 1.23 (1.06, 1.41); Lag 1: 1.11 (0.97, 1.28) OR for symptom score >2 per IQR increase in SO_2: 1-h max SO_2: Lag 0: 1.37 (0.87, 2.18); Lag 1: 0.76 (0.35, 1.64) 8-h max SO_2: Lag 0: 1.36 (1.08, 1.71); Lag 1: 0.91 (0.51, 1.60)
Mortimer et al. (2002) Eight urban areas: Baltimore, MD; Bronx, NY; Chicago, IL; Cleveland, OH; Detroit, MI; East Harlem, NY; St. Louis, MO; Washington, DC Period of Study: Jun-Aug 1993	Panel study of 846 asthmatic children 4-9 yrs from the National Cooperative Inner-City Asthma Study (NCICAS). Study children either had physician-diagnosed asthma and symptoms in the past 12 mos or respiratory symptoms consistent with asthma that lasted more than 6 wks during the previous yr. Respiratory symptoms recorded in daily diary and included cough, chest tightness, and wheeze. Mixed effects models and GEE models used to evaluate the effect of air pollutants on PEF and respiratory symptoms. Models adjusted for day of study, previous 12-h avg temperature, urban area, diary number, rain in the past 24 h.	3-h avg SO_2 (8 a.m.-11 a.m.) for all 8 areas (shown in figure): 22 ppb Avg intradiary range: 53 ppb Copollutants: O_3 (r = 0.29) NO_2 PM_{10}	None of pollutants associated with evening PEF or evening symptoms. Using single-pollutant model, SO_2 had little effect on morning PEF (data not shown). Significant associations between moving avg of 1- to 2-day lag of SO_2 and incidence of morning asthma symptoms. OR for morning symptoms associated with 20 ppb increase in 3-h avg SO_2 concentration (Lag 1-2 day): 8 urban areas: Single-pollutant model: 1.19 (1.06, 1.35) SO_2 with O_3 model: 1.18 (1.05, 1.33) 7 urban areas: Single-pollutant model: 1.22 (1.07, 1.40) SO_2 with O_3 and NO_2 model:1.19 (1.04, 1.37) 3 urban areas: Single-pollutant model: 1.32 (1.03, 1.70) SO_2 with O_3, NO_2, and PM_{10} model:1.23 (0.94, 1.62)

Study	Method	Pollutant Data	Findings
Neas et al. (1995) Uniontown, PA Period of Study: Summer 1990	Panel study of 83 fourth-fifth graders in Uniontown, Pennsylvania. Participants reported twice-daily PEF and presence of cold, cough, or wheeze. During summer of 1990, there were 3,582 child-days. PEF analyzed with autoregressive linear regression model that included a separate intercept for evening measurements, trend, temperature and 12-h avg air pollutant concentration, weighted by the number of hours child spent outdoors during the previous 12 h.	12-h avg SO_2: 10.2 ppb Max: 44.9; IQR: 11.1 Daytime 12-h avg SO_2 (8 am-8 pm): 14.5 ppb Overnight 12-h avg SO_2 (8 pm-8 am): 5.9 ppb Copollutants: PM_{10} $PM_{2.5}$ O_3 total sulfate particles particle-strong acidity (r = 0.44)	Incidence of new evening cough episodes significantly associated with the preceding daytime 12-h avg SO_2. Mean deviation in PEF not associated with SO_2. Effects associated with 10 ppb increase in 12-h avg SO_2: Change in mean deviation in PEF: −0.63 L/min (−1.33, 0.07) OR for evening cough: 1.19 (1.00, 1.42) Concentration weighted by proportion of hours spent outdoors during prior 12-h: Change in mean deviation in PEF: −1.25 L/min (−2.75, 0.25) OR for evening cough: 1.53 (1.07, 2.20)
Newhouse et al. (2004) Tulsa, OK Period of Study: Sep-Oct 2000	Panel study of 24 patients 9-64 yrs with physician-diagnosed asthma. Subjects performed twice-daily PEF (morning and evening) measurements, and recorded medications, symptoms. Simple linear regression, forward stepwise multiple regression, correlation analysis performed. Multiple regression analyses used to develop predictive models for other environmental factors. Analyses produced complex models with different predictor variables for each symptom.	24-h avg SO_2: 0.01 ppm Range: 0.00, 0.02 Copollutants: $PM_{2.5}$ CO O_3 pollen fungal spores	Of the atmospheric pollutants, avg and max O_3 were most significant factors that influenced symptoms. Quantitative results not provided for SO_2. Avg or max SO_2 found to be negative predictors of asthma in subgroup analyses of women and nonsmokers and rhinitis in all patients. Avg SO_2 also negative predictor of evening PEF. Quantitatively useful effect estimates not provided.
Ross et al. (2002) East Moline, IL Period of Study: April-Oct 1994	Panel study of 59 asthmatics 5-49 yrs. Analysis based on 40 subjects, due to withdrawal or failure to provide requested health data. Study assessed the effect of single and combined exposures to air pollutants and airborne allergens on PEF, symptom scores and medication use frequency. Multivariate linear-regression models with 1st order autoregression used for analysis of daily means of mean –standardized PEF, symptom scores and asthma medication use; logistic regression used for dichotomized data for symptom score and medication use, log-linear models for log-transformed symptom scores and medication use frequency.	24-h avg SO_2: 3.4 ppb (SD 3.1) Median: 2.8 IQR: 2.4 Range: 0, 27.3 Copollutants: PM_{10} O_3 NO_2 pollen fungi	No associations observed with SO_2. No effect estimates provided.

Study	Method	Pollutant Data	Findings
Schildcrout et al. (2006) Albuquerque, NM; Baltimore MD; Boston MA; Denver, CO; San Diego, CA; Seattle, WA; St. Louis, MO; Toronto, Ontario, Canada Period of Study : Nov 1993-Sept 1995	Meta-analysis of 8 panel studies with 990 children of the Childhood Asthma Management Program (CAMP), during the 22-mos prerandomization phase to investigate effects of criteria pollutants on asthma exacerbations (daily symptoms and use of rescue inhalers). Poisson regression and logistic regression models used in analyses. Within city models controlled for day of wk, ethnicity, annual family income, flexible functions of age and log-transformed sensitivity to the methacholine challenge using natural splines with knots fixed at 25th, 50th, and 75th percentiles. Also controlled for confounding due to seasonal factors. All city-specific estimates included in calculations of study-wide effects except Albuquerque where SO_2 data were not collected.	24-h avg SO_2: Median (10th, 25th, 75th, 90th percentile): Albuquerque: NA Baltimore: 6.7 ppb (3.2, 4.7, 9.8, 14.2) Boston: 5.8 ppb (2.7, 3.7, 9.1, 14.1) Denver: 4.4 ppb (1.2, 2.5, 6.7, 9.5) San Diego: 2.2 ppb (1.2, 1.7, 3.1, 4.4) Seattle: 6.0 ppb (3.7, 4.7, 7.5, 9.5) St. Louis: 7.4 ppb (3.9, 5.3, 10.7, 13.6) Toronto: 2.5 ppb (0.2, 1.0, 4.8, 8.8) Copollutants: O_3 ($-0.03 \le r \le 0.44$) NO_2 ($0.23 \le r \le 0.68$) PM_{10} ($0.31 \le r \le 0.65$) CO ($0.19 \le r \le 0.67$)	All SO_2 lags positively related to increased risk of asthma symptoms, but only the 3-day moving avg was statistically significant. Stronger associations observed for CO and NO_2. Data analyzed using 2-pollutant models based on the sum of the 2 within-subject pollutant effects, which were intended to provide insight into the increased risk of asthma symptoms associated with simultaneous shift in 2-pollutants. In 2-pollutant models with CO, NO_2, and PM_{10}, the SO_2 effect estimates remained robust. SO_2 not associated with rescue inhaler use rates. OR for daily symptoms associated with 10 ppb increase within-subject 24-h avg SO_2 concentration: Lag 0: 1.06 (0.99, 1.13) Lag 1: 1.05 (0.95, 1.16) Lag 2: 1.06 (0.99, 1.12) 3-day moving sum : 1.04 (1.00, 1.08) Rate ratio for number of rescue inhaler used associated with 10 ppb increase within-subject concentration of SO_2: Lag 0: 1.01 (0.97, 1.06) Lag 1: 1.01 (0.97, 1.06) Lag 2: 1.04 (0.99, 1.09) 3-day moving sum: 1.02 (0.99, 1.05) Results for 2-pollutant models shown in figure.
Schwartz et al. (1994) Kingston-Harriman, TN (Apr-Aug 1986); Portage, WI; (Apr-Aug 1987); St. Louis, MO; (Apr-Aug 1986); Steubenville, OH; (Apr-Aug 1987); Topeka, KS (Apr-Aug 1988) Watertown, MA (Apr-Aug 1985);	Longitudinal study of 1,844 children in grades 2-5 from the Six Cities Study to examine the effects of PM and SO_x on respiratory health. Daily diaries completed by parents, recording symptoms, such as cough, chest pain, phlegm, wheeze, sore throat, and fever. Logistic regression models adjusting for aurocorrelation were used for the analysis. To examine possible non-linearity in the relationship, smooth functions of the air pollution variables were fit using GAM and the significance of the deviation from linearity was tested.	24-h avg SO_2: Median: 4.1 ppb IQR: 1.4, 8.2 Max: 81.9 Copolllutants: O_3 ($r = -0.09$) NO_2 ($r = 0.51$) PM_{10} ($r = 0.53$) $PM_{2.5}$ ($r = 0.55$) $PM_{2.5}$ sulfur ($r = 0.50$) H^+ ($r = 0.23$)	SO_2 associated with incidence of cough and LRS. Local smooth showed increased cough incidence for only above a 4-day avg of 20 ppb (less than 5% of data). Test for nonlinearity was significant ($p = 0.002$). No increase in incidence of LRS was seen until 24-h avg SO_2 concentrations exceeded 22 ppb. ORs for cough and LRS related to were substantially reduced after adjustment for PM_{10}, suggesting the SO_2 associations might be confounded by particles. OR for cough incidence associated with 10 ppb increase in 4-day avg SO_2 concentration: Single-pollutant model: 1.15 (1.02, 1.31) SO_2 with PM_{10} model: 1.08 (0.93, 1.25) SO_2 with O_3 model: 1.15 (1.01, 1.31) SO_2 with NO_2 model: 1.09 (0.94, 1.30) OR for LRS associated with 10 ppb increase in 24-h avg SO_2 concentration: Single-pollutant model: 1.28 (1.13, 1.46) SO_2 with PM_{10} model: Not presented. Stated as not statistically significant.

Study	Method	Pollutant Data	Findings
EUROPE			
Boezen et al. (1998) Amsterdam and Meppel, the Netherlands Winter of 1993-1994	Panel study of 189 adults (48-73 yrs) w/ and w/out chronic respiratory symptoms in urban and rural areas to investigate whether BHR and PEF variability can be used to identify subjects who are susceptible to air pollution. Spirometry and methacholine challenge were performed and subjects with a fall in FEV_1 of 20% or greater were considered BHR. Subjects performed twice-daily peak flow for 3 mos. A subject's basal PEF variability calculated over an 8-day period with low air pollution. PEF variability expressed as (highest PEF-lowest PEF/mean) or amplitude % mean PEF. After calculation of daily PEF variability, number of days where the amplitude % mean was greater than 5% was determined. This resulted in 2 groups of subjects; those with amplitude % mean PEF of 5% or less every day in the 8-day period, and those with an amplitude % mean PEF greater than 5% on at least 1 day. Effects of air pollutants on prevalence of symptoms assessed with logistic regression models that adjusted for autocorrelation of the residuals, daily min temp, time trend and weekends/holidays.	24-h avg SO_2 Urban Mean: 11.8 µg/m^3 Range: 2.7, 33.5 Rural Mean: 8.2 Range: 0.8, 41.5 Copollutants: PM_{10} BS NO_2	No association between SO_2 and respiratory symptoms in subjects with no BHR, BHR at a cumulative dose of methacholine ≤ 2.0 mg or ≤ 1.0 mg. In subjects with amplitude % mean PEF > 5% any day and those with amplitude % mean PEF > 5% for > 33% of days, SO_2 was associated with the prevalence of phlegm. Odds ratio (per 40 µg/m^3 SO_2) Subjects with no BHR URS: 0.86 (0.73, 1.03). LRS: 1.15 (0.90, 1.46) Cough: 1.01 (0.84, 1.21). Phlegm: 1.01 (0.86, 1.20) BHR at cumulative dose of methacholine ≤ 2.0 mg: URS: 1.11 (0.78, 1.56). LRS: 1.03 (0.72, 1.47) Cough: 0.89 (0.66, 1.19). Phlegm: 1.03 (0.78, 1.37) BHR at cumulative dose of methacholine ≤ 1.0 mg: URS: 1.02 (0.65, 1.61). LRS: 0.96 (0.63, 1.47) Cough: 0.96 (0.64, 1.44). Phlegm: 1.00 (0.68, 1.46) Amplitude % mean PEF ≤ 5%: URS: 0.82 (0.62, 1.08). LRS: 1.38 (0.93, 2.03) Cough: 0.72 (0.52, 0.98). Phlegm: 0.79 (0.59, 1.05) Amplitude % mean PEF > 5%, any day: URS: 1.04 (0.88, 1.23). LRS: 1.14 (0.96, 1.36) Cough: 1.07 (0.90, 1.26). Phlegm: 1.23 (1.05, 1.43) Amplitude % mean PEF > 5%, > 33% of days: URS: 1.10 (0.85, 1.41). LRS: 1.14 (0.91, 1.42) Cough: 1.14 (0.89, 1.47). Phlegm: 1.36 (1.14, 1.63)

Study	Method	Pollutant Data	Findings
Boezen et al. (1999) Amsterdam and Meppel (urban and rural), the Netherlands Period of Study: 3 winters of 1992-1995	Panel study of 632 children (7 to 11 yrs) living in rural and urban areas of the Netherlands, to investigate whether children with bronchial hyperresponsiveness (BHR) and relatively high serum concentrations of total IgE were susceptible to air pollution. 459 children had complete data. Methacholine challenge performed to determine BHR. Serum total IgE higher than the median (60kU/L) were defined as relatively high. Peak flow was measured twice daily and lower and URS were recorded daily for 3 mos. Association between symptoms and air pollutants assessed using logistic regression that adjusted for daily min temp, linear, quadratic and cubic time trend, weekends and holidays, and incidence of influenza. Examined 0, 1, 2 Lags and 5 day mean of air pollutants.	1992-9: Urban areas- Mean: 22.5 μg/m^3, Range: 1.4, 61.3 Rural areas- Mean: 9.8 Range: 1.3, 34.2 1993-4: Urban areas- Mean: 11.8, Range: 2.7, 33.5 Rural areas- Mean: 8.2, Range: 0.8, 41.5 1994-5: Urban areas- Mean: 8.3, Range: 0.6, 24.4 Rural areas- Mean: 4.3, Range: 0.5, 17.0 Copollutants: PM_{10} BS NO_2	For children with BHR and relatively high serum total IgE, the prevalence of LRS was associated with increases in PM_{10}, BS, SO_2, and NO_2. In the group with no BHR and relatively low IgE, and the group with BHR and low IgE, there was no consistent association between air pollutants with symptoms or decreased PEF. In children with no BHR but relatively high serum total IgE, there was a 28% to 149% increase in the prevalence of LRS per 40 μg/m^3 SO_2. Odds ratio (per 40 μg/m^3 SO_2) Children with BHR and relatively high IgE (N = 121): LRS: Lag 0: 1.45 (1.13, 1.85) Lag 1: 1.41 (1.09, 1.82) . 5-day mean: 2.25 (1.42, 3.55) URS: Lag 0: 1.17 (0.99, 1.38). Lag 1: 1.06 (0.90, 1.25) >10% morning PEF decrease Lag 0: 1.09 (0.89, 1.34) . Lag 1: 1.00 (0.81, 1.23) >10% evening PEF decrease Lag 0: 1.06 0.86, 1.30). Lag 1: 0.83 (0.68, 1.02) No BHR and low IgE (N = 167): LRS: Lag 0: 1.12 (0.76, 1.66). Lag 1: 0.61 (0.39, 0.94) URS :Lag 0: 1.01 (0.89, 1.13). Lag 1: 1.08 (0.96, 1.22) >10 morning PEF decrease Lag 0: 1.02 (0.89, 1.16). Lag 1: 1.00 (0.87, 1.15) >10% evening PEF decrease Lag 0: 1.10 (0.97, 1.25). Lag 1: 1.06 (0.93, 1.21) With BHR and low IgE (N = 67): LRS: Lag 0: 0.72 (0.41, 1.28). Lag 1: 1.03 (0.56, 1.91) URS: Lag 0: 0.82 (0.62, 1.09). Lag 1: 0.84 (0.64, 1.12) >10% morning PEF decrease Lag 0: 0.74 (0.51, 1.07). Lag 1: 0.96 (0.67, 1.37) >10% evening PEF decrease Lag 0: 1.23 (0.88, 1.73). Lag 1: 1.32 (0.96, 1.82) No BHR and high IgE (N = 104): LRS: Lag 0: 1.44 (1.17, 1.77) Lag 1: 1.28 (1.00, 1.64). 5-day mean: 2.49 (1.54, 4.04) URS: Lag 0: 0.98 (0.84, 1.14). Lag 1: 1.01 0.87, 1.18) >10% morning PEF decrease Lag 0: 0.92 (0.79, 1.08). Lag 1: 1.03 (0.89, 1.21) >10% evening PEF decrease Lag 0: 1.00 (0.85, 1.17). Lag 1: 1.05 (0.90, 1.23)

Study	Method	Pollutant Data	Findings
Boezen et al. (2005) Amsterdam, Meppel, Nunspeet, The Netherlands Period of Study: Two winters 1993-1995	Panel study of 327 elderly patients (50 to 70 yrs) to determine susceptibility to air pollution by AHR, high total immunoglobulin (IgE), and sex. Methacholine challenges were performed and subjects with greater than or equal to 20% fall in FEV_1 after inhalation of up to 2.0 mg methacholine were considered AHR+. Subjects with total serum IgE > 20 kU/L were defined as high total IgE (IgE+). Twice daily PEF measurements and daily symptoms recorded for 3 mos. Data analysis performed using logistic regression with modeling of first-order autocorrelation in the residuals that adjusted for daily min temperature, time trend, weekend/ holidays and influenza incident for the rural and urban areas and the two winters separately. Subjects were classified as IgE+ AHR+, IgE+ AHR−, IgE− AHR+ or IgE− AHR+. Examined effects of pollutants on the same day, Lag 1, Lag 2 and the 5-day mean concentration of Lag 0 to Lag 4 preceding that day. Groups that had effect estimates for PM_{10}, BS, SO_2, and NO_2 that were outside the 95% CI of the effect estimates for the AHR−/IgE− (control group) were considered to have increased susceptibility to air pollution.	24-h avg SO_2 (µg/m^3) in winter Winter 1993/1994 Urban: Mean: 11.8 µg/m^3 Median: 10.2 Range: 2.7, 33.5 Rural: Mean: 8.2 Median: 4.4 Range: 0.8, 41.5 Winter 1994/1995 Urban: Mean: 8.3 Median: 7.4 Range: 0.6, 24.4 Rural: Mean: 4.3 Median: .7 Range: 0.5, 17.0 Copollutants: PM_{10} BS NO_2	No consistent associations between the prevalence of LRS or >10% fall in evening PEF and air pollution in any of the four groups. In the AHR+/IgE+ group, the prevalence of URS was associated with SO_2 at 1 day lag, and the prevalence of >10% fall in morning PEF with SO_2 at Lag 1, Lag 2 and 5-day mean (avg of Lag 0 to Lag 4). For females who were AHR+/IgE+, the prevalence of >10% fall in PEF was associated with SO_2 Lag 1, Lag 2 and 5-day mean. In subjects with AHR−/IgE+ the prevalence of URS was associated with SO_2 the previous day and the mean of Lag 0 to Lag 4. The effect estimate was outside the 95% CI of the estimate for the control group AHR−/IgE−. No consistent positive associations found between prevalences of URS, cough or >10% fall in morning PEF and air pollutants in subjects with AHR+/IgE− or AHR−/IgE−. Based on results of the study, authors conclude that subjects with AHR+/IgE+ were the most responsive to air pollution. No AHR and low IgE (N = 125): URS: Lag 0: 0.99 (0.93, 1.05) Lag 1: 1.02 (0.97, 1.08). 5-day mean: 0.99 (0.88, 1.12) Cough: Lag 0: 1.03 (0.98, 1.08). Lag 1: 0.97 (0.93, 1.02) >10% fall in morning PEF. Lag 1: 1.00 (0.92, 1.08) No AHR and high IgE (N = 112): URS: Lag 0: 0.98 (0.92, 1.03) Lag 1: 1.07 (1.01, 1.12). 5-day mean: 1.15 (1.02, 1.29) Cough: Lag 0: 1.01 (0.95, 1.07). Lag 1: 1.02 (0.96, 1.08) >10% fall in morning PEF . Lag 1: 1.00 (0.92, 1.08) With AHR and low IgE (N = 42): URS: Lag 0: 1.05 (0.94, 1.17). Lag 1: 1.07 (0.96, 1.19) 5-day mean: 1.04 (0.83, 1.30) Cough: Lag 0: 1.03 (0.95, 1.12). Lag 1: 1.01 (0.93, 1.09) >10% fall in morning PEF. Lag 1: 0.99 (0.87, 1.12) With AHR and high IgE (N = 48): URS: Lag 0: 1.06 (0.97, 1.15) Lag 1: 1.13 (1.05, 1.23). 5-day mean: 1.18 (0.99, 1.40) Cough: Lag 0: 1.02 (0.94, 1.11). Lag 1: 1.02 (0.94, 1.10) >10% fall in morning PEF Lag 1: 1.15 (1.04, 1.27). Lag 2 : 1.18 (1.07, 1.30) 5-day mean: 1.26 (1.07, 1.49) With AHR and high IgE, by gender: URS, males: Lag 0: 1.09 (0.95, 1.25) Lag 1: 1.12 (0.98, 1.28). 5-day mean: 1.62 (1.25, 2.11) URS, females: Lag 0: 1.10 (0.97, 1.24) Lag 1: 1.12 (0.99, 1.25). 5-day mean: 1.02 (0.82, 1.28) >10% fall in morning PEF, males. Lag 1: 1.04 (0.87, 1.25) Lag 2: 0.92 (0.77, 1.10. 5-day mean: 0.88 (0.64, 1.21) >10% fall in morning PEF, females. Lag 1: 1.18 (1.03, 1.36) Lag 2: 1.24 (1.08, 1.42). 5-day mean: 1.31 (1.03, 1.66)

Study	Method	Pollutant Data	Findings
Cuijpers et al. (1994) Maastricht, the Netherlands Period of Study: Nov-Dec 1990 (baseline) Aug 8-16 (smog episode)	The effects of exposure to summer smog on respiratory health were studied in 535 children (age unspecified). During a smog episode, 212 children were randomly chosen to be reexamined for lung function and symptoms. Only 112 of the children had adequately completed summer questionnaires and were used for the symptom analysis. Lung function measurements made with forced oscillation technique were available for 212 children and valid spirometry was available for 208 children. Corrected baseline lung function compared using paired t test and difference in the prevalence in symptoms during baseline and episode compared.	24-h avg SO_2 Baseline 55 µg/m^3 Summer episode 23 µg/m^3 Copollutants: NO_2 BS O_3 PM_{10} Acid aerosol H^+	Small decrements in FEV_1 and FEF_{25-75} found in the 212 children during the episode compared to baseline. However, there was also a significant decrease in resistance parameters. No increases observed in the prevalence of acute respiratory symptoms. Change in lung function and impedance between baseline and smog episode: FEV_1: −0.032 L (SD 0.226), p < = 0.05 FEF_{25-75}: −0.086 L/s (SD 0.415), p < = 0.01 Resistance at 8 Hz: −0.47 cm H_2O (L/s) (SD 1.17), p < = 0.05
Desqueyroux et al. (2002a) Paris, France Period of Study : Oct 1995-Nov 1996	Panel study of 39 Parisian adults with severe COPD (avg age 67 yrs) to determine if air pollution affects health outcomes. Episodes of exacerbation were based on regular physician appointments and patient-initiated consultations. Exacerbation was confirmed as a decrease in "vesicular" breath sound, bronchial obstruction, tachycardia/arrhythmia, or cyanosis. Examined with logistic-regression analysis on the basis of GEE. Examined lag effects of 0 to 5 days.	24-h avg SO_2 (µg/m^3) Summer: Mean: 7 (SD 5) Range: 2, 27 Winter: Mean: 19 (SD 12) Range 3, 81 Copollutants: NO_2 PM_{10} O_3	No association between episodes of symptom exacerbation and SO_2, regardless of the lag. Mean 24-h avg SO_2 (per 10 µg/m^3) OR on incident episodes of exacerbation of COPD: Lag 1: 0.98 (0.64, 1.33). Lag 2: 0.96 (0.66, 1.40) Lag 3: 0.91 (0.63, 1.33). Lag 4: 0.89 (0.61, 1.29) Lag 5: 0.87 (0.63, 1.20). Lag 1-5: 0.83 (0.47, 1.50) Multipollutant model with O_3 and SO_2 24-h avg SO_2: Lag 1-5: 0.64 (0.19, 2.19)
Desqueyroux et al. (2002b) Paris, France Period of Study : Nov 1995-Nov 1996	Panel study of 60 patients with moderate to severe physician-diagnosed asthma (mean age 55 yrs). Asthma attacks were noted by physician at each consultation (regular or emergency). Asthmatic attacks defined as need to increase twofold the dose of beta2 agonist.	24-h avg SO_2 (µg/m^3) Summer: 7 (SD 5) Range: 2, 27 Winter 19 (SD 12) Range: 3, 81 Copollutants: PM_{10} NO_2 O_3	No association between asthma attacks and SO_2 for any lag or season. Mean 24-h avg SO_2 (per 10 µg/m^3).OR on incident of asthma attacks: Lag 1: 0.98 (0.76, 1.27). Lag 2: 0.92 (0.72, 1.19) Lag 3: 1.01 (0.82, 1.23). Lag 4: 1.01 (0.86, 1.19) Lag 5: 1.05 (0.85, 1.29). Lag 1-5: 0.99 (0.76, 1.30)
Forsberg et al. (1993) Pitea, Northern Sweden Period of Study: Mar to Apr	Panel study of 31 asthmatic patients (9 to 71 yrs) to assess relationship between daily occurrence of asthma symptoms and fluctuations in air pollution and meteorological conditions. Subjects recorded symptoms (shortness of breath, wheezing, cough, phlegm) for 14 consecutive days.	24-h avg SO_2 (µg/m^3) Mean: 5.7 Range: 1.3, 12.9 Correlations: NO_2 (r = 0.24) BS (r = 0.70)	No significant association observed with SO_2. Positive association between severe shortness of breath and BS. Regression coefficient and 90% CI Subjects with shortness of breath (N = 28): 0.0345 (−0.49, 0.118) Subjects with 5 or more incident episodes of severe shortness of breath (N = 10): −0.0266 (−0.140, 0.087)

Study	Method	Pollutant Data	Findings
Higgins et al. (1995) United Kingdom Study Period: NR	Panel study of 75 patients with physician diagnosed asthma or chronic bronchitis (avg age 50, range 18 to 82 yrs) to determine if air pollution affects respiratory function and symptoms. Subjects asked to keep symptom records and perform PEF for 28 days. PEF values recorded every 2 h beginning at 02.00 h each day. Methacholine challenge performed on each subject. Those with PM_{20} FEV_1 of < 12.25 µmol were considered as methacholine reactors. PEF variability was calculated as the amplitude % Mean: (highest-lowest PEF value/mean) ×100. 75 patients had PEF records, 62 completed satisfactory symptom questionnaires.	Max 24-h avg SO_2 117 µg/m^3 Copollutants: O_3 NO_2	The amplitude % mean was significantly associated with increasing levels of SO_2, on the same day for all subjects and among reactors. Mean daily PEF and min PEF associated with SO_2 among reactors only. Significant associations also observed with wheeze and SO_2 on the same day, at 24-h lag, and 48-h lag for all subjects and meta-choline reactors; and with bronchodilator use for all subjects at 24-h lag. Regression coefficient per 10 µg/m^3 SO_2 All subjects: Mean PEF (L/min): Same day 0.021 (0.031); 24-h Lag 0.003 (0.033); 48-h Lag 0.021 (0.032) Minimum PEF(L/min): Same day 0.062 (0.039); 24-h Lag −0.048 (0.041); 48-h Lag −0.001 (0.040) Amplitude (% mean): Same day: 0.167 (0.072); 24-h Lag 0.191 (0.76); 48-h Lag 0.022 (0.075) Wheeze: Same day 1.14 (1.03, 1.26); 24-h Lag 1.22 (1.09, 1.37); 48-h Lag 1.14 (1.02, 1.27) Dyspnoea: Same day 1.03 (0.94, 1.14); 24-h Lag 1.07 (0.96, 1.18); 48-h Lag 0.94 (0.85, 1.05) Cough: Same day 1.03 (0.95, 1.12); 24-h Lag 1.04 (0.95, 1.13); 48-h Lag 1.02 (0.94, 1.12) Bronchodilator use: Same day 1.11 (0.97, 1.26); 24-h Lag 1.16 (1.01, 1.34); 48-h Lag 1.12 (0.98, 1.27) Reactors: Mean PEF (l/min): Same day 0.087 (0.054); 24-h Lag −0.44 (0.058); 48-h Lag 0.012 (0.057) Minimum PEF(L/min): Same day 0.168 (0.071) 24-h Lag −0.078 (0.076); 48-h Lag −0.026 (0.075) Amplitude (% mean): Same day 0.157 (0.120); 24-h Lag 0.083 (0.127); 48-h Lag 0.005 (0.126) Wheeze: Same day 1.26 (1.08, 1.47); 24-h Lag 1.57 (1.30, 1.89); 48-h Lag 1.24 (1.06, 1.45) Dyspnoea: Same day 1.04 (0.90, 1.20); 24-h Lag 1.17 (1.00, 1.37); 48-h Lag 1.03 (0.89, 1.20) Cough: Same day 1.09 (0.96, 1.24); 24-h Lag 1.05 (0.91, 1.20); 48-h Lag 1.00 (0.87, 1.15) Bronchodilator use: Same day 1.18 (0.99, 1.42); 24-h Lag 1.23 (1.02, 1.50); 48-h Lag 1.31 (1.09, 1.58)
Hiltermann et al. (1998) Bilthoven, The Netherlands Period of Study: Jul-Oct 1995	Panel study of 60 adult (18 to 55 yrs) nonsmoking patients with intermittent to severe persistent asthma to examine the association of summertime air pollution (O_3 and PM_{10}) with respiratory symptoms, medication use and PEF. Subjects were followed over 96 days. Twice daily PEF, respiratory symptoms, and medication use and whether they were exposed to environmental tobacco smoke were recorded daily. Analysis controlled for time trends, aeroallergens, environmental tobacco smoke exposures, day of wk and temperature. Examined Lag effects of 0 to 2 days.	24-h avg SO_2 (µg/m^3) Mean: 6.2 Range: 0.1, 16.2 Correlation with BS r = 0.53 Correlation with copollutants: O_3 (r = 0.30) PM_{10} (r = 0.37) NO_2 (r = 0.49) BS (r = 0.53)	SO_2 not included in the analysis since levels were negligible during the study period (< 17 µg/m^3) Effect estimates not provided.

Study	Method	Pollutant Data	Findings
Hoek and Brunekreef (1992) The Netherlands Period of Study: Winter only, 1987-1990	Panel study of 1,078 children (7 to 11 yrs) to examine the effects of low-level winter air pollution with respiratory symptoms. Pulmonary function test were performed 6 to 10 times on predetermined days. Parents filled out symptom diary that was turned in every 2 wks. Symptoms include hoarseness, cough, cough with phlegm, wheeze, runny/stuffed nose, aching throat, shortness of breath, chest tightness, eye irritation, and sneezing. Association of symptom prevalence and symptom incidence was analyzed using individual regression slopes.	24-h avg SO_2 (µg/m^3) Mean (SD): 14.9 (14.5) Range: 0.4, 94.3 Correlation with copollutants: NO_2 (r = 0.46) PM_{10} (r =0.50) SO_4^{2-} (r =0.41) NO_3^- (r =0.39) HONO (r =0.40)	No association between pulmonary function and SO_2 concentration. SE and medians of individual regression slopes FVC Same day 0.26 (0.21). Lag 1: 0.54 (0.18), p < 0.05 FEV_1 Same day 0.15 (0.20). Lag 1: 0.21 (0.17) PEF Same day -0.83 (1.07). Lag 1: -0.54 (0.87) MMEF Same day -0.58 (0.53). Lag 1: -0.44 (0.44) Odds ratio and 95% confidence interval: Cough. Same day 1.10 (0.78, 1.55). Lag 1: 0.80 (0.55, 1.18) LRS. Same day 1.25 (0.81, 1.93). Lag 1: 1.73 (1.11, 2.72) URS. Same day 1.28 (0.96, 1.70). Lag 1: 1.11 (0.82, 1.51) Any respiratory symptoms. Same day 0.76 (0.56, 1.03). Lag 1: 1.09 (0.83, 1.44)
Hoek and Brunekreef (1993) Wageningen, The Netherlands Period of Study: Winter 1990-1991	Panel study of 112 children (7 to 12 yrs, non-urban) to assess effects of winter air pollution pulmonary function and respiratory symptoms. Parents filled out symptom diary that was turned in every 2 wks. Pulmonary function test performed by technician every 3 wks. Additional pulmonary function tests performed when SO_2 was predicted to be higher than 125 µg/m^3 or NO_2 > 90 µg/m^3.	Daily concentrations presented in graph; Highest 24-h avg conc SO_2: 105 µg/m^3 (air pollution episode) Copollutants: PM_{10} BS NO_2	During the winter episode, pulmonary function of schoolchildren was significantly lower than baseline. Significant negative associations between SO_2 and FVC, FEV_1 and MMEF. No significant associations found with prevalence of respiratory symptoms. Authors noted that it is not clear which components of episode mix responsible for association and that the concentrations of acid aerosol and SO_2 were too low for direct effects to be likely. SO_2 moderately correlated with PM_{10} (r = 0.69) and BS (r = 0.63) but not NO_2 (r = 0.28). Mean of individual regression slopes and SE FVC Same day −0.55 (0.10), p < 0.05 Lag 1: −0.74 (0.15) p < 0.05. 1 wk −0.94 (0.20) p < 0.05 FEV_1 Same day −0.51 (0.09) p < 0.05 Lag 1: −0.21 (−0.63) p < 0.05. 1 wk −0.78 (0.18) p < 0.05 PEF Same day −0.64 (−0.44) Lag 1: −0.21 (0.63). 1 wk −0.34 (0.81) p < 0.05 MMEF. Same day −0.54 (0.20) Lag 1: −0.40 (0.29). 1 wk −0.61 (0.37) Prevalence of acute respiratory symptoms regression coefficient from time-series model and SE Cough. Same day 0.02 (0.18); Lag 1: −0.14 (0.19); 1 wk 0.13 (0.76) URS. Same day 0.12 (0.16); Lag 1: −0.02 (0.17); 1 wk −0.24 (0.76) LRS. Same day 0.06 (0.26); Lag 1: −0.11 (0.29); 1 wk −0.54 (0.92) Any respiratory symptoms. Same day 0.01 (0.13); Lag 1: −0.03 (0.13); 1 wk −0.11 (0.60)
Hoek and Brunekreef (1995) Deurne and Enkhuizen, The Netherlands Period of Study: Mar-Jul 1989	Panel study of 300 children (7-11 yrs) to examine the effects of photochemical air pollution on acute respiratory symptoms. Occurrence of respiratory symptoms recorded by parents in daily diary. Symptoms included cough, shortness of breath, upper and LRS, throat and eye irritation, headache and nausea. Association of symptom prevalence and incidence assessed using first order autoregressive, logistic regression model.	Daily concentration of SO_2 < 43 µg/m^3 Copollutants: O_3 PM_{10} SO_4^2 NO_3^-	Same day concentrations of SO_2 and NO_2 not associated with symptom prevalence. No effect estimates for SO_2 provided.
Just et al (2002) Paris, France Period of Study: 1996	Panel study consisting of 82 medically diagnosed asthmatic children, 7-15 yrs old, followed for 3 mos (Jan-Mar). Examined the association between air pollution and asthma symptoms using regression analyses based on generalized estimating equations (GEE).	24-h avg (µg/m^3): 11.6 (5.7) Copollutants: PM BS NO_2 O_3	SO_2 was not analyzed because it was only present at low concentrations.

Study	Method	Pollutant Data	Findings
Lagorio et al. (2006) Rome, Italy Period of Study: May 24 to June 24, 1999 and Nov 18 to Dec 22, 1999	Panel study of 29 patients with either COPD (N: 11, mean age 67 yrs), asthma (N: 11, mean age 33 yrs) or ischemic heart disease (N: 7, mean age 63 yrs) to evaluate whether daily levels of air pollutants have a measurable impact on lung function in adults with preexisting lung or heart disease.	24-h avg SO_2 ($\mu g/m^3$) Spring mean 4.7 SD 1.8 Winter mean 7.9 SD 2.2 Overall mean 6.4 SD: 2.6 Copollutants: $PM_{2.5}$, $PM_{10-2.5}$, PM_{10}, Cd, Cr, Fe, Ni, Pb, Pt, V, Zn, NO_2, CO, O_3 Correlation with copollutants: $PM_{2.5}$ (r = 0.34) $PM_{10-2.5}$ (r = −0.16) PM_{10} (r = 0.21) NO_2 (r = 0.01) O_3 (r = −0.61) CO (r = 0.65)	Because avg 24-h concentrations of SO_2 were low and showed little variability, SO_2 was not considered in the analysis
Neukirch et al. (1998) Paris, France Period of Study: Nov 15, 1992 to May 9, 1993	Panel study of 40 nonsmoking, mild to moderate asthmatics (16 to 70 yrs, mean 46) to examine the short-term effects of winter air pollution in asthma symptoms and three daily peak flow measurements. Patients were followed for 23 wks. Used GEE models that controlled for autocorrelation of responses, weather, and time trends. Analysis conducted on entire study population and for subgroup of subjects who took inhaled B2 agonists as needed. Assessed air pollution effect on both incident and prevalence of symptoms, Z-transformed morning PEF and daily PEF variability.	24-h avg SO_2 Mean: 21.7 (13.5) $\mu g/m^3$ Range: 4.4, 83.8 Copollutants NO_2, PM_{13}, BS Correlation with copollutants: NO_2 (r = 0.54) PM_{13} (r = 0.83) BS (r = 0.89)	Significant effects on incidence and prevalence of symptoms. Effects at Lag days 3-6 and weekly avg exposures. Based on group avg PEF of 407 l/min, a 50 $\mu g/m^3$ increase SO_2 caused a maximum decrease in morning PEF of 5.5%. Odds ratio per 50 $\mu g/m^3$ SO_2. All subjects - Incident episodes: Wheeze: Lag 5: 1.66 (1.01, 2.70) Nocturnal cough: Lag 3: 1.60 (0.98, 2.62); Lag 4: 1.71 (0.86, 3.40); Lag 6: 1.72 (1.16, 2.55) Respiratory infections: Lag 3: 3.14 (1.30, 7.59); Lag 4: 2.70 (1.36, 5.37); Lag 5: 2.79 (0.95, 8.21); Wk: 8.52 (1.20, 60.5) All subjects - Prevalent episodes: Wheeze: Lag 5: 1.35 (1.01, 1.81); Lag 6: 1.39 (1.04, 1.87); Wk: 1.64 (0.91, 2.94) Nocturnal cough: Lag 6: 1.34 (1.00, 1.79) Shortness of breath: Wk: 1.56 (1.06, 2.32) Respiratory infections: Lag 4: 2.40 (1.33, 4.33); Lag 5: 2.72 (1.67, 4.44); Lag 6: 2.94 (1.80, 4.79); Wk: 6.30 (1.31, 30.2) Subjects taking B2 agonists - Incident episodes: Asthma attacks: Lag 6: 2.19 (0.91, 5.29) Wheeze: Lag 5: 1.84 (1.13, 3.00) Nocturnal cough: Lag 3: 2.41 (1.47, 3.93); Lag 4: 2.35 (0.88, 6.26); Lag 6: 1.86 (1.14, 3.04) Subjects taking B2 agonists - Prevalent episodes: Asthma attacks: Lag 5: 1.88 (0.95, 3.73); Lag 6: 2.82 (1.57, 5.07) Wheeze: Lag 5: 1.51 (1.02, 2.23); Lag 6: 1.57 (1.06, 2.32) Nocturnal cough: Lag 3: 1.73 (1.06, 2.82); Lag 4: 2.28 (1.27, 4.11); Lag 5: 1.91 (1.17, 3.12); Lag 6: 1.91 (1.17, 3.12) Shortness of breath: Lag 4: 1.81 (1.22, 2.67); Lag 5: 1.65 (1.11, 2.44); Lag 6: 1.61 (1.20, 2.16); Wk: 3.03 (1.26, 7.33) Regression coefficients of the effects and SE (per 1 $\mu g/m^3$) Z-transformed morning PEF: Lag 5: −0.450 (0.138) p = 0.001 Lag 6: −0.337 (0.164) p = 0.03 PEF daily variability, Lag 2: 0.025 (0.013) p = 0.05

Study	Method	Pollutant Data	Findings
Peacock et al. (2003) Southern England Period of Study: Nov 1, 1996 to Feb 14, 1997	Panel study of 177 children (mean age 10.7 yrs, range 7 to 13) from three schools (two urban and 1 rural location) to investigate effects of winter air pollution on respiratory function. Children were followed for 13 wks. Used two sources of air pollution in the rural area, one that was "locally validated" and the other "nationally validated."	24-h avg SO_2 (ppb) Rural (nationally validated) Mean: 5.1 (4.7) Range: 0.0, 35.6 Rural (locally validated) Mean: 5.4 (5.1) Range: 0.0, 39.1 Urban 1 Mean: 6.0 (6.0) Range: 0.5, 32.5 Copollutants: O_3 NO_2 PM_{10} SO_4	No statistically significant association between winter SO_2 and PEFR, 0.70% decline in PEFR for a 10 ppb increase in the five-day mean concentration of SO_2 (community monitor) Regression Coefficient (95% CI) per 1 ppb SO_2 Community monitor Lag 0: 0.05 (−0.05, 0.16). Lag 1: −0.04 (−0.13, 0.06) Lag 2: −0.08 (−0.19, 0.04). Lag 0-4: −0.23 (−0.65, 0.18) Local monitor Lag 0: −0.01 (−0.10, 0.07). Lag 1: 0.02 (−0.05, 0.10) Lag 2: −0.09 (−0.18, 0.01). Lag 0-4: −0.09 (−0.25, 0.07) Odds of 20% decrement in PEF below the median – all children Lag 0: 0.987 (0.958, 1.017). Lag 1: 1.007 (0.986, 1.030) Lag 2: 0.992 (0.963, 1.023). Lag 0-4: 0.972 (0.887, 1.066) Odds of 20% decrement in PEF below the median – wheezy children Lag 0: 0.981 (0.925, 1.041). Lag 1: 0.999 (0.957, 1.042) Lag 2: 0.995 (0.939 1.054). Lag 0-4: 1.019 (0.890, 1.167)
Peters et al. (1996) Erfurt and Weimar, former German Democratic Republic; Sokolov, Czech Republic Period of Study: Sep 1990 to June 1992	Panel study of 102 adult (32 to 80 yrs) and 155 children (7 to 15 yrs) with asthma from the former German Democratic Republic and Czech Republic to investigate the acute effects of winter type air pollution on symptoms, medication intake and PEF. Used regression analyses and distributed Lag models.	Winter 1990/1991 Erfurt: Mean: 125 µg/m³ Max: 564 µg/m³ IQR: 113 µg/m³ Weimar Mean: 236 µg/m³ Max: 1018 µg/m³ IQR: 207 µg/m³ Sokolov Mean: 90 µg/m³ Max: 492 µg/m³ IQR: 94 µg/m³ Winter 1991/1992 Erfurt Mean: 96 µg/m³ Max : 462 µg/m³, IQR: 80 µg/m³ Weimar Mean: 153 µg/m³ Max: 794 µg/m³ IQR: 130 µg/m³ Sokolov Mean: 71 µg/m³ Max: 383 µg/m³ IQR: 66 µg/m³ Copollutants: TSP, PM_{10}, SO_4, PSA (particle strong acidity)	5-day mean concentration of SO_2 associated with PEF and symptoms in children (combined analysis from former German Democratic Republic and Czech Republic). Correlation coefficient between SO_2 and TSP in Erfurt was r = 0.8, 0.9 during both winters and in Weimar during the first winter. Correlation with TSP in Sokolov and in Weimar during the second winter was r = 0.4, 0.5. Combined analysis for children % change in PEF Concurrent day 0.18 (−0.44, 0.09) per 133 µg/m³ 5-day mean −0.90 (−1.35, −0.46) per 128 µg/m³ % change in symptom score Concurrent day −0.1 (−5.9, 5.7) per 133 µg/m³ 5-day mean 14.7 (0.8, 28.6) per 128 µg/m³ Combined analysis for adults % change in PEF Concurrent day −0.20 (−0.53, 0.12) per 133 µg/m³ 5-day mean −0.28 (−0.72, 0.16) per 128 µg/m³
Pikhart et al. (2000) Czech Republic Period of Study: 1993-1994	SAVIAH study of 3045 children by questionnaire to determine association of SO_2 to wheezing. Used ecological and multilevel analysis	Median: 73.9 µg/m³ 25th percentile: 63.5 75th percentile: 95.5 Copollutant: NO_2	Positive association of SO_2 with wheezing Odds Ratio (95% CI) per 10 µg/m³ increase SO_2 Logistic Regression: Individual outcome and area exposure: 1.08 (0.98, 1.20). Individual outcome and individual exposure: 1.08 (0.98, 1.19). Ecological analysis: 1.05 (0.96, 1.16)

Study	Method	Pollutant Data	Findings
Pinter et al. (1996) Tata Area, Hungary Period of Study: winter mos between Dec 1993-Mar 1994	Longitudinal (children < 14 yrs) and cross-sectional study (9 to 11 yrs) to examine air pollution and respiratory morbidity in children. In the longitudinal prospective study, respiratory morbidity was evaluated daily and on a weekly basis. In cross-sectional study, anthropometric parameters, physical status, pulse and blood pressure, lung function parameters, eosinophils in the nasal smear, hematological characteristics and urinary excretion of some metabolites were examined and measured. Anova and linear regression used in analysis.	Avg SO_2 exceeded the limit of yearly avg 150 µg/m^3 Daily peaks reached as high as 450 µg/m^3 No specific values given Copollutant: NO_2	Significant correlation between SO_2 levels and acute daily respiratory morbidity, but no correlation with weekly incidence. Authors stated that in the cross-sectional study, almost all health parameters were impaired but no results were shown. Results only provided in graph. No p-values provided.
Pönka, 1990 Helsinki, Finland 1991	Survey study to compare weekly changes in ambient SO_2, NO_2, and temperature and the incidence of respiratory diseases, and absenteeism for children in day-care centers and schools and for adults in the work place during a 1-yr period (1987).	Avg weekly concentration of SO_2 (µg/m^3) Mean: 21.1 SD: 11.7 Median: 17.0 Range: 9, 61.5 Mean of daily max Mean: 53 SD: 20.8 Median: 48 Range: 25.9, 130.3 Copollutant: NO_2	Mean SO_2 concentration correlated with the incidences of URI and tonsillitis reported from health centers. SO_2 also correlated with absenteeism due to febrile illness among children in day care centers and adults. When comparing incidences during the low and high levels of SO_2, the number of cases of URI and tonsillitis reported from health centers increased as well as absenteeism. After standardization for temperature, the only difference that was statistically significant was the occurrence of URI diagnosed at health centers. Frequency of URI was 15% higher during high levels of SO_2 compared to low. Statistical significance of product moment correlation coefficients (correlation coefficient) between SO_2 and respiratory disease and absenteeism Respiratory tract infections diagnosed at health centers: URI: SO_2 arithmetic mean: $p < 0.001$ (0.553) Mean of daily maximums: $p = 0.0012$ (0.437) Tonsillitis: SO_2 arithmetic mean: $p = 0.0098$ (0.355) Mean of daily maximums: NS Absenteeism due to febrile illness: Day care centers: SO_2 arithmetic mean: $p = 0.012$ (0.404) Mean of daily maximums: $p = 0.048$ (0.323) School children: SO_2 arithmetic mean: NS. Mean of daily maximums: NS Adults: SO_2 arithmetic mean: $p < 0.0001$ (0.644) Mean of daily maximums: $p < 0.0001$ (0.604) No significant correlation between SO_2 and URI, tonsillitis, otitis, or LRI in day care center children Statistical significance of weekly frequency of respiratory tract disease and absenteeism during low and high levels of SO_2: Respiratory infections diagnosed at health centers: URI: SO_2 arithmetic Mean: $p < 0.001$ Mean of daily max: $p = 0.0005$ Tonsillitis: SO_2 arithmetic mean: 0.0351. SO mean of daily max: NS Absenteeism due to febrile illness: Day care center children: $p = 0.0256$ School children: $p = 0.0014$. Adults: $p = 0.0005$

Study	Method	Pollutant Data	Findings
Roemer et al. (1993) Bennekom and Wageningen, Netherlands Period of Study: Winter 1990-1991	Panel of 73 children (mean age 9.3 yrs, range 6 to 12 yrs) with chronic respiratory symptoms to investigate effects of winter air pollution on lung function, symptoms and medication use. Subjects performed twice-daily PEF measurements, largest of three PEF readings used in regression analysis. Both incidence and prevalence of symptoms analyzed, using logistic regression.	Daily concentrations of SO_2 shown in graph Highest 24-h avg concentration SO_2: 105 µg/m^3 Copollutants: NO_2 PM_{10} BS Correlation with copollutants: NO_2 (r = 0.26) PM_{10} (r = 0.65) BS (r = 0.63)	Positive association between incidence of phlegm and runny nose with SO_2 on the same day. Significant association also found between evening PEF and SO_2 on, the same day, previous day and 1 wk (avg of same day and 6 days before). The use of bronchodilators also associated with SO_2. Mean of individual regression coefficient Morning PEF: Same day −0.021 (0.024); Lag 1 −0.024 (0.031); Wk −0.50 (0.069) Evening PEF: Same day −0.048 (0.018) p < 0.05; Lag 1 −0.039 (0.021) p < 0.10; Wk −0.110 (0.055) p < 0.05 Prevalence of symptoms (per 50 µg/m^3 SO_2) Asthma attack: Same day 0.008 (0.012); Lag 1 0.016 (0.011); 1 Wk 0.058 (0.027) p < 0.05 Wheeze: Same day 0.033 (0.17) p < 0.10; Lag 1 0.042 (0.016) p < 0.05; Wk 0.069 (0.032) p < 0.05 Waken with symptoms: Same day 0.033 (0.019) p < 0.10; Lag 1 0.032 (0.018) p < 0.10; Wk 0.058 (0.045) Shortness of breath: Same day 0.029 (0.016) p < 0.10; Lag 1 0.016 (0.015); Wk 0.044 (0.035) Cough: Same day 0.018 (0.025); Lag 1 0.012 (0.023); Wk 0.072 (0.066) Runny nose: Same day 0.070 (0.026) p < 0.05; Lag 1 −0.11 (0.025); Wk 0.153 (0.074) p < 0.05 Phlegm: Same day 0.011 (0.022); Lag 1 0.014 (0.020); Wk −0.005 (0.056)
Roemer et al. (1998) 14 European Centers: Amsterdam, The Netherlands; Athens, Greece; Berlin and Hettstadt, Germany; Budapest, Hungary; Krakow and Katowice, Poland; Kuopi, Finland; Malmö and Umeå, Sweden; Oslo, Norway; Pisa, Italy; Prague and Teplice, Czech Republic Period of Study: Winter 1993-1994	Multicenter panel study of the acute effects of air pollution on respiratory health of 2,010 children (aged 6 to 12 yrs) 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). Calculated effect estimates of air pollution on PEF or the daily prevalence of respiratory symptoms and bronchodilator use from the panel-specific effect estimates	Range: 2.7 µg/m^3 (Umeå, urban), 113.9 µg/m^3 (Prague, urban) Copollutants: PM_{10}, BS NO_2	No clear associations between PM_{10}, BS, SO_2, or NO_2 and morning PEF, evening PEF, prevalence of respiratory symptoms, or bronchodilator use could be detected. Previous day PM_{10} was negatively associated with evening PEF, but only in locations where BS was high compared to PM_{10} concentrations. No consistent differences in effect estimates between subgroups based on urban versus suburban, geographical location or mean levels of PM_{10}, BS, SO_2, and NO_2. Combined effect estimates with 95% CI of air pollution on PEF. Morning: Lag 0: 0.2 (−0.2, 0.6) Lag 1: 0.2 (−0.2, 0.6). Lag 2: 0.6 (0.2, 1.0) 7-day mean: 0.6 (−1.3, 2.5) Afternoon: Lag 0: 0.1 (−0.3, 0.5) Lag 1: 0.0 (−0.4, 0.4). Lag 2: 0.1 (−0.4, 0.6) 7-day mean: 0.2 (−0.5, 0.9)

Study	Method	Pollutant Data	Findings
Segala et al. (1998) Paris, France Period of Study: Nov 15, 1992 to May 9, 1993	Panel study of 84 children (7 to 15 yrs) with physician diagnosed asthma to examine the effects of winter air pollution on childhood asthma. For 25 wks, parents recorded the presence or absence of asthma attacks, upper or lower respiratory infections with fever, the use of supplementary inhaled B2 agonist, the severity of symptoms (wheeze, nocturnal cough and shortness of breath). Children also recorded PEF three times a day. GEE models adjusted for age, sex, weather and time trend. Investigated effects of SO_2 at 0 to 6 day Lags.	SO_2 avg (SD): 21.7 (13.5) µg/m^3 Range: (4.4, 83.8) µg/m^3 Copollutants: NO_2 PM_{13} BS Correlation with copollutants: NO_2 (r = 0.54) PM_{13} (r = 0.43) BS (r = 0.89)	SO_2 associated with both incident and prevalent episodes of asthma, use of supplementary beta 2 agonist, incident episodes of nocturnal cough, prevalent episodes of shortness of breath and respiratory infection. OR per 50 µg/m^3 SO_2 (Only effects at 0 and 1-days lag shown below unless statistically significant) Incident episodes: Mild asthmatics (N: 43) Asthma: Lag 0: OR 2.86 (1.31, 6.27). Lag 1: 2.45 (1.01, 5.92) Wheeze: Lag 0: 1.47 (0.90, 2.41). Lag1: 1.27 (0.48, 3.38) Nocturnal cough: Lag 3: 1.93 (1.18, 3.15). Lag 4: 2.12 (1.43, 3.13) Respiratory infections: Lag 1: 1.52 (0.38, 5.98) Prevalent episodes: Mild asthmatics (N: 43) Asthma: Lag 0: 1.71 (1.15, 2.53). Lag 1: 1.55 (0.86, 2.78) Wheeze: Lag 4: 1.48 (0.90, 2.41) Shortness of breath : Lag 1: 1.36 (0.92, 2.01) Lag 2: 1.45 (0.98, 2.14). Lag 3: 1.52 (1.03, 2.25) Lag 4: 1.51 (1.02, 2.24) Respiratory infections: Lag 0: 1.58 (0.72, 3.46) Lag 1: 1.91 (0.79, 4.62). Lag 2: 2.13 (0.97, 4.67) Lag 3: 2.09 (1.05, 4.15). Lag 4: 2.05 (1.14, 3.68) Beta2 agonist: Lag 4: 1.63 (1.00, 2.66) Beta2 agonist: Lag 4: 2.02 (1.02, 4.01). Lag 5: 1.96 (0.99, 3.88) Moderate asthmatics (N: 41) Statistically significant (only) prevalent episodes: Beta2 agonist: Lag 0: 3.67 (1.25, 10.8). Lag 1: 4.60 (2.10, 10.1) Lag 2: 7.01 (3.53, 13.9). Lag 3: 4.74 (1.96, 11.5)
Søyseth et al. (1995a) Ardal and Laerdal regions, Norway Period of Study: Winters, 1989-1992	Cross sectional study of 620 children (ages 7 to 13 yrs) to determine whether short term exposure to SO_2 and fluoride on the number of capillary blood eosinophils is related to prevalence of BHR. Ardal is located in a SO_2 emitting aluminum smelter and Laerdal is nonindustrialized. Parents filled out respiratory questionnaires. Clinical examinations used skin prick tests and spirometry to test for atopy and BHR, respectively. Multiple regression and logistic regression models used in analyses.	24-h avg SO_2 (µg/m^3): Median: 22.2 10th: 1.9 90th: 85.3	A significant positive association between BHR and SO_2 was observed in atopic children. Eosinophils and SO_2 exposure also had a positive correlation. Odds ratio for BHR (per 10 µg/m^3 SO_2) Last 24-hours: 1.12 (1.01, 1.24) Last 1-30 days: 0.94 (0.73, 1.21)
Taggart et al. (1996) Runcorn and Widnes in NW England Period of Study: Jul-Sep 1993	Panel study of 38 nonsmoking asthma subjects (18 to 70 yrs) to investigate the relationship between asthmatic BHR and pulmonary function (PEF, FEV_1, FVC) and summertime ambient air pollution. Used univariate nested (hierarchical) analysis of variance to test hypothesis that BHR or spirometry measurements varied with air pollution levels. Analysis was limited to within-subject variation of (BHR, FEV_1, or FVC).	24-h avg SO_2 Max: 103.7 µg/m^3 Copollutants: NO_2, O_3, smoke Correlation with copollutants: O_3 (r = 0.13) NO_2 (r = 0.65) Smoke (r = 0.48)	No association between SO_2 and FEV_1 or FVC. Changes in BHR correlated significantly with changes in 24-h mean SO_2, NO_2, and smoke. Percentage change in BHR per 10 µg/m^3 SO_2 24-h mean SO_2 −6.3 % (−13.6, 0.6) 48-h mean −2.9 % (−12.8, 8.2) 24-h Lag 7.4 % (−4.5, 20.8)

Study	Method	Pollutant Data	Findings
Timonen and Pekkanen (1997) Kuopio (urban and suburban), Finland Period of Study: Winter, 1994	Panel study of 169 children (7 to 12 yrs) with asthma or cough symptoms living in urban and suburban areas of Kuopio, Finland to determine association between air pollution and respiratory health. In the urban areas there were 39 asthmatics and 46 with cough only; in the suburban areas there were 35 asthmatics and 49 with cough who were included in the final analysis. Twice daily PEF and daily symptoms were recorded for 3 mos. First order autoregressive models used to assess associations between air pollutants and PEF and logistic regression models used for symptom prevalences and incidences. Analysis conducted on daily mean PEF deviations. Mean morning or evening PEF calculated for each child was subtracted from the daily value of morning or evening PEF. The daily deviations were then averaged to obtain daily mean PEF deviation for morning or evening PEF.	24-h avg SO_2 ($\mu g/m^3$) Urban area: Mean: 6.0 25th percentile: 2.6 50th percentile: 3.6 75th percentile: 7.1 Max: 32.0 Copollutants: PM_{10} BS NO_2 Correlation coefficient with SO_2 PM_{10} (r = 0.21) BS (r = 0.20) NO_2 (r = 0.22)	Among children with cough only, morning and evening deviations in PEF in the urban panel was negatively associated with SO_2. SO_2 was also associated with an increase in the incidence of URS in children with cough only in the urban area. When excluding the three highest SO_2 days, these effects were no longer statistically significant. No associations found between SO_2 and morning or evening PEF or respiratory symptoms in children with cough only in the suburban panel. Asthmatic: Lag 0: 0.198 (0.804). Lag 1: 0.382 (0.789) Lag 2: 0.648 (0.715). 4-day Mean: 1.39 (1.14) Odds ratio (per 10 $\mu g/m^3$) URS: Lag 1: 1.46 (1.07, 2.00). Lag 2: 1.46 (1.14, 1.87) 4-day Mean: 1.55 (1.08, 2.24) Odds ratio when excluded 3 highest SO_2 days (no 95% CI provided, but effects were not significant) Lag 1: 1.13. Lag 2: 1.46. 4-day Mean: 1.12 Regression coefficient (SE) (per 10 $\mu g/m^3$ SO_2): Morning PEF deviations Children with cough alone: Lag 0: −0.229 (0.608) Lag 1: −1.38 (0.564). Lag 2: −0.683 (0.523) 4-day Mean: −1.28 (0.633) Evening PEF deviations Children with cough alone. Lag 0: −1.84 (0.673) Lag 1: −0.144 (0.711) . Lag 2: −0.291 (0.613) 4-day Mean: −0.878 (0.868) Asthmatics: Lag 0: 1.28 (0.711). Lag 1: 0.575 (0.727) Lag 2: 0.819 (0.642). 4-day Mean: 1.34 (1.05)

Study	Method	Pollutant Data	Findings
van der Zee et al. (1999) The Netherlands: Amsterdam and Meppel (1993-1994) Amsterdam and Nunspeet (1994-1995) Bodegrven/Reeuwijk and Rotterdam (1992-1993) Period of Study: 3 winters from 1992 to 1995	Panel study of 633 children (aged 7 to 11 yrs) with and without chronic respiratory symptoms, living in urban and nonurban areas in the Netherlands. Volunteers measured daily PEF and reported the occurrence of respiratory symptoms and bronchodilator use in a diary. Association between air pollution and decrements in PEF, symptoms and bronchodilator use evaluated with logistic regression models that adjusted for first order autocorrelation, min daily temperature, day of wk, time trend, incidence of influenza and influenza-like illness.	Median and max 24-h avg concentration (µg/m^3) 1992-1993 Urban 23 (152); Nonurban 8.9 (43) 1993-1994 Urban 11 (34); Nonurban 5.0 (42) 1994-1995 Urban 6.0 (24); Nonurban 3.6 (17) Copollutants: PM_{10} BS Sulfate NO_2	The correlation between SO_2 and PM varied from 0.5 to 0.8 during first two winters. Correlation with NO_2 about 0.50. In the urban areas, SO_2 was associated with > 10% decrements in evening PEF, LRS and use of bronchodilator in children with symptoms (n = 142). Most consistent associations found with PM_{10}, BS, and sulfate. No association found between SO_2 and prevalence of URS, cough, phlegm, and > 10% decrements in morning PEF. In the nonurban areas, no associations found with SO_2. In children without symptoms, no consistent associations with SO_2. Authors concluded that children with symptoms are more susceptible to particulate air pollution effects and that use of medication for asthma did not prevent the adverse effects of PM in children with symptoms. Odds ratio (per 40 µg/m^3 SO_2) Children with symptoms: Urban areas: Evening PEF: Lag 0: 1.32 (0.96, 1.80). Lag 1: 0.83 (0.60, 1.14). Lag 2: 1.67 (1.28, 2.19) Symptoms of lower respiratory tract Lag 0: 1.35 (1.01, 1.79). Lag 1: 1.23 (0.93, 1.64) Symptoms of upper respiratory tract Lag 0: 0.97 (0.82, 1.14).Lag 1: 1.10 (0.94, 1.28) Cough: Lag 0: 0.90 (0.77, 1.05). Lag 1: 1.12 (0.96, 1.30) Use of bronchodilator: Lag 0: 0.92 (0.72, 1.18) Lag 1: 1.45 (1.13, 1.86) Nonurban areas: Evening PEF: Lag 0: 1.20 (0.91, 1.58). Lag 1: 0.89 (0.68, 1.17) Symptoms of lower respiratory tract. Lag 0: 0.91 (0.69, 1.19) Lag 1: 0.91 (0.69, 1.22) Symptoms of upper respiratory. Lag 0: 0.94 (0.81, 1.09) Lag 1: 0.97 (0.83, 1.13). 5-day Mean: 0.67 (0.47, 0.94) Cough: Lag 0: 1.08 (0.94, 1.23). Lag 1: 0.98 (0.85, 1.12) Use of bronchodilator. Lag 0: 0.86 (0.59, 1.25) Lag 1: 1.18 (0.80, 1.74) Odds ratio (per 40 µg/m^3 SO_2) Children without symptoms: Urban areas: Evening PEF: Lag 0: 1.13 (0.88, 1.47). Lag 1: 1.16 (0.90, 1.50) URS: Lag 0: 0.92 (0.76, 1.11). Lag 1: 1.10 (0.91, 1.34) Lag 2: 0.83 (0.70, 0.99) Cough: Lag 0: 0.93 (0.78, 1.11). Lag 1: 1.02 (0.84, 1.23) Nonurban areas: Evening PEF: Lag 0: 1.10 (0.87, 1.39). Lag 1: 1.07 (0.85, 1.35) URS: Lag 0: 1.07 (0.92, 1.25). Lag 1: 0.85 (0.72, 1.00) Cough: Lag 0: 0.86 (0.76, 0.97). Lag 1: 0.95 (0.83, 1.08) Two-Pollutant Models Odds Ratio (95% CI) (per 40 µg/m^3 ppm SO_2) Evening PEF: SO_2 + PM_{10}. Lag 0: 1.14 (0.80, 1.61) Lag 1: 0.75 (0.51, 1.09). Lag 2: 1.56 (1.13, 2.13) 5 Day mean: 1.03 (0.50, 2.10)

Study	Method	Pollutant Data	Findings
van der Zee (2000) Netherlands, 3 winters from 1992 to 1995 Rotterdam 1992-1993	Panel study of 489 adults (aged 50 to 70 yrs) with and without chronic respiratory symptoms, living in urban and nonurban areas in the Netherlands. Volunteers measured daily PEF and reported the occurrence of respiratory symptoms and bronchodilator use in a diary. Association between air pollution and decrements in PEF, symptoms and bronchodilator use evaluated with logistic regression models that adjusted for first order autocorrelation, min daily temperature, day of wk, time trend, incidence of influenza and influenza-like illness.	Avg (max) conc 1992/1993: Urban 25 (61) µg/m^3 1993/1994 Urban 11 (34) µg/m^3 Nonurban 5.0 (42) µg/m^3 1994/1995 Urban 6.0 (24) Nonurban 3.6 (17) µg/m^3 Copollutants PM_{10} BS Sulfate NO_2	Among symptomatic adults (n = 138) living in urban areas, the prevalence of >20% decrement in morning PEF was associated with SO_2. Moreover, there were no associations found with prevalence of bronchodilator use, LRS, >10% decrement in morning PEF and >10% and >20% decrement in evening PEF. In the nonurban areas, there was no consistent association between air pollution and respiratory health. In the nonsymptomatic adults, no consistent associations observed between health effects and air pollutants, but a significant and positive association was observed with URS in the nonurban area at 1 day Lag. Range of Spearman correlation coefficients between 24-h avg conc SO_2 and copollutants: PM_{10}: 0.31, 0.78. BS: 0.21, 0.75 Sulfate: 0.29, 0.69. NO_2: 0.47, 0.51 Odds ratio (per 40 µg/m^3 SO_2) symptomatic adults In urban areas >10% decline in PEF; Morning Lag 0: 0.86 (0.60, 1.23); Lag 1: 0.97 (0.68, 1.39) >20% decline in PEF; Morning Lag 0: 1.33 (0.66, 2.71); Lag 1: 1.98 (1.03-3.79) LRS: Lag 0: 1.01 (0.84, 1.20)l Lag1: .97 (0.82, 1.16) 5-day mean: 0.71 (95% CI: 0.53 to 0.95) URS: Lag 0: 1.15 (0.97, 1.37) Lag 1: 1.06 (0.90, 1.26) Bronchodilator use: Lag 0: 1.09 (0.93, 1.28) Lag 1: 1.05 (0.89, 1.24). Lag 2: 0.85 (0.72, 0.99) In nonurban areas >10 % decline in PEF; Morning Lag 0: 79 (0.48, 1.29); Lag 1: 1.08 (0.68, 1.72) >20% decline in PEF; Morning Lag 0: 0.79 (0.22, 2.88); Lag 1: 71 (0.13, 4.02) LRS: Lag 0: 1.11 (0.94, 1.30); Lag 1: 1.04 (0.88, 1.22) URS: Lag 0: 0.97 (0.79, 1.20); Lag 1: 1.20 (0.98, 1.47) Bronchodilator use: Lag 0: 1.04 (0.91, 1.18); Lag 1: 1.08 (0.95, 1.22)
Ward et al. (2002b) Birmingham and Sandwell, England Period of Study: Jan-Mar 1997, May-Jul 1997	Children ages 9-yrs old in 5 different schools were given a questionnaire and administered PEF measurement in summer and/or winter. Study used bivariate correlation, linear and logistic regressions for analysis	Median, Range (ppb): Winter: 5.4 (2-18) Summer: 4.7 (2-10) Copollutants: NO_2 ; O_3; PM_{10} ; $PM_{2.5}$; H+; Cl^-; HCl; HNO_3; NH_3; NH_4+; NO_3−; SO_4^{2-}	Study does not provide evidence for day-to-day respiratory health effects of pollutants. Effect size, CI Winter: ΔPEF morning (L/min): -0.60 (-2.51, 1.32) ΔPEF afternoon: -0.32 (-2.71, 2.04). Cough: 0.92 (0.82, 1.05) Ill: 1.09 (1.01, 1.18). SOB: 1.02 (0.93, 1.13) Wake: 1.00 (0.91, 1.10). Wheeze: 0.96 (0.85, 1.07) Summer: ΔPEF morning (L/min): 0.91 (-0.95, 2.78). ΔPEF afternoon: -0.89 (-2.61, 0.83). Cough: 1.018 (1.02, 1.15) Ill: 1.05 (0.96, 1.14). SOB: 0.98 (0.87, 1.10) Wake: 1.00 (0.87, 1.14). Wheeze: 1.05 (0.92, 1.19)

Study	Method	Pollutant Data	Findings
Ward et al. (2002a) Birmingham and Sandwell, England Period of Study: Jan-Mar 1997 May-July 1997	Panel study of 162 children (9 yrs at time of enrollment) from two inner city locations to investigate the association between ambient acid species with PEF and symptoms. Daily symptoms and twice-daily peak flow measurements were recorded over 8 wk periods in the summer and winter. 39 of the children reported wheezing in the past 12 mos. Linear regression used for PEF and logistic regression for symptoms.	24-h avg SO_2 Winter: Jan 13-Mar 10, 1997 Median: 5.4 ppb Range: 2, 18 ppb Summer: May 19-July 14, 1997 Median: 4.7 ppb Range: 2, 10 ppb Copollutants: NO_2 , O_3, PM_{10} , H^+ , Cl^- , HCl , HNO_3 , NH_3 , NH_4^+ , NO_3^- , SO_4^{2-} SO_2 concentrations were not related to changes in PEF or respiratory symptoms	In the summer, changes in morning PEF were associated with SO_2 at 3-days lag and the 7-day mean SO_2. Prevalence of cough associated with SO_2 on the same day. In the winter SO_2 was only associated with symptom of feeling ill on the same day. 24-h avg SO_2 (per 4.0 ppb in winter; per 2.2 ppb in summer). Data also available for 3-,4-, and 7-day Lag ΔPEF (L/min) Morning: Lag 0-day Winter: -0.60 (-2.51, 1.32); Summer: 0.91 (-0.95, 2.78) Afternoon: Lag 0-day Winter: -0.32 (-2.71, 2.04); Summer: -0.89 (-2.61, 0.83) Morning: Lag 1-day Winter: 0.08 (-1.67,1.86); Summer: 0.29 (-1.56, 2.14) Afternoon: Lag 1-day Winter: -0.88 (-2.87, 1.10); Summer: -0.02 (-1.68, 1.65) Odds ratio for symptoms Cough:Lag 0-day Winter: 0.92 (0.81, 1.05); Summer: 1.08 (1.02, 1.15) Ill:Lag 0-day Winter 1.09 (1.01, 1.18); Summer 1.05 (0.96, 1.14) SOB: Lag 0-day Winter: 1.02 (0.93, 1.13); Summer: 0.98 (0.87,1.10) Cough:Lag 1-day Winter: 1.00 (0.87, 1.15); Summer: 1.04 (0.97, 1.11) Ill: Lag 1-day Winter: 1.03 (0.95, 1.11); Summer: 1.02 (0.94, 1.12) SOB: Lag 1-day Winter: 1.00 (0.90, 1.09); Summer: 1.00 (0.89, 1.13) Wake at night with cough: Lag 0 day Winter: 1.00 (0.91, 1.10); Summer: 1.00 (0.87, 1.14) Wake at night with cough: Lag 1 day Winter: 1.05 (0.96, 1.15); Summer: 1.02 (0.89, 1.16) Wheeze: Lag 0 day Winter: 0.96, (0.85, 1.07); Summer: 1.05 (0.92, 1.19) Wheeze: Lag 1 day Winter: 0.96 (0.86, 1.07); Summer: 1.00 (0.88, 1.13 Summer ΔPEF 2.7 (1.03, 4.38) per 2.2 ppb SO_2 Lag 3 days ($p < 0.05$) Summer ΔPEF 6.83 (0.98, 12.69) per 2.2 ppb SO_2 Lag 0-6 days ($p < 0.05$)
LATIN AMERICA			
Pino et al. (2004) Santiago, Chile Period of Study: 1995-1997	Cohort study of 504 infants recruited at 4 mos of age and followed through the first yr of life to determine the association between air pollution on wheezing bronchitis.	Mean concentration of SO_2 (ppb) Mean: 11.6 SD: 8.1 Median: 10.0 Copollutants: $PM_{2.5}$ NO_2	No consistent association was found between the 24-h avg SO_2 and risk of wheezing bronchitis. However, after a 7-day lag, a 10-ppb increase in the 24-h avg SO_2 was associated with a 21% increase in risk of wheezing bronchitis. Increase in wheezing bronchitis (95% CI) per 10 ppb SO_2 21% (8, 39%)
Romieu et al. (1996) Mexico City, Mexico Period of Study: Apr-Jul 1991 Nov 1991-Feb 1992	Panel study of 71 mildly asthmatic children (5 to 13 yrs) to assess the relationship between air pollution and childhood asthma exacerbation. Children measured PEF three times daily and recorded daily symptoms and medication use. Examined both incidence and prevalence of symptoms. LRS, cough, phlegm, wheeze, and/or difficulty breathing.	24-h avg SO_2 (ppm) Mean: 0.09 SD: 0.05 Range: 0.02, 0.20 Copollutants: O_3 PM_{10} $PM_{2.5}$ NO_2	SO_2 concentrations were not related to changes in PEF or respiratory symptoms. ΔPEF per 10-ppb increase in SO_2 0.26 (-0.35, 0.88, 1.01) L/min Odds ratio per 10-ppb SO_2 Coughing: 0.96 (0.92, 1.01) LRS: 0.97 (0.94, 1.01)

Study	Method	Pollutant Data	Findings
ASIA			
Chen et al. (1999) Three towns in Taiwan: Sanchun, Taihsi, Linyuan Period of Study: May 1995-Jan 1996	Cross-sectional panel study of 895 children (8 to 13 yrs) to evaluate the short-term effect of ambient air pollution on pulmonary function. Single and multipollutant models adjusted for sex, height, BMI, community, temperature, and rainfall. Examined 1, 2, and 7-day lag effects.	Peak concentrations of SO_2 Range: 0, 72.4 ppb Day-time avg and 1-day lag Copollutants: CO NO_3 PM_{10} (r = 0.68) NO_2 (r = 0.71)	Daytime peak SO_2 at 2 days lag significantly associated with FVC using the single-pollutant model. Association also observed with NO_2 and CO with FVC. No PM_{10} effects. Only O_3 effects significant in multipollutant models. ΔFVC (mL) daytime avg SO_2 Lag 1: -3.18 (1.80); Lag 2: -2.70 (1.49); Lag 7: 0.61 (2.59) Daytime peak SO_2 Lag 1: -0.91 (0.73); Lag 2: -1.27 (0.59), $p < 0.05$; Lag 7: -1.05 (1.29) ΔFEV_1 (mL) daytime avg SO_2 Lag 1: -1.95 (1.69); Lag 2: -1.12 (1.41); Lag 7: -1.05 (1.29) Daytime peak SO_2 Lag 1: -0.57 (0.68); Lag 2: -0.64 (0.56); Lag 7: -1.96 (1.22)
Jadsri et al. (2006) Thailand Period of Study: 1993-1996	Spatial regression analysis of outpatient disease occurrence (respiratory system diseases; ICD chapter 10) in 25 communities in Rayong Province.	--- Copollutants: TSP, NO_X	During summer, SO_2 played a role in adverse health effects after taking into account distance between community and health providers. During winter, no relationship was found.
Min et al. (2008) Korea	Panel study consisting of 867 smokers, former smokers, and never smokers 20-86 yrs old. Used linear regression analysis, adjusting for age, height, gender, and a diagnosis of asthma to examine the combined effects of cigarette smoking and SO_2 on lung function. Lung function measurements used in this analysis included forced vital capacity (FVC), forced expiratory volume in 1 sec (FEV_1), percent predicted value of FVC (FVC % pred), and percent predicted value of FEV_1 (FEV_1 % pred).	24-h avg (ppm): 0.006	Found a short, marked decrease in FVC and FEV_1 in smokers after exposure to SO_2 that lasted for up to 30 h. Study did not provide effect estimates.
Park et al. (2002) Seoul, Korea Period of Study: Mar 2, 1996 to Dec 22, 1999	Time-series analysis of school absenteeism due to illness and air pollution in one elementary school in Seoul. School located in area with heavy traffic. Avg enrollment in 1996 was 1,264.	24-h avg SO_2 Mean: 9.19 ppb SD: 4.61 Range: 2.68, 28.11 Copollutants: PM_{10} NO_2 CO (r = 0.67) O_3	SO_2, PM_{10}, and O_3 associated with illness related school absenteeism. SP2 and O_3 are protective for non-illness related absences. Relative risk per IQR SO_2 (5.68 ppb) Total absences: 1.03 (1.02, 1.05) Non-illness related absences: 0.95 (0.92, 0.99) Illness related absences: 1.09 (1.07, 1.12) 2-pollutant model with O_3: 1.10 (1.08, 1.13)
Park et al. (2005a) Korea Period of Study: Mar to June 2002	Panel study of 69 patients (16 to 75 yrs) diagnosed with asthma by bronchial challenge or by bronchodilator response. Patients recorded twice-daily PE, symptoms at the end of each day (cough, wheeze, chest tightness, shortness of breath, sputum changes and the next morning, night awakenings). During the study period, 14 Asian dust days were identified. GEE and generalized additive Poisson regression model used in analysis.	Daily avg SO_2 Control Days: 0.0069 (0.0019) ppm Dust days: 0.0052 (0.0010) ppm Copollutants: PM_{10}, NO_2, CO, O_3	During the dust days, SO_2 levels were significantly lower compared to control days. SO_2 had no significant effect on PEF variability or night symptoms. Relative risk based on Poisson log-linear regression analysis PEF variability (>20%) 0.76 (0.37, 1.56) Night symptoms: 0.98 (0.59, 1.51)

Study	Method	Pollutant Data	Findings
Xu et al. (1991) Beijing, China Three areas: industrial, residential, and suburban (control) Period of Study: Aug 1986	Cross sectional survey of 1140 adults (40 to 69 yrs) who had never smoked living in three areas of Beijing, to determine respiratory health effects of indoor and outdoor air pollution. A trained interviewer obtained pulmonary function measurements and determined history of chest illnesses, respiratory symptoms, cigarette smoking, occupational exposure, residential history, education level, and type of fuel used for cooking and heating.	Annual mean concentration of SO_2 ($\mu g/m^3$) Residential: 128 Industrial: 57 Suburban: 18 Copollutants: TSP	An inverse linear association found between Ln outdoor SO_2 and FEV_1 and FVC after adjusting for age, height and sex. Regression estimate and standard error per Ln SO_2 ($\mu g/m^3$) Height-adjusted FEV_1 (mL): −35.6 (17.3) Height-adjusted FVC (mL): −131.4 (18.8)

Table F-2. Short-term exposure to SO_2 and emergency department visits and hospital admissions for respiratory diseases.

Study	Methods	Pollutant Data	Findings
UNITED STATES			
Gwynn* et al. (2000) Buffalo and Rochester, NY U.S. Period of Study: May 1988-October 1990 Days: 1,090	Hospital Admissions Outcome(s) (ICD9): Respiratory admissions: Acute bronchitis/ bronchiolitis (466); Pneumonia (480-4860); COPD and Asthma (490-493, 496) Age groups analyzed: 6 Study design: Time-series N: 24 Statistical analyses: Poisson regression with GLM and GAM Covariates: season, day of wk, holiday, temperature, relative humidity Lag: 0-3 days	24-h avg SO_2 (ppb): Min: 1.63 25th: 8.4 Mean: 12.2 75th: 15.4 Max: 37.7 Copollutants: H+ (r = 0.06) SO_4^{2-} (r = 0.19) PM_{10} (r = 0.19) O_3 (r = 0.02) NO_2 (r = 0.36) CO (r = 0.11) COH (r = 0.29)	Significant associations observed between several pollutants and various health-effect outcomes make it difficult to discriminate the influence of a single-pollutant. This is likely a result of the relatively high intercorrelations among the various pollutants, as well as the possible interactive role of several pollutants in the reported associations. Increment: 25.5, 7.0 ppb (Max-Mean; IQR) SO_2 alone: Max-Mean RR 1.096 (t = 3.05) lag 0 IQR RR 1.025 (t = 3.05) lag 0

Study	Methods	Pollutant Data	Findings
Ito et al. (2007) New York, NY Period of Study: Jan 1999-Dec 2002	ED Visits Outcome(s): Asthma Study design: Time-series Statistical Analysis: Poisson GLM Age groups analyzed: All ages Covariates: Adjustment for temperature (same day and avg lag 1-3), dew point (same day and avg lag 1-3) # Hospitals: 11 Lag(s): Avg 0 and 1 day	All yr 24-h avg (ppb): 7.8 (4.6) 5th: 3 25th: 5 50th: 7 75th: 10 95th: 17 Warm mos (Apr-Sep) 24-h avg (ppb): 5.4 (2.2) 5th: 3 25th: 4 50th: 5 75th: 7 95th: 10 Cold Mos (Oct-Mar) 24-h avg (ppb): 10.2 (5.1) 5th: 4 25th: 6 50th: 9 75th: 13 95th: 19 Copollutants: $PM_{2.5}$; NO_2; O_3; CO	In single-pollutant models, NO_2 was found to have the most significant association with asthma ED visits for all-yr and warm mos. SO_2 was significantly associated with asthma ED visits for all single-pollutant models for all-yr and both the warm and cold mos. In copollutant models for the warm mos, NO_2 eliminated the association between SO_2 and asthma ED visits. This result is consistent with the monitor-to-monitor correlations, which suggested that NO_2 had less exposure error compared to SO_2. Warm Mos (Apr-Sep) (Weather model including smoothing terms for same day temperature and avg lag 1-3 day temperature.) Relative Risk (95% CI) (per 6 ppb SO_2) 1.20 (1.13, 1.28)
Jaffe et al. (2003) 3 cities, Ohio, U.S. (Cincinnati, Cleveland, Columbus) Period of Study: Jul 1991-Jun 1996 (June-Aug months only)	ED Visits Outcome(s) (ICD9): Asthma (493) Age groups analyzed: 5-34 Study design: Time-series; N: 4,416 Statistical analyses: Poisson regression using a standard GAM approach Covariates: City, day of wk, wk, yr, min temperature, overall trend, dispersion parameter Season: June to Aug only Dose-response investigated: Yes Statistical package: NR Lag: 0-3 days	24-h avg: Cincinnati: 35.9 (25.1) µg/m^3 Range: 1.7, 132 Cleveland: 39.4 (25.3) µg/m^3 Range: 2.6, 167 Columbus: 11.1(8.5) µg/m^3 Range: 0, 56.8 Copollutants: Cincinnati: PM_{10} (r = 0.31) NO_2 (r = 0.07) O_3 (r = 0.14) Cleveland: PM_{10} (r = 0.29) NO_2 (r = 0.28) O_3 (r = 0.26) Columbus: PM_{10} (r = 0.42) NO_2 (r = NR) O_3 (r = 0.22)	Wide confidence intervals for data from Cleveland and Columbus make these data not significant and unstable. Only data for Cincinnati was considered statistically significant and demonstrated a concentration response function that was positive. No multipollutant models were utilized. Increment: 50 µg/m^3 Cincinnati: 35% (9, 21) lag 2 Cleveland: 6% (−7, 21) lag 2 Columbus: 26% (−25, 213) lag 3 All cities: 12% (1, 23) Attributable risk from SO_2 increment: Cincinnati: 4.2% Cleveland: 0.66% Columbus: 2.94%

Study	Methods	Pollutant Data	Findings
Lin et al. (2004d) New York (Bronx County), U.S. Period of Study: 6/1991-12/1993	Hospital Admissions Outcome(s) (ICD9): Asthma (493) Age groups analyzed: 0-14 Study design: Case-control N: 2,629 cases; 2,236 controls Statistical analyses: logistic regression Covariates: race and ethnicity, age, gender, season Statistical package: Lag: 0,1,2,3, 0-3	Cases: 24-h avg: 16.78 ppb 50th: 13.72 Range: 2.88, 66.35 Controls: 24-h avg: 15.57 ppb 50th: 13.08 Range: 2.88, 66.35 Quartile Concentrations (ppb) : Q1: 2.88, 8.37 Q2: 9.37, 13.38 Q3: 13.5, 20.91 Q4: 20.21, 66.35	Odds ratios for risk of hospitalization for asthma increased with each quartile of SO_2 concentration. Lag 1, 2, or 3 all showed a concentration response that was positive for odds ratio as each quartile was compared to the total exposure group (trend p > 0.001). Quartile (24-h avg) Q2 OR 1.26 lag 3 Q3 OR 1.45 lag 3 Q4 OR 2.16 (1.77, 2.65) lag 3 Quartile (1-h max) Q4 OR 1.86 (1.52, 2.27) lag 3 For a 4 ppb increase in SO_2 (24-h avg) RR 1.07 (1.04, 1.11)
Michaud et al. (2004) Hilo, Hawaii Period of Study: 2/21/1997-5/31/2001	ED Visits Outcome(s) (ICD9): COPD (490-496); Asthma (493, 495); bronchitis (490, 491), other COPD (492, 494, 496) Age groups analyzed: All Study design: Time-series Statistical analyses: Exponential regression models Covariates: temporal variables, day of wk, meteorology Statistical package: Stata, SAS Lag: 0,1,2,3 days	1-h max: 1.92 (12.2) ppb Range: 0.0, 447 24-h avg: 1.97 (7.12) ppb Range: 0.0, 108.5 Copollutants: PM_1	The lack of organic carbon shows the pure SO_2 effect uncontaminated by vehicle emissions. Asthma is associated with vog, but vog is not a major cause of asthma in Hawaii. The strongest association was with the mo of the yr. Admission for asthma and respiratory conditions was higher in the winter compared to the summer, based on admission per day (observational- not statistical analysis). Increment: 10 ppb COPD: RR 1.04 (0.99, 1.09) lag 1; RR 1.04 (1.00, 1.09) lag 2; RR 1.07 (1.03, 1.11) lag 3 Asthma: RR 1.01 (1.00, 1.10) lag 1; RR 1.02 (1.03, 1.12) lag 2; RR 1.02 (1.03, 1.12) lag 3 Bronchitis: RR 1.01 (0.93, 1.13) lag 1; RR 0.99 (0.88, 1.05) lag 2; RR 1.01 (1.00, 1.14) lag 3 Other COPD: RR 1.00 (0.78, 1.23) lag 1; RR 0.96 (0.62, 1.11) lag 2; RR 0.98 (0.75, 1.16) lag 3

Study	Methods	Pollutant Data	Findings
Moolgavkar* et al. (1997) U.S.: Minneapolis-St. Paul; Birmingham Period of Study: Jan 1986-Dec 1991	Hospital Admissions Outcome(s) (ICD9): COPD including asthma (490-496), Pneumonia (480-487) Age groups analyzed: 65+ Study design: Time-series Statistical analyses: Semi-parametric Poisson regression, GAM Covariates: day of wk, season, temporal trends, temperature Statistical package: S Plus Lag: 0-3 days	SO_2 24-h avg (ppb): Minneapolis: Mean: 4.82 10th: 1.9 25th: 2.66 50th: 4.02 75th: 6.0 90th: 8.5 Birmingham: Mean: 6.58 10th: 2.2 25th: 3.7 50th: 6.0 75th: 8.6 90th: 11.6 Copollutants: Minneapolis: PM_{10} (r = 0.08) NO_2 (r = 0.09) CO (r = 0.07) O_3 (r = −0.12) Birmingham: PM_{10} (r = 0.17) CO (r = 0.16) O_3 (r = 0.02)	SO_2 with NO_2 and PM_{10} were associated with hospital admissions. Evidence of mixture effects was found. No single-pollutant was more important than the other for respiratory admissions. Each pollutant was associated with admissions except CO. Consideration of four pollutants together showed the strongest association with O_3. No pollutant other than O_3 was stable in its association with hospital admissions. No effects were reported for Birmingham. Positive results were only observed in Minneapolis. Increment: 3.5 ppb Sum of Pneumonia and COPD: 1.6% (−0.1, 3.3) lag 2 Pneumonia Only Minneapolis: 65+ 0.9% (−1.1, 2.9) lag 2 20 df 0.5% (−1.5, 2.5) lag 2 130 dfS
Moolgavkar (2000a) Multicity, U.S.: Cook, Los Angeles, Maricopa County, (Phoenix) Period of Study: 1987-1995	Hospital Admissions Outcome(s) (ICD9): COPD including asthma (490-496) Age groups analyzed: 0-19, 20-64, 65+ (LA only) Study design: Time-series Statistical analyses: Poisson regression, GAM Covariates: Day of wk, temporal trends, temperature, relative humidity Lag: 0-5 days	Cook: Median: 6 ppb 25th: 4 75th: 8 Range: 0.5, 36 Los Angeles: Median: 2 ppb 25th: 1 75th: 4 Range: 0, 16 Maricopa: Median: 2 ppb 25th: 0.5 75th: 4 Range: 0, 14 Copollutants: Cook: PM_{10} (r = 0.42) CO (r = 0.35) NO_2 (r = 0.44) O_3 (r = 0.01) Los Angeles: $PM_{2.5}$ (r = 0.42) PM_{10} (r = 0.41) CO (r = 0.78) NO_2 (r = 0.74) O_3 (r = −0.21) Maricopa: PM_{10} (r = 0.11) CO (r = 0.53) NO_2 (r = 0.02) O_3 (r = −0.37)	In Los Angeles there was a significant association with hospital admissions for COPD. SO_2 may be acting as a surrogate for other pollutants since heterogeneous responses found in different cities are inconsistent with a cause-effect model. Increment: 10 ppb COPD, >65 yrs Cook lag 0: 4.87 (t = 3.18) GAM-100 LA lag 0: 2.84 (t = 13.32) GAM-30 LA lag 0: 1.80 (t = 9.60) GAM-100 LA lag 0: 1.78 (t = 7.72) NS-100

Study	Methods	Pollutant Data	Findings
NY DOH (2006) Bronx and Manhattan, NY Period of Study: Jan 1999-Dec 2000	ED Visits Outcome(s) (ICD9): Asthma (493), for infants (466.1 and 786.09) Study design: Time-series N: ≈ 36,000 Statistical Analysis: Poisson regression with GLM Statistical package: S-Plus Age groups analyzed: All ages Covariates: Season, day-of-wk, temperature # Hospitals: 22 Lag(s): Avg 0- to 4-day lags	24-h avg (ppm): 0.011 (0.0072) Copollutants: PM_{10} $PM_{2.5}$ OC EC Cr Fe Pb Mn Ni Zn H+ Sulfate O_3 NO_2 SO_2	In single-pollutant models, $PM_{2.5}$, SO_2, O_3, and NO_2 were all found to be significantly associated with asthma ED visits in a community, Bronx, with a high prevalence of asthma. This association was maintained in both two- and three-pollutant models for O_3 and SO_2. Single-Pollutant Models Relative Risk: (95% CI) (per 0.011 ppm SO_2) 5-day moving avg Manhattan: 0.99 (0.88, 1.12); Bronx: 1.11 (1.06, 1.17) Relative Risk: (95% CI) (per 0.0072 ppm SO_2) Bronx: 1.07 (1.04, 1.11) Relative Risk based on Daily Max Hourly SO_2: (95% CI) (per 0.0227 ppm SO_2) Manhattan: 0.96 (0.86, 1.07); Bronx: 1.07 (1.03, 1.12) Relative Risk:(95% CI) (per 0.0072 ppm SO_2)-model excludes temperature Manhattan: 0.99 (0.88, 1.11); Bronx: 1.11 (1.06, 1.17) Relative Risk: (95% CI) (per 0.0072 ppm SO_2)- by Gender Manhattan: Male: 0.90 (0.75, 1.07); Female: 1.08 (0.91, 1.29) Bronx: Male: 1.08 (1.00, 1.17); Female: 1.14 (1.06, 1.23) Relative Risk: (95% CI) (per 0.0072 ppm SO_2)-By Age Manhattan: 0-4: 0.82 (0.59, 1.15); 5-18: 1.03 (0.77, 1.37); 19-34: 1.01 (0.76, 1.35); 35-64: 1.04 (0.86, 1.25); 65+: 0.88 (0.57, 1.37) Bronx: 0-4: 1.13 (1.01, 1.26); 5-18: 1.03 (0.92, 1.16); 19-34: 1.06 (0.93, 1.21); 35-64: 1.18 (1.07, 1.30); 65+: 1.12 (0.88, 1.42) Two-Pollutant Models Relative Risk: (95% CI) (per 0.0072 ppm SO_2) 5-day moving avg Manhattan: SO_2 + Max 8-h O_3: 0.99 (0.88, 1.12); SO_2 + FRM $PM_{2.5}$: 0.97 (0.85, 1.11); SO_2 + Max $PM_{2.5}$: 0.98 (0.85, 1.12); SO_2 + NO_2: 1.01 (0.87, 1.16) Bronx: SO_2 + Max 8-h O_3: 1.11 (1.05, 1.17); SO_2 + FRM $PM_{2.5}$: 1.11 (1.04, 1.18); SO_2 + Max $PM_{2.5}$: 1.09 (1.03, 1.16); SO_2 + NO_2: 1.11 (1.04, 1.17)
Norris et al. (1999) Seattle, Washington Period of Study: 1995-1996	ED Visits Outcome(s) (ICD9): Asthma (493) Study design: Time-series Statistical Analysis: Semiparametric Poisson regression model Statistical package: S-Plus Age groups analyzed: < 18 Covariates: adjustments for day-of-wk indicator variables, time trends, temperature, dew point temperature # Hospitals: 6 Lag(s): 0, 2	24-h avg (ppb): 6.0 (3.0) Range: 1.0, 21.0 1-h max (ppb): 16.0 (14.0) Range: 2.0, 84.0 Copollutants: PM_{10}, Dry light scattering, NO_2,CO, O_3	A significant association was found between asthma emergency department visits in children and $PM_{2.5}$ and CO. Estimates were not found to be different between high and low hospital utilization areas. SO_2 was negatively associated with asthma emergency department visits in high utilization areas, and positively associated in low utilization areas. Relative Rates (95% CI) (per 3 ppb 24-h avg SO_2; per 12 ppb 1-h max SO_2) High Utilization Areas: 24-h avg: 0.92 (0.83, 1.03) 1-h max: 0.99 (0.89, 1.10) Low Utilization Areas 24-h avg: 1.09 (1.00, 1.19) 1-h max: 1.09 (1.00, 1.19) All Areas 24-h avg: 0.97 (0.91, 1.04) lag 0 1-h max: 1.02 (0.95, 1.09) lag 2

Study	Methods	Pollutant Data	Findings
Peel et al. (2005) Atlanta, GA, U.S. Period of Study: 1/93-8/2000	ED Visits Outcome(s) (ICD 9): All respiratory (460-6, 477, 480-6, 480-6, 490-3, 496); Asthma (493); COPD (491-2, 496); Pneumonia (480-486); Upper Respiratory Infection (460-6, 477) Age groups analyzed: All Study design: Time-series N: ≈ 480,000 # of Hospitals: 31 Statistical analyses: Poisson Regression, GEE, GLM, and GAM (data not shown for GAM) Covariates: Day of wk, hospital entry/exit, holidays, time trend; season, temperature, dew point temperature Statistical package: SAS, S-Plus Lag: 0 to 7 days. 3 day moving avgs.	1-h max: 16.5 (17.1) ppb 10th%: 2.0 90th%: 39.0 Copollutants: O_3 NO_2 CO $PM_{2.5}$ Evaluated multipollutant models (data not shown)	Estimates from distributed lag models (0-13 days) tend to be higher than for 3-day moving avg. Positive associations for URI and COPD with SO_2 were noted for unconstrained lags (0-13 days) that covered the previous two weeks of exposure. Increment: 20 ppb All respiratory: RR 1.008 (0.997, 1.019) lag 0-2, 3-day moving avg Upper Respiratory Infection (URI): RR 1.010 (0.998, 1.024) lag 0-2, 3-day moving avg Asthma: All: 1.001 (0.984, 1.017) lag 0-2, 3-day moving avg Pneumonia: RR 1.003 (0.984, 1.023) lag 0-2, 3-day moving avg COPD: RR 1.016 (0.985, 1.049) lag 0-2, 3-day moving avg
Schwartz (1995) New Haven, CT Tacoma, WA U.S. Period of Study: 1988-1990	Hospital Admissions Outcome(s) (ICD 9): All respiratory admissions (460-519) Age groups analyzed: ≥65 Study design: Time-series N: 13,470 Statistical analyses: Poisson regression, log linear regression using GLM and GAM Covariates: dewpoint, temp, long-term trends, days of wk Statistical package: S- Plus Lag: 0-1	24-h avg New Haven Mean 78 μg/m³ (29.8 ppb) 10th: 23 25th: 35 50th: 78 75th: 100 90th: 159 Tacoma Mean: 44 μg/m³ (16.8 ppb) 10th: 15 25th: 26 50th: 40 75th: 56 90th: 74 Copollutants: PM_{10} O_3	In New Haven, risk associated with SO_2 was not affected by inclusion of $PM_{2.5}$ in the model and the effect of $PM_{2.5}$ was not strongly affected by inclusion of SO_2. This suggests that in New Haven, SO_2 and $PM_{2.5}$ acted independently. In Tacoma, 2-pollutant model analysis showed risk associated with SO_2 was attenuated by $PM_{2.5}$. This suggested risks associated with SO_2 and $PM_{2.5}$ were not independent. Possibly, SO_2 acts as a surrogate for $PM_{2.5}$ in this city. Increment: 50 μg/m³ or 18.8 ppb New Haven, CT RR = 1.03 (CI 1.02, 1.05), lag 0-1. $p < 0.001$ 2-pollutant model with PM_{10}: RR = 1.04 (CI 1.02, 1.06) $p < 0.001$ Tacoma, WA RR = 1.06 (CI 1.01, 1.12), lag 0-1. $p > 0.02$ 2-pollutant model with PM_{10}: RR = 0.99 (CI 0.93, 1.06) $p > 0.5$
Schwartz et al. (1996) Cleveland, OH Period of Study: 1988-1990	Hospital Admissions Outcome(s) (ICD9): All respiratory disease Age groups analyzed: ≥ 65 Study design: Time-series Statistical analyses: Poisson regression Covariates: Season, temperature, day of wk Statistical package: Lag: 0-1	24-h avg: 35 ppb 10th: 13 25th: 20 50th: 31 75th: 45 90th: 61 Copollutants: $PM_{2.5}$ O_3	Significant associations were seen for $PM_{2.5}$ and O_3, with somewhat weaker evidence for SO_2. Increment: 100 μg/m³ RR 1.03 (0.99, 1.06) lag 0-1

Study	Methods	Pollutant Data	Findings
Sheppard et al. (1999) Reanalysis (2003) Seattle, WA, U.S. Period of Study: Jan 1987-Dec 1994	Hospital Admissions Outcome(s) (ICD9): Asthma (493) Age groups analyzed: < 65 Study design: Time-series N: 7,837 # of Hospitals: 23 Statistical analyses: Poisson regression with adjustment for auto-correlation. Covariates: Statistical package: S-Plus Lag: 0,1,2,3	24-h avg: 8 ppb IQR: 5 ppb 10th: 3.0 25th: 5.0 50th: 8.0 75th: 10.0 90th: 13.0 Copollutants: PM_{10} (r = 0.31) $PM_{2.5}$ (r = 0.22) O_3 (r = 0.07) CO (r = 0.24)	Sources of SO_2 adjacent or near to monitoring site. Low concentrations. No association with SO_2 for asthma but positive association for appendicitis. Increment: 5 ppb (IQR) GAM with stricter criteria: 1.0% (−2.0, 3.0) lag 0 GLM with natural spline smoothing: 0.0% (−3.0, 4.0) lag 0
Sinclair and Tolsma (2004) Atlanta, GA Period of Study: 8/1/1998-8/31/2000	ED Visits Outcome(s): asthma, upper, and lower respiratory infections. Study design: Time-series investigation Statistical Analysis: Single pollutant Poisson general linear modeling Statistical package: SAS v. 8.02 Age Groups Analyzed: All # Hospitals: 10 Lag(s): 0-8 days	1-hour Max Mean: 19.28 ppb SD:16.28 Copollutants: $PM_{2.5}$ PM_{10} NO_2 CO O_3	No significant findings for child or adult asthma. Significant negative associations with upper respiratory infections for 6-8 day lag (RR = 0.98). Significant positive association with lower respiratory infections for 0-2 day lag (RR = 1.067). Not provided.
Tolbert et al. (2007) Atlanta, GA Period of Study: Jan 1993-Dec 2004	ED Visits Outcome(s) (ICD9): Cardiovascular (410-414, 427, 428, 433-437, 440, 443-445, 451-453); Respiratory (493, 786.07, 786.09, 491, 492, 496, 460-465, 477, 480-486, 466.1, 466.11, 466.19) Study design: Time-series Statistical Analysis: Poisson Generalized Linear Model (GLM). Statistical package: SAS Age groups analyzed: All ages Covariates: Adjustment for day-of-wk, hospital entry, holidays, time, temperature, dew point temperature # Hospitals: 41 N: 238,360 (Cardiovascular) 1,072,429 (Respiratory) Lag(s): 3-day moving avg	1-h max (ppb): 14.9 Range: 1.0, 149.0 10th: 2.0 25th: 4.0 75th: 20.0 90th: 35.0 Copollutants: PM_{10} $PM_{2.5}$ O_3 NO_2 CO Sulfate Total Carbon Organic Carbon EC Water-Soluble Metals Oxygenated Hydrocarbons	In single pollutant models, O_3, PM_{10}, CO, and NO_2 significantly associated with ED visits for respiratory outcomes. Relative Risk (95% CI) (per 16.0 ppb SO_2) 1.003 (0.997, 1.009)

Study	Methods	Pollutant Data	Findings
Wilson et al. (2005) Multicity, U.S. (Portland, ME and Manchester, NH) Period of Study: Jan 1996-Dec 2000 (Manchester) Jan 1998-Dec 2000 (Portland)	ED Visits Outcome(s) (ICD 9 codes): All respiratory (460-519); Asthma (493) Age groups analyzed: 0-14 yrs; 15-64 yrs; ≥65 yrs Study design: Time-series Statistical analyses: Multiple regression analysis standard GAM with more stringent criteria parameters Covariates: Time-trend, season, influenza, temperature, humidity, precipitation Statistical package: S-Plus Lag: 0-2	SO_2 1-h max: Mean, (SD) (ppb) Portland All yr: 11.1 (9.1) Winter: 17.1 (12.0) Spring: 10.0 (7.1) Summer: 9.1 (8.0) Fall: 9.7 (7.1) Manchester All yr: 16.5 (14.7) Winter: 25.7 (15.8) Spring: 14.8 (12.0) Summer: 10.6 (15.1) Fall: 14.6 (11.1) Copollutants: O_3 $PM_{2.5}$	Elevated levels of SO_2 were positively associated with elevated respiratory and asthmatic ER visits. The significance of these relationships is not sensitive to analytic or smoothing techniques. Increment: 6.3 ppb (IQR) for Portland; IQR for Manchester Portland: All respiratory: All ages RR 1.05 (1.02, 1.07) lag 0; 0-14 yrs RR 0.98 (0.93, 1.02) lag 0; 15-64 yrs RR 1.06 (1.03, 1.09) lag 0; >65 yrs RR 1.10 (1.05, 1.15) lag 0 Asthma: All ages RR 1.06 (1.01, 1.12) lag 2; 0-14 yrs RR 1.03 (0.93, 1.15) lag 2; 15-64 yrs 1.07 (1.01, 1.15) lag 2; >65 yrs RR 1.07 (0.90, 1.26) lag 2 Manchester: All respiratory: All ages RR 1.01 (0.99, 1.02) lag 0; 0-14 yrs RR 1.00 (0.96, 1.04) lag 0; 15-64 yrs RR 1.00 (0.98, 1.03) lag 0; >65 yrs RR 1.04 (0.97, 1.11) lag 0 Asthma: All ages RR 1.03 (0.98, 1.09) lag 2; 0-14 yrs RR 1.11 (0.98, 1.25) lag 2; 15-64 yrs 1.02 (0.96, 1.08) lag 2; >65 yrs RR 1.06 (0.83, 1.36) lag 2
CANADA			
Bates et al. (1990) Vancouver Region, BC, Canada Period of Study: 7/1/1984-10/31/1986	ED Visits Outcome(s) (ICD 9): Asthma (493); Pneumonia (480-486); Chronic bronchitis (491,492,496); Other respiratory (466) Age groups analyzed: All; 15-60 Study design: # of Hospitals: 9 Statistical analyses: Pearson correlation coefficients were calculated between asthma visits and environmental variables Season: Warm (May-Oct); Cool (Nov-Apr) Covariates: NR Lag: 0, 1, 2	May-Oct SO_2 1-h max: Range: 0.0137, 0.0151 ppm Nov-Apr Range: 0.012, 0.0164 ppm Number of stations: 11 Copollutants: May-Oct: O_3 (r = 0.23) NO_2 (r = 0.67) COH (r = 0.34) SO_4 (r = 0.46) Nov-Apr: O_3 (r = 0.47) NO_2 (r = 0.61) COH (r = 0.64) SO_4 (r = 0.54)	SO_2 effects depend on the season. In the summer a rise in ambient SO_2 levels was seen to coincide with a rise in respiratory related hospital admissions. Correlation Coefficients: Warm Season (May-Oct) Asthma (15-60 yrs): r = 0.118 lag 0 p < 0.01; r = 0.139 lag 1 Respiratory (15-60 yrs): r = 0.134 lag 0 p < 0.001; r = 0.164 lag 1 p < 0.001 Cool Season (Nov-Apr) Respiratory (1-14 yrs): r = 0.205 lag 0 p < 0.001; r = 0.234 lag 1 p < 0.001; r = 0.234 lag 2 p < 0.001 (15-60 yrs): r = 0.180 lag 0 p < 0.001; r = 0.214 lag 1 p < 0.001; r = 0.215 lag 2 p < 0.001 (≥ 61 yrs 0: r = 0.257 lag 0 p < 0.001; r = 0.308 lag 1 p < 0.001; r = 0.307 lag 2 p < 0.001 Asthma (≥ 61 yrs): r = 0.125 lag 0 p < 0.001; r = 0.149 lag 1 p < 0.001; r = 0.148 lag 2 p < 0.001 Total ER admissions (≥ 61 yrs): r = 0.13 lag 1 p < 0.01; r = 0.13 lag 2 p < 0.01
Burnett* et al. (1997a) 16 cities, Canada Period of Study: 4/1981-12/1991 Days: 3,927	Hospital Admissions Outcome(s) (ICD9): All respiratory admissions (466, 480-6, 490-4, 496) Study design: Time-series. N: 720,519 # of Hospitals: 134. Statistical analyses: random effects relative risk regression model Covariates: Long-term trend, season, day of wk, hospital Statistical package: NR Lag: 0, 1, 2 day	1-h max SO_2 (ppb) Mean: 14.4. SD: 22.2 25th: 3 50th: 10 75th: 19 95th: 45 99th: 97 O_3 r = 0.04 Copollutants: CO, NO_2, COH	Control of SO_2 reduced but did not eliminate the O_3 association with respiratory hospital admissions. Increment: 10 ppb Single-pollutant SO_2 and respiratory admissions, p = 0.134 Multipollutant model (adjusted for CO, O_3, NO_2, COH, dew point): RR 1.0055 (0.9982, 1.0128) lag 0

Study	Methods	Pollutant Data	Findings
Burnett* et al. (1997b) Toronto, Canada Period of Study: Summer only, 1992-1994	Hospital Admissions Outcomes (ICD 9 codes): Respiratory tracheobronchitis (480-6), COPD (491-4, 496) Study design: Time-series Statistical analyses: Poisson regression, GEE, GAM Covariates: Temperature, dew point temperature, Long-term trend, season, influenza, day of wk Season: Summers only Lag: 0,1,2,3,4 days	Avg SO_2: 7.9 ppb CV: 64 Range: 0, 26 5th: 1 25th: 4 50th: 7 75th: 11 95th: 18 Number of stations: 6-11 Copollutants: CO (r = 0.37) H+ (r = 0.45) SO_4 (r = 0.42) TP (r = 0.55) FP (r = 0.49) CP (r = 0.44) COH (r = 0.50) O_3 (r = 0.18) NO_2 (r = 0.46)	Risks of hospitalization for respiratory disease were summed for O_3, NO_2, and SO_2 at 11% increase in admissions. The proportion associated with the single-pollutant SO_2 was 3.6%. CoH was the strongest predictor of hospitalization indicating particle associated pollutants are responsible for effects and outcomes measured. Increment: 4.00 ppb (IQR) Respiratory-percent increase 4.0% (t = 4.14) lag 0 Copollutant and multipollutant models RR (t-statistic): SO_2, COH: 1.012 (1.10) SO_2, H+: 1.022 (1.96) SO_2, SO_4: 1.021 (1.93) SO_2, TP: 1.021 (1.72) SO_2, FP: 1.022 (1.92) SO_2, CP: 1.023 (2.03) SO_2, O_3, NO_2: 1.019 (1.64)
Burnett* et al. (1999) Toronto, Canada Period of Study: Jan 1980-Dec 1994	Hospital Admissions Outcome(s) (ICD9): Asthma (493); obstructive lung disease (490-2, 496); Respiratory infection (464, 466, 480-7, 494) Study design: Time-series N: ≈ 60,000 (asthma) Statistical analyses: Poisson regression model with stepwise analysis Covariates: Long-term trends, season, day of wk, daily max temperature, daily min temperature, daily avg dew point temperature, daily avg relative humidity Statistical package: S-Plus, SAS Lag: 0,1,2 days, cumulative	24-h Avg: 5.35 ppb CV = 110; 5th: 0 25th: 1 50th: 4 75th: 8 95th: 17 100th: 57 Number of stations: 4 Copollutants: $PM_{2.5}$ (r = 0.46) $PM_{10-2.5}$ (r = 0.28) PM_{10} (r = 0.44) CO (r = 0.37) NO_2 (r = 0.54) O_3 (r = 0.02)	The percent hospital admissions associated with SO_2 increased for: asthma, COPD, and respiratory infection. However, in multipollutant models significant increases were only seen in asthma and respiratory infection. SO_2 effects could be largely explained by other variables in the pollution mix as demonstrated by the Multipollutant model. The greatest contribution of SO_2 is to respiratory infection. However, overall SO_2 is a small factor in total hospitalization response. Increment: 5.35 ppb (Mean) Single-pollutant model percent increase (t statistic) Asthma: 1.01% (1.76) lag 0-2; OLD: 0.03% (0.05) lag 0-1 Respiratory infection: 2.40% (5.04) lag 0-2 Multipollutant model percent increase (SE) Asthma: SO_2 + CO + O_3: 0.89% (SE < 2); SO_2 + CO + O_3 + $PM_{2.5}$: 0.69% (SE < 2); SO_2 + CO + O_3 + $PM_{10-2.5}$: 0.16% (SE < 2); SO_2 + CO + O_3 + $PM_{2.5}$: 0.76% (SE < 2) Respiratory infection: SO_2 + NO_2 + O_3: 1.85%; SO_2 + NO_2 + O_3 + $PM_{2.5}$: 0.67 (SE < 2); SO_2 + NO_2 + O_3 + $PM_{10-2.5}$: 1.71 (SE ≥ 3); SO_2 + NO_2 + O_3 + $PM_{2.5}$: 1.00 (SE > 2)
Burnett* et al. (2001) Toronto, Canada Period of Study: 1980-1994	Hospital Admissions Outcome(s) (ICD9): Croup (464.4), pneumonia (480-486), asthma (493), acute bronchitis/bronchiolitis (466) Age groups analyzed: < 2 yrs Study design: Time-series Statistical analyses: Poisson regression with GAM Covariates: Temporal trend, day of wk, temperature, relative humidity Statistical package: S-Plus Lag: 0-5 days	1-h max SO_2 (ppb) Mean: 11.8 CV: 93 5th: 0 25th: 5 50th: 10 75th: 15 95th: 32 99th: 55 100th: 110 Number of stations: 4 Copollutants: O_3 (r = 0.39) SO_2 CO $PM_{2.5}$ $PM_{10-2.5}$	SO_2 had the smallest effect on respiratory admissions of all pollutants considered. Increment: NR All respiratory admissions: Single-pollutant: Percent increase: 3.1% (t = 1.900) lag 3 Multipollutant (adjusted for O_3): Percent increase: 1.21% (t = 0.67) lag 3

Study	Methods	Pollutant Data	Findings
Cakmak et al. (2007) Canada (Calgary, Edmonton, Halifax, London, Ottawa, Saint John, Toronto, Vancouver, Windsor, Winnipeg) Period of Study: 4/1/1993-3/31/2000	Hospital Admissions Outcome(s) (ICD9): Respiratory (466, 480-486, 490-494, 496) Study design: Time-series Statistical Analysis: Poisson Statistical package: S-Plus Age groups analyzed: All ages Covariates: Day-of-wk, mean daily temperature, max daily temperature, min daily temperature, change in barometric pressure, mean relative humidity N: 215,544 Lag(s): 2.6 days	24-h avg: 4.6 ppb Range: 2.8 ppb to 10.2 ppb Copollutants: O_3 NO_2 CO	SO_2 associated with increased hospital admissions. % increase (per 4.6 ppb SO_2) Overall Single-pollutant model: 1.1% (0.5, 1.8) Multi-pollutant model: 0.5% (0.1, 0.9) By Gender: Male: 0.4% (−0.2, 1.1); Female: 0.9% (−0.4, 2.1) By Education: <Grade 9: 0.8% (0.1, 1.5); Grades 9-13: 0.9% (−0.1, 1.9): Some university/trade school: 0.8% (−0.1, 1.7); University diploma: 0.3 % (−0.9, 1.5) By Income: < 21,309: 0.7% (−0.1, 1.5); 21,309-28,161: 0.5% (−0.4, 1.4); 28,161-35,905: 0.0% (−1.0, 1.0); >35,905: 0.7% (−0.4, 1.8)
Fung et al. (2006) Vancouver, BC, Canada Period of Study: 6/1/95-3/31/99	Hospital Admissions Outcome(s) (ICD9): All respiratory hospitalizations (460-519) Age groups analyzed: 65+ Study design: (1) Time-series (2) Case-crossover, (3) DM-models (Dewanji and Moolgavkar, 2000, 2002) N: 40,974 Statistical analyses: (1) Poisson, (2) conditional logistic regression, (3) DM method–analyze recurrent data in which the occurrence of events at the individual level over time is available Covariates: Day of wk Statistical package: S-Plus and R Lag: Current day, 3 and 5 day lag	SO_2 24-h avg: Mean: 3.46 ppb SD: 1.82 IQR: 2.50 ppb Range: 0.00, 12.50 Copollutants: CO (r = 0.61) COH (r = 0.65) NO_2 (r = 0.57) PM_{10} (r = 0.61) $PM_{2.5}$ (r = 0.42) $PM_{10-2.5}$ (r = 0.57) O_3 (r = −0.35)	No significant association was found between hospital admissions and current day SO_2 levels (lag 0). Significant associations were found with SO_2 using a 3, 5, and 7 day moving avg, with the strongest association observed with a 7 day lag. The DM method produced slightly higher relative risks compared to the Time-series and case crossover results. Increment: 2.5 ppb (IQR) SO_2 Time-series: RR 1.013 (0.997, 1.028) lag 0; RR 1.030 (1.010, 1.051) lag 0-3; RR 1.032 (1.008, 1.056) lag 0-5; RR 1.031 (1.003, 1.060) lag 0-7 SO_2 Case-crossover: RR 1.010 (0.992, 1.027) lag 0; RR 1.028 (1.005, 1.050) lag 0-3; RR 1.030 (1.004, 1.057) lag 0-5; RR 1.028 (0.998, 1.058) lag 0-7 SO_2 DM model: RR 1.013 (0.998, 1.027) lag 0; RR 1.034 (1.015, 1.053) lag 0-3; RR 1.039 (1.016, 1.061) lag 0-5; RR 1.044 (1.018, 1.070) lag 0-7 DM method produced slightly higher RR estimates on O_3, SO_2 and $PM_{2.5}$ compared to time-series and case-crossover, and slightly lower RR estimates on COH, NO_2, and PM_{10}, though the results were not significantly different from one another.
Kesten et al. (1995) Toronto, ON, Canada Period of Study: 7/1/1991-6/30/1992	ED Visits Outcome(s) (ICD 9): Asthma (493) Age groups analyzed: all ages Study design: Time-series N: 854 # of Hospitals: 1 Statistical analyses: Auto regression Statistical package: SAS Lag: 1 or 7	SO_2 24-h avg No data was provided for concentration or for correlation with other pollutants. Copollutants: NO_2 O_3 API (TRS, CO, TSP)	Fit of an auto-regression model with covariates linked to same day gave no evidence of association between asthma and SO_2. Despite multiple attempts to correlate individual or combinations of pollutants with air quality indices, no association was found between ER visits for asthma and ambient daily, weekly, or monthly levels of SO_2, NO_2, or O_3. No relative risks were provided.

Study	Methods	Pollutant Data	Findings
Lin et al. (2003) Toronto, ON, Canada Period of Study: 1981-1993	Hospital Admissions Outcome(s) (ICD9): Asthma (493) Age groups analyzed: 6-12 Study design: Bi-directional case-crossover N: 7,319 Statistical analyses: Conditional logistic regression Covariates: Daily max and min temperatures and avg relative humidity Lag: Cumulative lag of 1-7 days.	SO_2 24-h avg: 5.36 ppb SD: 5.90 Range: 0, 57.00 25th: 1.00 50th: 4.00 75th: 8.00 Number of stations: 4 Copollutants: CO (r = 0.37) NO_2 (r = 0.54) PM_{10} (r = 0.44) O_3 (r = −0.01) $PM_{2.5}$ (r = 0.46) $PM_{10-2.5}$ (r = 0.28)	SO_2 is positively associated with asthma hospitalizations, although the relationship varies in boys and girls. Increment: 7 ppb (IQR) Boys 6-12 yrs; Girls 6-12 yrs: Lag 0: OR 1.00 (0.95, 1.05); 1.04 (0.97, 1.11); Lag 0-1: OR 0.99 (0.93, 1.06); 1.04 (0.95, 1.13 Lag 0-2: OR 0.98 (0.90, 1.06); 1.05 (0.95, 1.16) Lag 0-3: OR 0.96 (0.87, 1.05); 1.09 (0.98, 1.22) Lag 0-4: OR 0.95 (0.86, 1.05); 1.13 (1.00, 1.28) Lag 0-5: OR 0.93 (0.83, 1.03); 1.17 (1.02, 1.34) Lag 0-6: OR 0.93 (0.83, 1.04); 1.20 (1.04, 1.39) Multipollutant model with $PM_{10-2.5}$ and $PM_{2.5}$ Boys 6-12 yrs; Girls 6-12 yrs: Lag 0: OR 0.98 (0.93, 1.04); 1.06 (0.98, 1.14) Lag 0-1: OR 0.99 (0.91, 1.06); 1.03 (0.93, 1.14) Lag 0-2: OR 0.96 (0.88, 1.05); 1.04 (0.92, 1.17) Lag 0-3: OR 0.95 (0.85, 1.05); 1.08 (0.95, 1.23) Lag 0-4: OR 0.94 (0.84, 1.06); 1.12 (0.97, 1.29) Lag 0-5: OR 0.91 (0.80, 1.04); 1.18 (1.00, 1.38) Lag 0-6: OR 0.91 (0.80, 1.04); 1.28 (1.08, 1.51)
Lin* et al. (2004c) Vancouver, BC, Canada Period of Study: 1987-1998	Hospital Admissions Outcome(s) (ICD9): Asthma (493) Age groups analyzed: 6-12 Study design: Time-series N: 3,754 (2,331 male, 1,423 female) Statistical analyses: Semi-parametric Poisson regression with GAM (with default and more stringent criteria) Covariates: Trend, day of wk, Statistical package: S-Plus Lag: Cumulative 1-7 day	24-h avg SO_2 (ppb) Mean: 4.77 SD: 2.75 Min: 0 25th: 2.75 50th: 4.25 75th: 6.00 Max: 24.00 Number of stations: 30 Copollutants: CO (r = 0.67) NO_2 (r = 0.67) O_3 (r = −0.10)	Results presented are default GAM, but authors state that use of natural cubic splines with a more stringent convergence rate produced similar results Increment: 3.3 ppb (IQR) Boys 6-12 yrs by SES status: Low; High Lag 0 RR 1.02(0.94, 1.10); 1.03 (0.95, 1.12) Lag 0-1 RR 1.03 (0.94, 1.13); 1.06 (0.96, 1.17) Lag 0-2 RR 1.03 (0.93, 1.15); 1.06 (0.95, 1.18) Lag 0-3 RR 1.01 (0.90, 1.13); 1.04 (0.92, 1.17) Lag 0-4 RR 0.98 (0.88, 1.10); 1.02 (0.90, 1.14) Lag 0-5 RR 0.97 (0.86, 1.10); 1.02 (0.89, 1.16) Lag 0-6 RR 0.98 (0.86, 1.12); 1.05 (0.91, 1.21) Girls 6-12 yrs by SES status: Low; High Lag 0 RR 1.05 (0.95, 1.16); 1.07 (0.96, 1.19) Lag 0-1 RR 1.11 (0.99, 1.25); 1.07 (0.94, 1.21) Lag 0-2 RR 1.11 (0.97, 1.26); 1.07 (0.93, 1.23) Lag 0-3 RR 1.18 (1.02, 1.36); 1.02 (0.87, 1.19) Lag 0-4 RR 1.18 (1.02, 1.35); 0.99 (0.85, 1.15) Lag 0-5 RR 1.19 (1.01, 1.40); 0.95 (0.80, 1.13) Lag 0-6 RR 1.15 (0.97, 1.36); 0.98 (0.81, 1.17) Multipollutant model (adjusted for NO_2) Girls, Low SES: 1.17 (1.00, 1.37), 4-day avg; 1.19 (1.00, 1.42), 6-day avg
Lin et al. (2005) Toronto, ON Period of Study: 1998-2001	Hospital Admissions Outcome(s) (ICD9): Respiratory infections (464,466, 480-487) Age groups analyzed: 0-14 Study design: Case-crossover N: 6,782 Statistical analyses: Conditional logistic regression Covariates: Statistical package: SAS 8.2 Lag: 0-6 days	24-h avg: Mean: 4.73 ppb SD: 2.58 ppb Range: 1.00, 19.67 25th: 3.00 50th: 4.00 75th: 6.00 Number of monitors: 5 Copollutants: $PM_{2.5}$ (r = 0.47) $PM_{10-2.5}$ (r = 0.29) PM_{10} (r = 0.48) CO (r = 0.12) NO_2 (r = 0.61)	Asthma hospitalization for boys was associated with SO_2 before the adjustment for fine and coarse PM. Asthma hospitalization for girls was not associated with SO_2 for any lag. Increment: 3 ppb (IQR) Unadjusted Model: Boys only: OR 1.06 (0.97, 1.16) lag 0-3; OR 1.02 (0.92, 1.13) lag 0-5 Girls only: OR 1.05 (0.94, 1.16) lag 0-3; OR 1.07 (0.95, 1.21) lag 0-5 Boys and Girls: OR 1.06 (0.99, 1.13) lag 0-3; OR 1.04 (0.96, 1.13) lag 0-5 Adjusted Boys only: OR 1.11 (1.01, 1.21) lag 0-3; OR 1.08 (0.97, 1.21) lag 0-5 Girls only: OR 1.07 (0.96, 1.19) lag 0-3; OR 1.12 (0.98, 1.28) lag 0-5 Boys and Girls: OR 1.10 (1.02, 1.18) lag 0-3; OR 1.10 (1.01, 1.20) lag 0-5 Multipollutant model with $PM_{2.5}$ and $PM_{2.5}$ Boys only: OR 1.02 (0.90, 1.15) lag 0-3; OR 0.99 (0.85, 1.16) lag 0-6 Girls only: OR 1.09 (0.0.94, 1.26) lag 4; OR 1.07 (0.90, 1.28) lag 6 Boys and Girls: OR 1.05 (0.95, 1.15) lag 4; OR 1.03 (0.91, 1.16) lag 6

Study	Methods	Pollutant Data	Findings
Luginaah et al. (2005) Windsor, ON, Canada Period of Study: 4/1/95-12/31/00	Hospital Admissions Outcome(s) (ICD9): Respiratory admissions (460-519) Age groups analyzed: 0-14, 15-64, 65+, all ages Study design: (1) Time-series and (2) case-crossover N: 4,214. # of Hospitals: 4 Statistical analyses: (1)Poisson regression, GAM with natural splines (stricter criteria), (2) conditional logistic regression with Cox proportional hazards model Covariates: Temperature, humidity, change in barometric pressure, day of wk Statistical package: S-Plus Lag: 1,2,3 days	SO_2 avg 24-h Max: 27.5 ppb, SD: 16.5; Range: 0, 129 Number of stations: 4 Copollutants: NO_2 (r = 0.22) CO (r = 0.16) PM_{10} (r = 0.22) COH (r = 0.14) O_3 (r = −0.02) TRS (r = 0.13)	The effect of SO_2 on respiratory hospitalization varies considerably, especially at low levels of exposure. Increment: 19.25 ppb (IQR) Time-series, females; males: All ages: 1.041 (0.987, 1.098); 0.953 (0.900, 1.009) lag 1 0-14 yrs: 1.111 (1.011, 1.221); 0.952 (0.874, 1.037) lag 1 15-65 yrs: 1.031 (0.930, 1.144); 0.971 (0.845, 1.15) lag 1 65+ yrs: 1.030 (0.951, 1.115); 0.9409 (0.860, 1.029) lag 1 Case-crossover, females; males All ages: 1.047 (0.978, 1.122); 0.939 (0.874, 1.009) lag 1 0-14 yrs: 1.119 (0.995, 1.259); 0.923 (0.831, 1.025) lag 1 15-65 yrs: 1.002 (0.879, 1.141); 0.944 (0.798, 1.116) lag 1 65+ yrs: 1.020 (0.924, 1.126); 0.968 (0.867, 1.082) lag 1
Stieb et al. (1996) St. John, New Brunswick, Canada Period of Study: 1984-1992 (May-Sep only)	ED Visits. Outcome(s): Asthma ICD9 codes: NR Age groups analyzed: 0-15, >15 Study design: Time-series N: 1,987 # of Hospitals: 2 Statistical analyses: SAS NLIN (Equivalent to Poisson GEE) Covariates: Day of wk, long-term trends Season: Summers only (May-Sep) Dose-response investigated?: Yes Statistical package: SAS Lag: 0-3 days	1-h max SO_2 (ppb) Mean: 38.1 Range: 0, 390 95th 110 Copollutants: O_3 (r = 0.04) NO_2 (r = −0.03) SO_4^{2-} (r = 0.23) TSP (r = 0.16)	SO_2 did not affect the rate of asthma ED visits when O_3 was included in the model. Increment: NR $SO_2 + O_3$: β = −0.0030 (0.0027) lag 0

Study	Methods	Pollutant Data	Findings
Stieb* et al. (2000) Saint John, New Brunswick, Canada Period of Study: Retrospective: 7/92-6/94 Prospective: 7/94-3/96	ED Visits Outcome(s): Asthma; COPD; Respiratory infection (bronchitis, bronchiolitis, croup, pneumonia); All respiratory ICD9 codes: NR Age groups analyzed: All Study design: Time-series N: 19,821 Statistical analyses: Poisson regression, GAM Covariates: Day of wk, selected weather variables in each model Season: All yr, summer only Dose-response investigated: Yes Statistical package: S-Plus Lag: all yr = 0; summer only = 0-3	24-h avg: Annual Mean: 6.7 (5.6) ppb 95th: 18.0 Max: 60.0 Warm season: Mean: 7.6 (5.2) ppb 95th: 18.0 Max: 29.0 1-h max: Annual Mean: 23.8 (21.0) ppb 95th: 62.0 Max: 161.0 Warm season: Mean: 25.4 (17.8) ppb 95th: 62.0 Max: 137.0 Copollutants: CO (r = 0.31) O_3 (r = 0.10) NO_2 (r = 0.41) TRS (r = 0.08) PM_{10} (r = 0.36) $PM_{2.5}$ (r = 0.31) H+ (r = 0.24) SO_4^{2-} (r = 0.26) COH (r = 0.31) H2S (r = −0.01) Assessed multipollutant models	Non-linear effect of SO_2 on summertime respiratory visits observed and log transformation strengthened the association. Increment: 23.8 ppb (mean) 1-h max: Respiratory visits: All yr: 3.9% lag 5 May to Sept: 3.9% lag 0-3 Multipollutant model (SO_2, O_3, NO_2) All yr: 3.7% (1.5, 6.0) lag 5 Multipollutant model (ln (NO_2), O_3, SO_2 COH) May to Sept: 3.9% (1.1, 6.7) lag 0-3
Villeneuve et al., (2006b) Toronto, ON, Canada Period of Study: 1995-2000 Days: 2,190	GP Visits Outcome(s) (ICD9): Allergic Rhinitis (177) Age groups analyzed: ≥65 Study design: Time-series N: 52,691 Statistical analyses: GLM, using natural splines (more stringent criteria than default) Covariates: Day of wk, holiday, temperature, relative humidity, aero-allergens Season: All Yr; Warm, May-Oct; Cool, Nov-Apr Statistical package: S-Plus Lag: 0-6	24-h avg: 4.7 ppb SD: 2.8 IQR: 3.2 ppb Range: 0, 24.8 Number of stations: 9 Copollutants: NO_2 O_3 CO PM_{10} $PM_{10-2.5}$ $PM_{2.5}$	There were positive associations between allergic rhinitis and SO_2 for exposures occurring on the same day as physician visits, but only during the winter time. Increment: 10.3 ppb (IQR) All results estimated from Stick Graph: All Yr: Mean increase: 1.7% (−0.4, 2.8) lag 0 Warm: Mean increase: 0.3% (−1.9, 2.5) lag 0 Cool: Mean increase: 1.9% (−0.2, 4.1) lag 0

Study	Methods	Pollutant Data	Findings
Yang et al. (2003b) Vancouver, Canada Period of Study: 1986-1998 Days: 4748	Hospital Admissions Outcome(s) (ICD9): All respiratory admissions (460-519) Study design: Case-crossover Age groups analyzed: < 3, ≥ 65 Statistical analyses: conditional logistic regression Lag: 0-5 days	24-h avg SO_2 (ppb): Mean: 4.84 SD: 2.84 5th: 1.50 25th: 2.75 50th: 4.25 75th: 6.25 100th: 24.00 IQR: 3.50 Number of stations: 30 Copollutants: CO NO_2 O_3 (r = −0.37) COH	SO_2 showed the weakest effect among children and the second weakest effect among older adults when compared to all other pollutants considered in the study. Increment: 3.50 ppb (IQR) All respiratory admissions < 3 yrs: SO_2 alone: OR 1.01 (0.98, 1.05) lag 2 SO_2 + O_3: OR 1.01 (0.97, 1.04) lag 2 SO_2 + O_3 + CO + COH + NO_2: OR 0.98 (0.94, 1.03) lag 2 All respiratory admissions ≥ 65 yrs: SO_2 alone: OR 1.02 (1.00, 1.04) lag 0 SO_2 + O_3: OR 1.02 (1.00, 1.04) lag 0 SO_2 + O_3 + CO + COH + NO_2: OR 1.01 (0.98, 1.03) lag 0
Yang et al. (2005) Vancouver, BC, Canada Period of Study: 1994-1998 Days: 1826	Hospital Admissions Outcome(s) (ICD9): COPD excluding asthma (490-2, 494, 496) Age groups analyzed: 65+ Study design: Time-series N: 6,027 Statistical analyses: Poisson regression with GAM (with more stringent criteria) Covariates: Temperature, relative humidity, day of wk, temporal trends, season Statistical package: S-Plus Lag: 0-6 days, moving averages	24-h avg: 3.79 ppb SD: 2.12; IQR: 2.75 ppb; Range: 0.75, 22.67 Winter: 4.10 (2.87) Spring: 3.40 (1.58) Summer: 4.10 (1.79) Fall: 3.56 (1.92) Number of stations: 5 Copollutants: PM_{10} (r = 0.62) NO_2 (r = 0.61) CO (r = 0.67) O_3 (r = −0.34)	This study produced a marginally significant association between COPD hospitalization and 6-day SO_2 exposure. Most previous studies have not detected a significant effect of SO_2 on respiratory ED visits or hospitalizations. Increment: 2.75 ppb (IQR) COPD >65 yrs, yr round: RR 1.00 (0.97, 1.04) lag 0; RR 1.02 (0.98, 1.06) lag 0-1; RR 1.04 (0.99, 1.08) lag 0-2; RR 1.04 (0.99, 1.09) lag 0-3; RR 1.05 (0.99, 1.11) lag 0-4; RR 1.06 (1.00, 1.13) lag 0-5; RR 1.06 (0.99, 1.13) lag 0-6 2-pollutant model: NO_2: RR 0.99 (0.91, 1.08) lag 0; CO: RR 0.97 (0.87, 1.07) lag 0-6; O_3: RR 1.07 (1.00, 1.14) lag 0-6; PM_{10}: 0.97 (0.88, 1.06) lag 0-6 Multipollutant models: SO_2, CO, NO_2, O_3, PM_{10}: RR 0.94 (0.85, 1.05); SO_2, CO, NO_2, O_3: RR 0.96 (0.86, 1.06)
EUROPE			
Anderson et al. (1997) Multicity, Europe (Amsterdam, Barcelona, London, Milan, Paris, Rotterdam) Period of Study: 1977-1989 for Amsterdam and Rotterdam 1986-1992 for Barcelona 1987-1991 for London 1980-1989 for Milan 1987-1992 for Paris	Hospital Admissions Outcome(s) (ICD 9): COPD–unspecified bronchitis (490), chronic bronchitis (491), emphysema (492), chronic airway obstruction (496) Study design: Time-series Statistical analyses: APHEA protocol, Poisson regression, meta-analysis Covariates: Trend, season, day of wk, holiday, influenza, temperature, humidity Season: Cool, Oct-Mar; Warm, Apr-Sep Lag: 0,1,2 days and 0-3 cumulative	24-h all yr avg (μg/m³): Amsterdam: 21 Barcelona: 40 London: 31 Milan: 53 Paris: 23 Rotterdam: 32 1-h max Amsterdam: 50 Barcelona: 60 London: NR Milan: NR Paris: 47 Rotterdam: 82 Copollutants: NO_2 BS TSP O_3	The effect of SO_2 varied considerably across the cities; however, the summer estimate was significantly associated with COPD for the 1-h measure and borderline significant for the daily mean. Both 24-h and 1-h SO_2 concentrations were significantly associated with COPD ER admissions in the warm season. Only cumulative lags of SO_2 showed borderline significance. Increment: 50 μg/m³ COPD-Warm season: 24 h avg 1.05 (1.01, 1.10) 1-h 1.02 (1.00, 1.04) COPD-Cool season: 24 h avg 1.02 (0.98, 1.05) 1-h 1.01 (0.99, 1.03) COPD-All yr: 24-h avg 1.022 (0.981, 1.055) lag 1 24-h avg 1.021 (0.998, 1.045) lag 0-3, cumulative 1-h max 1.011 (0.994, 1.029) lag 1 1-h max 1.015 (1.003, 1.027) lag 0-3, cumulative

Study	Methods	Pollutant Data	Findings
Anderson et al. (1998) London, England Period of Study: Apr 1987-Feb 1992 Days: 1,782	Hospital Admissions Outcome(s) (ICD 9): Asthma (493) Age groups analyzed: < 15, 15-64, 65+ Study design: Time-series Statistical analyses: APHEA protocol, Poisson regression Covariates: Time trends, seasonal cycles, day of wk, public holidays, influenza epidemics, temperature, humidity Season: Cool (Oct- Mar); Warm (Apr-Sep) Statistical package: NR Lag: 0, 1, 2 days	24-h avg SO_2 ($\mu g/m^3$) Mean: 32.0 SD: 11.7 Range: 9, 100 5th: 16 10th: 18 25th: 24 50th: 31 75th: 38 90th: 46 95th: 52 # of monitors: 2 Copollutants: O_3 NO_2 BS	The strongest association between SO_2 and asthma admissions was for those ≥65 yrs in the cool season. A weaker association was observed for children in the warm season and all yr. The adult population showed no association. In 2-pollutant models O_3 was overall the strongest pollutant associated with hospital admission with weaker associations with NO_2 and BS. The most consistent yr-round association for All ages was found with BS. When looking at all ages combined, SO_2 association remained significant in all 2-pollutant models except with NO_2, both for all yr and the summer (warm) season. Increment: 10 ppb in 24-h avg SO_2 0-14 yrs Whole yr: 1.64% (0.29, 3.01) lag 1; 2.04% (0.29, 3.83) lag 0-3; + O_3 1.77% (0.22, 3.36) lag 1; + NO_2 1.23% (−0.22, 2.69) lag 1; + BS 1.66% (0.23, 3.12) lag 1 Warm season: 3.33% (1.09, 5.63) lag 1; 3.40% (0.41, 6.48) lag 0-3; + O_3 3.35% (0.89, 5.87) lag 1; + NO_2 2.92% (0.58, 5.32) lag 1; + BS 3.66% (1.35, 6.02) lag 1 Cool season: 0.56% (−1.16, 2.32) lag 1; 1.24% (−0.95, 3.49) lag 0-2 15-64 yrs Whole yr: −0.69% (−2.28, 0.94) lag 2; −0.71% (−2.69, 1.30) lag 0-2 Warm season: −1.39% (−3.97, 1.27) lag 0; −2.2% (−5.46, 11.8) lag 0-2 Cool season: −0.24% (−2.28, 1.84) lag 0; 0.20% (−2.28, 2.74) lag 0-2 ≥ 65 yrs Whole yr: 2.82% (−0.82, 5.96) lag 2; 3.06% (−0.72, 6.98) lag 0-3 Warm season: −2.62% (−7.31, 2.31) lag 2; −4.27% (−9.89, 1.71) lag 0-3 Cool season: 5.85% (1.81, 10.05) lag 2; 7.28% (2.19, 12.62) lag 0-3; + O_3 7.84% (2.48, 13.48) lag 1; + NO_2 4.19% (−0.53, 9.13) lag 1; + BS 5.29% (0.42, 10.40) lag 1 All Ages Whole yr: 1.64% (0.54, 2.75) lag 1; 2.75% (1.22, 4.30) lag 0-3; + O_3 1.48% (0.24, 2.73) lag 1; + SO_2 1.14% (−0.04, 2.33) lag 1; + BS 1.54%(0.36, 2.73) lag 1 Warm season: 2.02% (0.22, 3.85) lag 1; 2.60% (0.02, 5.25) lag 0-3; + O_3 1.91% (0.05, 3.81) lag 1; + NO_2 1.64% (−0.23, 3.56) lag 1 + BS 2.18% (0.32, 4.07) lag 1 Cool season: 1.41% (0.0, 2.83) lag 1; 2.83% (0.89, 4.81) lag 0-3; + O_3 −0.09% (−1.61, 1.82) lag 1; + NO_2 0.83% (−0.67, 2.34) lag 1; + BS 1.11% (−0.41, 2.66) lag 1
Anderson* et al. (2001) West Midlands conurbation, United Kingdom Period of Study: 10/1994-12/1996	Hospital Admissions Outcome(s) (ICD9): All respiratory (460-519), Asthma (493), COPD (490-496, excluding 493) Age groups analyzed: 0-14, 15-64, 65+ Study design: Time-series Statistical analyses: followed APHEA 2 protocol, GAM Covariates: Season, temperature, humidity, epidemics, day of wk, holidays Statistical package: S-Plus 4.5 Pro Lag: 0,1,2,3, 0-1, 0-2, 0-3	24-h avg: 7.2 ppb, 4.7 (SD) Min: 1.9 ppb Max: 59.8 ppb 10th: 3.3 ppb 90th: 12.3 ppb # of monitors: 5 Copollutants: PM_{10} (r = 0.55) $PM_{10-2.5}$ (r = 0.31) $PM_{2.5}$ (r = 0.52) BS (r = 0.50) SO_4^{2-} (r = 0.19) NO_2 (r = 0.52) O_3 (r = -0.22) CO (r = -0.29)	When admissions were analyzed by subgroups, respiratory and asthma admissions were positively correlated with SO_2. SO_2 significantly associated with asthma and respiratory admissions for the 0 to 14-yr-age group; however, little evidence of a seasonal interaction was observed. Increment: 9 ppb (90th-10th) All respiratory: All ages: 1.3% (−0.7, 3.4) lag 0-1 0-14 yrs: 4.6% (1.40, 7.8) lag 0-1 15-64 yrs: −0.9% (−4.8, 3.3) lag 0-1 ≥ 65 yrs: −2.0% (−4.9, 1.1) lag 0-1 COPD with asthma: 0-14 yrs: 10.9% (4.50, 17.8) lag 0-1 15-64 yrs: 2.4% (−5.5, 10.9) lag 0-1 ≥ 65 yrs: −4.2% (−8.9, 0.8) lag 0-1

Study	Methods	Pollutant Data	Findings
Atkinson et al. (1999b) London, England Period of Study: 1992-1994 Days: 1,096	Hospital Admissions Outcome(s) (ICD9): All respiratory (460-519); Asthma (493); Asthma and COPD (490-496); LRD (466,480-486) Age groups analyzed: all ages, 0-14 yr, 15-64 yr and ≥65 yr Study design: Time-series N: 165,032 (respiratory admissions), 189,032 (cardiovascular admissions) Statistical analyses: Poisson regression following APHEA protocol Covariates: Long-term seasonal patterns, day of wk, temperature, humidity, influenza. Statistical package: SAS Investigated Dose/Response: Yes Lag: 0,1,2,3 days	SO_2− 24-h (μg/m³) Mean: 21.2 (7.8) μg/m³ Min: 7.4 10th: 13 50th: 19.8 90th: 31 Max: 82.2 # of monitors: 5 Copollutants: O_3, CO, PM_{10}, BS, NO_2 Correlation coefficients ranged between r = 0.5 and 0.6	Asthma was closely linked with PM, CO, NO_2, and traffic pollution. When SO_2 and PM_{10} were included in the same model, the magnitude of the individual associations was reduced, as were their statistical significance. This reduction occurred in children, adults and the elderly. The other pollutants all had the effect of reducing the magnitude of the individual SO_2 and $PM_{2.5}$ associations, although their statistical significance was unaffected. This indicates that both SO_2 and $PM_{2.5}$ were indicators of the same pollutant mixture. Increment: 18 μg/m³ All respiratory: All ages 2.01% (0.29, 3.76) lag 1; 0-14 yrs 5.14% (2.59, 7.76) lag 1; 15-64 yrs 1.90% (−0.79, 4.66) lag 3; ≥ 65 yrs 2.25 (−0.09, 4.65) lag 3 Asthma: All ages: 3.38 (0.42, 6.43) lag 1; 0-14 yrs: 6.74% (2.92, 10.69) lag 1; 15-64 yrs: 4.58% (−0.18, 9.57) lag 3; ≥ 65 yrs: 6.31% (−1.59, 14.83) lag 2 COPD and Asthma: ≥ 65 yrs: 1.53% (−1.83, 5.00) lag 3 Lower Respiratory: ≥ 65 yrs: 5.16% (1.19, 9.28) lag 3
Atkinson et al. (1999a) London, United Kingdom Period of Study: 1/92-12/94	ED Visits Outcome(s) (ICD 9): Respiratory ailments (490-496), including asthma, wheezing, inhaler request, chest infection, COPD, difficulty in breathing, cough, croup, pleurisy, noisy breathing Age groups analyzed: 0-14; 15-64; ≥ 65; All ages Study design: Time-series N: 98,685 # of Hospitals: 12 Statistical analyses: Poisson regression, APHEA protocol Covariates: Long-term trend, season, day of wk, influenza, temperature, humidity Statistical package: SAS Lag: 0,1,0-2 and 0-3 days	24-h avg: 21.2 μg/m³, SD: 7.8 10th: 13.0 50th: 19.8 90th: 31.0 Range: 7.4, 82.2 # of Stations: 5 Copollutants: SO_2 O_3 (8 h) CO (24 h avg), PM_{10} (24 h avg) BS	SO_2 was closely related to PM_{10}, but 2-pollutant models showed that the effect of SO_2 was decreased by NO_2 and PM_{10} inclusion. Inclusion of other pollutants did not significantly decrease the influence of SO_2 on ER admissions in 2-pollutant models. Increment: 18 μg/m³ in 24-h Single-pollutant model Asthma only: 0-14 yrs 9.92% (4.75, 15.34) lag 1 15-64 yrs 4.19% (−0.53, 9.13) lag 1 All ages 4.95% (1.53, 8.48) lag 1 All respiratory: 0-14 yrs 6.01% (2.98, 9.12) lag 2 15-64 yrs 2.72% (−0.18, 5.70) lag 3 65+ yrs −1.82% (−5.72, 2.25) lag 3 All Ages 2.81% (0.72, 4.93) lag 1 Copollutant models for asthma among children: SO_2 + NO_2: 5.42% (0.18, 10.93) SO_2 + O_3: 8.39% (3.82, 13.17) SO_2 + CO: 8.05% (3.45, 12.86) SO_2 + PM_{10}: 5.63 (0.53, 10.98) SO_2 + BS: 8.03 (3.32, 12.96)

Study	Methods	Pollutant Data	Findings
Atkinson et al. (2001) Multicity, Europe (Barcelona, Birmingham, London, Milan, Netherlands, Paris, Rome, Stockholm) Period of Study: 1997-1998	Hospital Admissions Outcome(s) (ICD 9): Asthma (493), COPD (490-496), All respiratory (460-519) Study design: Time-series Statistical analyses: APHEA protocol, Poisson regression, meta-analysis Covariates: Season, temperature, humidity, holiday, influenza Statistical package: NR Lag: NR	1-h max of SO_2 ($\mu g/m^3$) Barcelona: NR Birmingham: 24.3 London: 23.6 Milan: 29.1 Netherlands: 8.5 Paris: 17.7 Rome: 9.8 Stockholm: 3.8 Copollutants: NO_2, O_3, CO, BS, PM_{10} Correlation coefficients with PM_{10}: Barcelona: 0.32 Birmingham: 0.77 London: 0.72 Milan: 0.64 Netherlands: 0.67 Paris: 0.63 Rome: 0.15 Stockholm: 0.36	The inclusion of SO_2 in the models only modified PM_{10} associations in the 0- to 14-yr age group. Increment: 10 $\mu g/m^3$ for PM_{10}; change in SO_2 not described. Asthma, 0 to 14 yrs: For PM_{10}: 1.2 (0.2, 2.3) For PM_{10} + SO_2: 0.8 (−3.7, 5.6) Asthma, 15 to 64 yrs: For PM_{10}: 1.1 (0.3, 1.8) For PM_{10} + SO_2: 1.6 (0.6, 2.6) COPD + Asthma, ≥ 65 yrs: For PM_{10}: 1.0 (0.4, 1.5) For PM_{10} + SO_2: 1.3 (0.7, 1.8) All respiratory, ≥ 65 yrs of age: For PM_{10}: 0.9 (0.6, 1.3) For PM_{10} + SO_2: 1.1 (0.7, 1.4)
Boutin-Forzano et al. (2004) Marseille, France Period of Study: 4/97-3/98	ED Visits Outcome(s): Asthma ICD 9 Code(s): NR Age groups analyzed: 3-49 Study design: Case-crossover N: 549 Statistical analyses: Logistic regression Covariates: Minimal daily temperature, max daily temperature, min daily relative humidity, max daily relative humidity, day of wk Statistical package: NR Lag: 0-4 days	Mean: SO_2: 22.5 $\mu g/m^3$ Range: 0.0, 94.0 Copollutants: NO_2 (r = 0.56) O_3 (r = −0.25)	No association was observed between ER visits for asthma and SO_2 levels. Only single-pollutant models were utilized. Increment: 10 $\mu g/m^3$ Increased ER visits: OR 1.0023 (0.9946, 1.0101) lag 0 OR 0.9995 (0.9923, 1.0067) lag 1 OR 0.9996 (0.9923, 1.0069) lag 2 OR 0.9970 (0.9896, 1.0045) lag 3 OR 0.9964 (0.9889, 1.0040) lag 4
Buchdahl et al. (1996) London, United Kingdom Period of Study: 3/1/92-2/28/93	ED visits. Outcomes: Daily acute wheezy episodes Age groups analyzed: ≤ 16 Study design: Case-control N: 1,025 cases, 4,285 controls # of Hospitals: 1 Statistical analyses: Poisson regression Covariates: Season, temperature, wind speed Season: Spring (Apr-Jun), Summer (Jul-Sep), Autumn (Oct-Dec), Winter (Jan-Mar) Statistical package: Stata. Lag: 0-7 days	SO_2 1-h yr round Mean: 22 $\mu g/m^3$, SD: 14 Spring: 20 (14) Summer: 18 (22) Fall: 24 (14) Winter: 25 (14) Copollutants: NO_2 (r = 0.62) O_3 (r = −0.28)	Variations in SO_2 could not explain the U-shaped relationship between O_3 and incidence of asthma. Increment: 14 $\mu g/m^3$ (Std. Dev.) No adjustments to model: RR 1.16 (1.10, 1.23) lag not specified Adjusted for temperature and season: RR 1.12 (1.06, 1.19) lag not specified Adjusted for temperature, season and wind speed: RR 1.08 (1.00, 1.16) lag not specified

Study	Methods	Pollutant Data	Findings
Castellsague et al. (1995) Barcelona, Spain Period of Study: 1986-1989	ED visits Outcome(s): Asthma Age groups analyzed: 15-64 Study design: Time-series # of Hospitals: 4 Statistical analyses: Poisson regression Covariates: Long time trend, day of wk, temperature, relative humidity, dew point temperature Seasons : Winter : Jan-Mar; Summer : Jul-Sep Dose-response investigated: Yes Lag: 0, 1-5 days and cumulative; Summer: lag 2 days, Winter: lag 1 day	Mean SO_2 ($\mu g/m^3$) Summer: 40.8 25th: 25 50th: 36 75th: 54 95th: 82 Winter: 52.0 25th: 36 50th: 49 75th: 67 95th: 94 # of Stations: 15 manual, 3 automatic Copollutants: NO_2 O_3	Interaction between pollutants and asthma emergency room visits was influenced by soy-bean dust in the air. The daily mean of asthma visits and level of SO_2 were higher in the winter than in the summer. A positive but not statistically significant increase in relative risk was found for SO_2 in the summer. SO_2 levels were higher in the winter, but the RR was lower compared to the RR in the summer. SO_2 was not significantly associated with asthma related ER visits. Increment: 25 $\mu g/m^3$ Seasonal differences: Summer: RR 1.052 (0.980, 1.129) lag 2 Winter: RR 1.020 (0.960, 1.084) lag 1
Dab et al. (1996) Paris, France Period of Study: 1/1/87-9/30/92	Hospital Admissions Outcome(s) (ICD 9): All respiratory (460-519), Asthma (493), COPD (490-496) Age groups analyzed: All ages Study design: Time-series Number of hospitals: 27 Statistical analyses: Poisson regression, followed APHEA protocol Covariates: Temperature, relative humidity, influenza, long-term trend, season, holiday, medical worker strike Lag: 0,1,2 days, 0-3 cumulative	All Yr: 24-h avg: 29.7 $\mu g/m^3$ Median:23.0 5th: 7.0 99th: 125.0 1-h max: 59.9 Median: 46.7 5th: 14.0 99th: 232.7 Warm season 24-h avg: 20.1 Median:18.3 5th: 6.0 99th: 49.3 1-h max:42.7 Median:37.0 5th: 13.0 99th: 133.7 Cold season 24-h avg: 40.1 $\mu g/m^3$ Median:31.3 5th: 8.7 99th: 149.0 1-h max:78.3 Median:60.7 5th: 17.0 99th: 268.3 Copollutants: NO_2 O_3 PM_{13} BS	1-h max SO_2 levels yielded lower relative risk when compared to 24-h avg levels. COPD effects were only significantly associated with SO_2 with no lag. The strongest association was observed with PM_{13}; 4.5% increase in respiratory admission per 100 $\mu g/m^3$ increment. SO_2 was a close second. Neither analysis by age or by season showed a significant sensitivity for hospital admissions. The strongest association for asthma admission for all pollutants was with SO_2 24-h avg of 7% (0.14, 14.10), but 1-hr max level was not significant. The strongest association for admission with COPD diagnosis was also for 24-h avg of SO_2 (9.9% [2.3, 18]). Increment: 100 $\mu g/m^3$ All respiratory (1987-1990): 24-h avg RR 1.042 (1.005, 1.080) lag 0-2 1-h max RR 1.018 (0.988, 1.048) lag 0-2 Asthma (1987-1992): 24-h avg RR 1.070 (1.004, 1.141) lag 2 1-h max RR 1.047 (0.998, 1.098) lag 2 COPD: 24-h avg RR 1.099 (1.023, 1.180) lag 0 1-h max RR 1.051 (1.025, 1.077) lag 0

Study	Methods	Pollutant Data	Findings
de Diego Damiá et al. (1999) Valencia, Spain Period of Study: 3/1994-3/1995	ED visits Outcome(s) (ICD 9): Asthma (493) Age groups analyzed: > 12 N: 515 # of Hospitals: 1 Statistical analyses: Stepwise regression and ANOVA; Linear regression Covariates: Season and temperature Statistical package: SPS	24-h avg SO_2 (μg/m^3) Winter Mean: 56. Range: 30, 86 Spring Mean: 47. Summer Mean: 40. Autumn Mean: 50. # of monitors: 1 Copollutants: BS (r = 0.54)	The SO_2 concentration was averaged for each season and quartiles of concentration determined. Asthma visits that occurred in each season were examined. There were no significant associations with asthma ER visits with any season or with any quartile of SO_2 exposure. Mean number of asthma-related ED visits based on quartile of SO_2 All yr: < 41 μg/m^3: 8.6 41-50 μg/m^3: 9.1 51-56 μg/m^3: 11.6 >56 μg/m^3: 11.9
Fusco* et al. (2001) Rome, Italy Period of Study: 1/1995-10/1997	Hospital Admissions Outcomes (ICD 9 codes): All Respiratory (460-519, excluding 470-478); Acute respiratory infections including pneumonia (460-466, 480-486), COPD (490-492, 494-496), asthma (493) Age groups analyzed: All ages, 0-14 Study design: Time-series Statistical analyses: Poisson regression with GAM Covariates: Influenza epidemics, day of study, temperature, humidity, day of wk, holidays Statistical package: S-Plus 4 Lag: 0, 1, 2, 3, 4	24-h avg: 9.1 (5.8) μg/m^3 25th: 5.1 50th: 7.9 75th: 12.0 # of monitors: 5 Copollutants: O_3 (r = −0.35) CO (r = 0.56) NO_2 (r = 0.33) Particles; r = 0.25	SO_2 did not have an effect on respiratory hospitalizations. Increment: 6.9 μg/m^3 (IQR) Respiratory conditions: All ages: 0.4% (−1.3, 2.2) lag 0. 0.8% (−0.9, 2.4) lag 1. 0.3% (−1.3, 1.8) lag 2 0-14 yrs: −0.7% (−4.0, 2.7) lag 0; −2.0 (−5.2, 1.3) lag 1; −0.8 (−3.8, 2.3) lag 2 Acute respiratory infections: All ages: 0.4% (−2.1, 3.0) lag 0; 1.4% (−1.0, 3.9) lag 1; 1.2% (−1.0, 3.5) lag 2; 0-14 yrs:−0.1% (−3.9, 3.8) lag 0; −2.7% (−6.3, 1.0) lag 1; −1.2% (−4.5, 2.2) lag 2 Asthma: All ages: −1.5% (−6.6, 3.9) lag 0; −1.5% (−6.5, 3.7) lag 1; 2.5% (−2.2, 7.4) lag 2; 0-14 yrs: −2.6 (−10.4, 6.0) lag 0; 4.3% (−3.5, 12.7) lag 1; 5.5% (−1.8, 13.2) lag 2 COPD: All ages: 1.0% (−1.9, 4.0) lag 0; −1.1% (−3.9, 1.8) lag 1; −0.5% (−3.1, 2.1) lag 2
Galan et al. (2003) Madrid, Spain Period of Study: 1995-1998	ED Visits Outcome(s) (ICD9): Asthma (493) Age groups analyzed: All Study design:Time-series N: 4,827 Statistical analyses: Poisson regression, (1) classic APHEA protocol and (2) GAM with stringent criteria Covariates: Trend, yr, season, day of wk, holidays, temperature, humidity, influenza, acute respiratory infections, pollen Statistical package: NR Lag: 0-4 days	24-h Mean: 23.6 μg/m^3 SD: 15.4 10th: 9.2 25th: 12.3 50th: 18.7 75th: 31.3 90th: 43.9 Range: 5, 121.2 # of Stations: 15 Copollutants: PM_{10} (r = 0.581) NO_2 (r = 0.610) O_3 (r = −0.547)	SO_2 registered a predominately winter based pattern, and was positively correlated with $PM_{2.5}$, NO_2. The lag that described the strongest association was 3 days. Multipollutant models were fitted for cold season pollutants. SO_2 was the most affected when $PM_{2.5}$ was included in the model. Parametric estimates using APHEA protocol produced similar results as GAM. The SO_2 association may be due to the concealing effects of other pollutants. $PM_{2.5}$ accounted for most of the observed effects. Increment : 10 μg/m^3 Asthma: RR lag 0 1.018 (0.984, 1.054); RR lag 1 1.005 (0.972, 1.039); RR lag 2 1.002 (0.970, 1.036); RR lag 3 1.029 (0.997, 1.062); RR lag 4 1.025 (0.994, 1.058) Multipollutant model: SO_2/PM_{10} 0.966 (0.925, 1.009)

Study	Methods	Pollutant Data	Findings
Garty et al. (1998) Tel Aviv, Israel Period of Study: 1/1/1993-12/31/1993	ED Visits Outcome(s): Asthma ICD 9 Code(s): NR Age groups analyzed: 1-18 Study design: Descriptive study with correlations N: 1,076 Statistical analyses: Pearson correlation and partial correlation coefficients Covariates: Max and min ambient temperatures, relative humidity and barometric pressure Statistical package: Statistix	24-h mean of SO_2 (estimated from histogram): 27 µg/m^3 Range: 11, 64 Copollutants: NO_X SO_2 O_3	Asthma morbidity was higher in the autumn and winter than the rest of the yr. The number of ER visits is Sep was exceptionally high. The percent of total variance showed positive correlation between asthma ER visits in children and high levels of NO_X, SO_2, and increased barometric pressure. NO_X enhances the effects of SO_2, whereas O_3 had a reverse relation to SO_2. Air borne pollen was not a significant contributor to ER visits. Correlation between SO_2 and ER visits for asthma: All yr: Daily data r = 0.24; Running mean for 7 days r = 0.53 Excluding Sep: Daily data r = 0.31; Running mean for 7 days r = 0.64
Hagen et al. (2000) Drammen, Norway Period of Study: 1994-1997	Hospital Admissions Outcome(s) (ICD 9): All respiratory admissions (460-519) Age groups analyzed: All ages Study design: Time-series Number of hospitals: 1 Statistical analyses: Poisson regression with GAM (adhered to HEI phase 1.B report) Covariates: Time trends, day of wk, holiday, influenza, temperature, humidity Lag: 0,1,2,3 days	SO_2 24-h avg (µg/m^3): 3.64, SD: 2.41 25th: 2.16 50th: 2.92 75th: 4.38 # of Stations: 2 Copollutants: PM_{10} (r = 0.42) NO_2 (r = 0.58) benzene (r = 0.29) NO (r = 0.47) O_3 (r = −0.24) Formaldehyde (r = 0.54) Toluene (r = 0.48)	SO_2 was significantly associated with respiratory hospital admissions. This relationship was robust to the inclusion of $PM_{2.5}$, but attenuated when both $PM_{2.5}$ and benzene were included in the model. Increment: SO_2: 2.22 µg/m^3 (IQR) Single-pollutant model Respiratory disease only: 1.056 (1.013, 1.101) All disease: 0.990 (0.974, 1.007) 2-pollutant model with PM_{10} 1.051 (1.005, 1.099) 3-pollutant model with PM_{10} + Benzene 1.040 (0.993, 1.089)
Hajat et al. (1999) London, United Kingdom Period of Study: 1992-1994	GP visits Outcome(s) (ICD9): Asthma (493); Lower respiratory disease (464, 466, 476, 480-3, 490-2, 485-7, 4994-6, 500, 503-5, 510-5) Age groups analyzed: 0-14; 15-64; 65+; all ages Study design: Time-series analysis Statistical Analysis: Poisson regression, APHEA protocol Covariates: Long-term trends, seasonality, day of wk, temperature, humidity Season: Warm, Apr-Sep; Cool, Oct-Mar; All-yr Dose-response investigated? Yes Statistical package: SAS Lag: 0-3 days, cumulative	All yr 24-h avg: 21.2 µg/m^3, SD: 7.8 10th: 13.0 90th: 31.0 Warm: 24-h avg: 20.5 µg/m^3, SD: 6.5 10th: 13.4 90th: 28.4 Cool: 24-h avg: 22.0 µg/m^3, SD: 9.0 10th: 12.8 90th: 33.3 Copollutants: NO_2 (r = 0.61) BS (r = 0.57) CO (r = 0.51) PM_{10} (r = 0.63) O_3 (r = −0.11)	This study showed weak, but consistent associations between SO_2 and consultations for asthma and other LRD, especially in children. Bubble plot suggests a concentration-response relationship. Increment: 18 µg/m^3 (90th-10th percentile) Asthma: All ages: 3.6% (0.3, 6.9) lag 2; 4.4% (0.9, 7.9) lag 0-2; 0-14 yrs 4.9% (0.1, 9.8) lag 1; 4.4% (−0.7,9.7) lag 0-2 Warm: 9.0% (2.2, 16.2) lag 1; Cool: 2.0% (4.5, 8.9) lag 1 15-64 yrs 3.6% (−0.6, 8.0) lag 2; 3.5% (−1.0, 8.2) lag 0-3 Warm: 2.5% (−3.3, 8.7) lag 2; Cool : 4.5% (−1.4, 10.7) lag 2 65+ yrs 4.5% (−3.5, 13.1) lag 1; 4.8% (−2.9, 13.2) lag 0-1 Warm: 7.5% (−4.0, 20.3) lag 1; Cool: 2.0% (−8.6, 13.9) lag 1 Lower respiratory disease: All ages 1.8% (0.2, 3.4) lag 2; 2.2% (0.4, 4.1) lag 0-2; 0-14 yrs 4.5% (1.4, 7.8) lag 2; 5.7% (1.7, 9.7) lag 0-3; Warm: 2.4% (−2.6, 7.7) lag 2; Cool: 5.8% (1.6, 10.2) lag 2 15-64 yrs 1.5% (−0.7, 3.7) lag 1; 1.6% (−0.9, 4.1) lag 0-3 Warm: −0.5% (−3.8, 2.9) lag 1; Cool: 2.5% (−0.5, 5.5) lag 1 65 + −2.2% (−4.9, 0.6) lag 0; −1.4% (−4.4, 1.7) lag 0-1 Warm: −3.1% (−6.9, 0.9) lag 0; Cool: −1.6 % (−5.3, 2.3) lag 0 2-pollutant model – Asthma: SO_2 alone 4.9% (0.1, 9.8); SO_2/O_3 5.9% (1.1, 10.9); SO_2/NO_2 2.7% (−2.7, 8.4); $SO_2/PM_{2.5}$ 3.4% (−3.0, 10.2) 2-pollutant model-Lower respiratory disease: SO_2 alone 4.5% (1.4, 7.8); SO_2/O_3 4.8% (1.6, 8.1); SO_2/NO_2 3.1% (−0.6, 6.9); $SO_2/PM_{2.5}$ 3.8% (0.4, 7.2)

Study	Methods	Pollutant Data	Findings
Hajat* et al. (2001) London, United Kingdom Period of Study: 1992-1994	GP visits Outcome(s) (ICD9): Allergic Rhinitis (477) Age groups analyzed: 0-14; 15-64; 65+; all ages Study design:Time-series analysis N: 4,214 Statistical Analysis: Poisson regression, GAM Covariates: Long-term trends, seasonality, day of wk, temperature, humidity, variation in practice population, counts for lagged allergic pollen measures, daily number of consultations for influenza Dose-response investigated? Yes Statistical package: S-Plus Lag: 0-6 days, cumulative	24-h avg: 21.2 µg/m^3, SD: 7.8 10th: 13.0 90th: 31.0 Copollutants: NO_2 (r = 0.61) BS (r = 0.57) CO (r = 0.51) PM_{10} (r = 0.63) O_3 (r = −0.11)	The number of allergic rhinitis admissions peaked in Apr and June. After 2-pollutant model analysis, SO_2 still remained highly significant in the presence of other pollutants. For both children and adults exposure-response associations showed that risk levels off at higher SO_2 levels. Increment: 18 µg/m^3 (90th-10th percentile) Single-pollutant model < 1 to 14 yrs: 24.5% (14.6, 35.2) lag 4 24.9% (11.9, 39.4) lag 0-4 15 to 64 yrs: 14.3% (6.2, 23.0) lag 3 15.5% (9.1, 22.3) lag 0-5 >64 yrs-too small for analysis 2-pollutant models < 1 to 14 yrs: SO_2 & O_3: 22.1% (12.0, 33.1) SO_2 & NO_2: 28.5% (15.5, 42.9) SO_2 & PM_{10}: 27.2% (15.3, 40.2 15 to 64 yrs: SO_2 & O_3: 8.5% (3.4, 13.9) SO_2 & NO_2: 8.3% (1.7, 15.3) SO_2 & PM_{10}: 6.7% (0.7, 13.0)
Hajat* et al. (2002) London, United Kingdom Period of Study: 1992-1994	GP visits Outcome(s) (ICD9): Upper respiratory disease, excluding Rhinitis (460-3, 465, 470-5, 478) Age groups analyzed: 0-14; 15-64; 65+; all ages Study design: Time-series analysis Statistical Analysis: Poisson regression, GAM Covariates: Long-term trends, seasonality, day of wk, holidays, temperature, humidity, variation in practice population, counts for lagged allergic pollen measures, daily number of consultations for influenza Season: Warm, Apr-Sep; Cool, Oct-Mar Dose-response investigated? Yes Statistical package: S-Plus Lag: 0,1,2,3 days	All yr: 24-h avg: 21.2 µg/m^3, SD: 7.8 10th: 13.0 90th: 31.0 Warm: 24-h avg: 20.5 µg/m^3, SD: 6.5 10th: 13.4 90th: 28.4 Cool: 24-h avg: 22.0 µg/m^3, SD: 9.0 10th: 12.8 90th: 33.3 # of Stations: 3 Copollutants: NO_2 (r = 0.61) BS (r = 0.57) CO (r = 0.51) PM_{10} (r = 0.63) O_3 (r = −0.11)	Increased consultations for URD were most strongly associated with SO_2 in children. For adults and the elderly the strongest associations were for PM_{10} and NO_2. The most consistent lag in adults and the elderly for development of URD was 2 days (one day after a pollution event). Increment: 18 µg/m^3 (90th-10th percentile) Single-pollutant model: All yr: 0-14 yr: 3.5% (1.4, 5.8) lag 0; 15-64 yrs: 3.5% (0.5, 6.5) lag 1; >65 yrs: 4.6% (0.4, 9.0) lag 2 Warm: 0-14 yrs: 3.2% (−0.5, 7.0) lag 0; 15-64 yrs: 4.6% (1.5, 7.7) lag 1; ≥ 65 yrs: 1.6% (−4.8, 8.5) lag 2 Cool: 0-14 yrs: 5.5% (2.4, 8.7) lag 0; 15-64 yrs: 2.7 (0.0, 5.4) lag 1; >65 yrs: 5.7% (0.4, 11.4) lag 2 2-pollutant models 0-14 yrs: SO_2 & O_3: 1.0% (−2.2, 4.2); SO_2 & NO_2: 4.7% (2.2, 7.4); SO_2 & PM_{10}: 4.6% (2.1, 7.2) For 15-64 yrs: SO_2 & O_3: 3.7% (0.6, 7.0); SO_2 & NO_2: 2.6% (−0.0, 5.2); SO_2 & PM_{10}: 2.4% (−0.1, 5.0) For >65 yrs: SO_2 & O_3: 9.0% (1.7, 16.9); SO_2 & NO_2: 4.3% (−1.2, 10.2); SO_2 & PM_{10}: 3.2% (−1.9, 8.7)

Study	Methods	Pollutant Data	Findings
Llorca et al. (2005) Torrelavega, Spain Period of Study: 1992-1995 Days: 1,461	Hospital Admissions Outcome(s) (ICD 9): All respiratory admissions (460-519) Age groups analyzed: All ages Study design:Time-series Number of hospitals: 1 Statistical analyses: Poisson regression Covariates: Short and Long-term trends Statistical package: Stata Lag: NR	24-h avg SO_2: 13.3 µg/m^3, SD: 16.7 # of Stations: 3 Copollutants: NO_2 (r = 0.588) NO (r = 0.544) TSP (r = −0.40) SH2 (r = 0.957)	Associations between SO_2 and admissions observed in the single-pollutant model disappear in a 5-pollutant model. Only NO_2 was significantly associated with admissions. No relation was described for sulfur compounds including H_2S or SO_2. The concentration of SO_2 changes with temperature changes, which may be responsible for cardiac stress. SO_2 was not significantly associated with cardiac respiratory or cardio-respiratory admissions Increment: 100 µg/m^3 Single-pollutant model All cardio-respiratory admissions: RR 0.98 (0.89, 1.07) Respiratory admissions: 1.04 (0.90, 1.19) 5-pollutant model All cardio-respiratory admissions: RR 0.98 (0.80, 1.21) Respiratory admissions: 0.89 (0.64, 1.24)
Oftedal et al. (2003) Drammen, Norway Period of Study: 11/1994-12/2000	Hospital Admissions Outcomes (ICD 10): All respiratory admissions (J00-J99) Age groups analyzed: All ages Study design: Time-series Statistical analyses: Semi-parametric Poisson regression, GAM with more stringent criteria Covariates: Temperature, humidity, influenza Lag: 2,3 days	Mean: 2.9 µg/m^3, SD: 2.1 IQR: 2.03 µg/m^3 Copollutants: PM_{10} NO_2 O_3 Benzene Formaldehyde Toluene	The study found positive associations between daily number of hospital admissions for acute respiratory diseases and concentrations of SO_2; associations did not change substantially from the first to the second 3-yr period. Increment: 2.03 µg/m^3 (IQR) All respiratory disease 1.042 (1.011, 1.073)
Ponce de Leon et al. (1996) London, England Period of Study: 04/1987-1988; 1991-02/1992	Hospital Admissions Outcome(s) (ICD 9): All respiratory (460-519) Age groups analyzed: 0-14, 15-64, 65+, all ages Study design: Time-series N: 19,901 Statistical analyses: APHEA protocol, Poisson regression GAM Covariates: Long-term trend, season, influenza, day of wk, holiday, temperature, humidity Season: Cool, Oct-Mar; Warm: Apr-Sep Dose-response Investigated?: Yes Statistical package: SAS Lag: 0, 1, 2 days, 0-3 cumulative avg.	SO_2 24-h avg: 32.2 µg/m^3, SD: 12.6 5th: 15 10th: 18 25th: 24 50th: 31 75th: 39 90th: 47 95th: 54 # of stations: 2 Copollutants: NO_2 (r = 0.44) BS (r = 0.44) O_3 (r = −0.067)	Though significant effects were observed with SO_2 in some age groups, they were not consistent or similar in magnitude to those of O_3. Increment: 90th-10th percentile (24-h avg: 29 µg/m^3). All yr: All ages 1.0092 (0.9926, 1.0261) lag 1 0-14 yrs 1.0093 (0.9837, 1.0356) lag1 15-64 yr 1.0223 (0.9942, 1.0511) lag 1 ≥ 65 yr 1.0221 (0.9970, 1.0478) lag 2 Warm season: All ages 1.0111 (0.9864, 1.0364) lag 1 0-14 yrs 1.0468 (1.0066, 1.0885) lag 1 15-64 yr 0.9996 (0.9596, 1.0411) lag 1 >65 yr 1.0124 (0.9772, 1.0489) lag 2 Cool season: All ages 1.0079 (0.9857, 1.0306) lag 1 0-14 yrs 0.9848 (0.9515, 1.0192) lag 1 15-64 yr 1.0389 (1.0010, 1.0783) lag 1 >65 yr 1.0280 (0.9945, 1.0625) lag 2

Study	Methods	Pollutant Data	Findings
Pönkä (1991) Helsinki, Finland Period of Study: 1987-1989	Hospital Admissions Outcome(s) (ICD9): Asthma (493) Age groups analyzed: 0-14; 15-64; ≥ 65 yrs Study design: Time-series N: 4,209 Statistical analyses: Correlations and partial correlations Covariates: Min temperature Statistical package: Lag: 0-1	24-h avg: 19.2 (12.6) µg/m^3 Range: 0.2, 94.6 Number of monitors: 4 Copollutants: NO_2 (r = 0.4516) NO (r = 0.4773) O_3 (r = -0.1778) TSP (r = 0.1919) CO	The frequency of all admissions for asthma was significantly correlated to SO_2. Child asthma admissions were not significantly correlated with SO_2, but were correlated to O_3 and NO. SO_2 was also significantly correlated with elderly admissions. Increased hospitalization correlated with SO_2 was also observed for adults. Hospital admissions were more strongly correlated with SO_2 than other pollutants. ER visits were more strongly correlated with a mixture of pollutants (TSP, SO_2, O_3, and temperature). Multipollutant model co-linear results of SO_2, CO, NO_2, and NO suggest a mixture of pollutants is responsible for asthma admissions. Correlations between hospital admissions (HA) for asthma and pollutants and temperature by ages. 0-14 yrs: HA: −0.01391; Emergency HA: 0.0332 15-64 yrs: HA: 0.1039 p = 0.0006; Emergency HA: 0.1199 p < 0.0001 ≥ 65 yrs: HA: 0.0796 p = 0.0085; Emergency HA: 0.1169 p < 0.0001 Partial correlations between admissions for asthma and SO_2 were standardized for temperature. HA: 0.0770 p = 0.0172; Emergency HA: 0.1050; p = 0.0011
Pönkä and Virtanen (1994) Helsinki, Finland Period of Study: 1987-1989 Days: 1096	Hospital Admissions Outcome(s) (ICD 9): Chronic bronchitis and emphysema (493) Age groups analyzed: < 65, ≥ 65 Study design: Time-series Statistical analyses: Poisson regression Covariates: Season, day of wk, yr, influenza, humidity, temperature Season: Summer (Jun-Aug), Autumn (Sep-Nov), Winter (Dec-Feb), Spring (Mar-May) Lag: 0-7 days	24-h avg: 19 µg/m^3 SD: 12.6; Range: 0.2, 95 # of stations: 2 Copollutants: NO_2 O_3 TSP	SO_2 was significantly associated with increased admissions for chronic bronchitis and emphysema for patients < 65 yrs of age with a lag of 0 and 3 days. In the steps leading to regression analysis no association was observed between SO_2 levels and the ≥65 population. Multipollutant models were only used to examine NO_2 and SO_2. SO_2 had no significant association with morbidity caused by chronic bronchitis and emphysema in the ≥ 65 yr old population. Increment: NR Chronic bronchitis and emphysema: < 65 yrs: RR 1.31 (1.01, 1.70) lag 0; RR 0.96 (0.73, 1.27) lag 1; RR 0.78 (0.59, 1.03) lag 2; RR 1.39 (1.05, 1.86) lag 3; RR 0.89 (0.68, 1.16) lag 4; RR 1.28 (0.97, 1.70) lag 5; RR 0.91 (0.69, 1.20) lag 6; RR 1.09 (0.84, 1.40) lag 7 65+ yrs: NR
Pönkä and Virtanen (1996) Helsinki, Finland Period of Study: 1987-1989	Hospital Admissions Outcome(s) (ICD9): Asthma (493) Age groups analyzed: 0-14, 15-64, 65+ Study design: Time-series Statistical analyses: Covariates: Long-term trend, season, epidemics, day of wk, holidays, temperature, relative humidity Statistical package: Lag: 0-2	24-h avg (µg/m^3): Winter: 26 Spring: 22 Summer: 13 Fall: 15 Copollutants: NO_2 O_3 TSP	Significant associations were observed between daily SO_2 concentrations and daily counts of hospitalizations among 15- to 64-yr-old patients and among those over 64 yrs old, but not among children. These effects were observed when mean daily SO_2 values were lower than the max value recommended by WHO (125 µg/m^3). Parameter estimates (PE) and standard error (SE) for a 1-unit increase: Asthma: 15-64 yrs: PE 0.2176 (0.1081) p = 0.44 lag 2; PE 0.3086 (0.1545) p = 0.046 lag 0-3 Asthma: 65+ yrs: PE 0.2412 (0.0956) p = 0.012 lag 2

Study	Methods	Pollutant Data	Findings
Prescott et al. (1998) Edinburgh, United Kingdom Period of Study: 10/92-6/95	Hospital Admissions Outcome(s) (ICD 9): Pneumonia (480-7), COPD + Asthma (490-496) Age groups analyzed: < 65, 65+ Study design: Time-series Statistical analyses: Poisson log linear regression Covariates: Trend, seasonal and weekly variation, temperature, wind speed, day of wk Lag: 0,1, or 3 day rolling avg	SO_2: 14.5 (9.0) ppb Min: 0 ppb Max: 153 ppb # of Stations: 1 Copollutants: CO PM_{10} NO_2 O_3 BS	No effect of SO_2 on hospitalizations observed in either age category. Increment: 10 ppb Respiratory admissions: >65 yrs −2.5 (−11.0, 6.9) lag 0-2; < 65 yrs 0.0 (−8.3, 9.1) lag 0-2
Rossi et al. (1993) Oulu, Finland Period of Study: 10/1/1985-9/30/1986	ED Visits Outcome(s) (ICD 9): Asthma (493) Age groups analyzed: 15-85 Study design: Time-series N: 232 Statistical analyses: Pearson's and partial correlation coefficients and multiple regression with stepwise discriminate analysis Covariates: Temperature, humidity Statistical package: BMDP software Lag: 0,1,2,3	24-h avg: 10.0 µg/m^3 Range: 0, 56 1-h max: 31.0 µg/m^3 Range: 1, 24 # of monitoring stations: 4 Copollutants: NO_2 (r = 0.48) TSP (r = 0.31) H_2S	Same day ER visits were correlated to daily SO_2 levels, but the significance was lost with longer lag periods. When asthma visits were analyzed, SO_2 was positively and significantly correlated with asthma visits in the same wk and the wk after. After regression analyses, SO_2 became insignificant. Pearson correlation coefficients ED asthma visits and same day SO_2: r = 0.13 p < 0.01 lag 0 Weekly ED asthma visits and same wk SO_2: r = 0.28 p < 0.05 Weekly ED asthma visits and next wk SO_2: 0.30 p < 0.05 Multipollutant (NO_2; TSP; H_2S) Regression coefficient: All yr: β = 0.037, p = 0.535 Winter: β = −0.024, p = 0.710 Summer: β = −0.003, p = 0.991

Study	Methods	Pollutant Data	Findings
Schouten et al. (1996) Multicity, The Netherlands (Amsterdam, Rotterdam) Period of Study: 04/01/77-09/30/89	Hospital Admissions Outcome(s) (ICD 9): All respiratory (460-519), COPD (490-2, 494, 496), Asthma (493) Age groups analyzed: 15-64, 65+, all ages Study design: Time-series Statistical analyses: APHEA protocol, Poisson regression Covariates: Long-term trend, season, influenza, day of wk, holiday, temperature, humidity Season: Cool, Nov-Apr; Warm: May-Oct Lag: 0,1,2 days; and cumulative 0-1 and 0-3 day lags	24-h avg SO_2 Amsterdam Mean/Med: 28/21 µg/m^3 Rotterdam Mean: 40/32 µg/m^3 Daily 1-h max Amsterdam Mean/Med: 65/50 µg/m^3 Rotterdam Mean/Med: 99/82 µg/m^3 # of stations: 1 per city Copollutants: NO_2 BS O_3	The relationship between short-term air pollution and hospital admissions was not always consistent at low levels of exposure. One statistically significant association between hospital admissions and asthma (all ages) occurred in Amsterdam after a cumulative lag of 1-3 days in the summer. Higher SO_2 levels were reported for the winter; therefore, this association was not a concentration response. In Rotterdam neither 1 day nor cumulative lags in the summer or winter increased asthma admissions to statistical significance. Rotterdam had much higher mean SO_2 concentrations. There were no significant associations to hospital admissions when higher pollution levels were prevalent. The analysis of all respiratory hospital admissions for all ages in the entire country (Netherlands) produced a statistically significant association for both 1-h and 24-h periods (100 µg/m^3). Increment: 100 µg/m^3 increment. All respiratory, Amsterdam 24-h avg: 15-64 yrs: RR 0.944 (0.864, 1.032) lag 2; RR 0.915 (0.809, 1.035) lag 0-3; >65 yrs: RR 1.046 (0.965, 1.134) lag 2; RR 1.008 (0.899, 1.131) lag 0-3 1-h max: 15-64 yrs: RR 0.989 (0.952, 1.028) lag 2; RR 0.977 (0.927, 1.030) lag 0-3; >65 yrs: RR 1.022 (0.985, 1.060) lag 2; RR 1.010 (0.955, 1.068) lag 0-3; RR 0.941 (0.863, 1.026) lag 0-3 COPD, Amsterdam 24-h avg–all ages: RR 0.907 (0.814, 1.011) lag 0; RR 0.948 (0.838, 1.072) lag 0-1 1-h max–all ages: RR 0.978 (0.933, 1.026) lag 0; RR 0.995 (0.940, 1.053) lag 0-1 Asthma, Amsterdam 24-h avg–all ages: RR 0.802 (0.696, 0.924) lag 1; RR 0.792 (0.654, 0.958) lag 0-3 1-h max–all ages: RR 0.995 (0.942, 1.051) lag 0 All respiratory, Rotterdam 24-h avg: 15-64 yrs: RR 0.941 (0.855, 1.036) lag 1; RR 0.895 (0.787, 1.019) lag 0-2; >65 yrs (1977-1981): RR 1.027 (0.904, 1.165) lag 2; RR 1.011 (0.834, 1.227) lag 0-3; >65 yrs (1982-1984): RR 1.087 (0.890, 1.328) lag 0; RR 1.258 (0.926, 1.710) lag 0-3; >65 yrs (1985-1989): RR 1.045 (0.908, 1.204) lag 0; RR 0.968 (0.787, 1.190) lag 0-3 1-h max: 15-64 yrs: RR 0.989(0.953, 1025) lag 1; RR 0.965 (0.915, 1.018) lag 0-2; >65 yrs (1977-1981): RR 0.892 (0.842, 0.945) lag 0; RR 0.987 (0.907, 1.074) lag 0-3; >65 yrs (1982-1984): RR 1.005 (0.933, 1.081) lag 0; RR 1.062 (0.938, 1.202) lag 0-3; >65 yrs (1985-1989): RR 1.010 (0.955, 1.068) lag 0; RR 1.064 (0.992, 1.141) lag 0-1 COPD, Rotterdam 24-h avg–all ages: RR 0.963 (0.874, 1.059) lag 2; RR 1.019 (0.887, 1.172) lag 0-3 1-h max–all ages: RR 0.991 (0.955, 1.029) lag 2; RR 1.013 (0.953, 1.076) lag 0-3

Study	Methods	Pollutant Data	Findings
Spix et al. (1998) Multicity (Amsterdam, London, Milan, Paris, Rotterdam), Europe Period of Study: 1977 and 1991	Hospital Admissions Outcome(s) (ICD9): All respiratory (460-519); Asthma (493) Age groups analyzed: 15-64, 65+ Study design: Time-series Statistical analyses: Poisson regression following APHEA protocol. Pooled meta-analysis adjusted for heterogeneity Covariates: trend, seasonality, day of wk, holiday, temperature, humidity, unusual events (strikes, etc.) Lag: 1 to 3 days	SO_2 daily avg ($\mu g/m^3$) London: 29 Amsterdam: 21 Rotterdam: 25 Paris: 23 Milan: 66 Copollutants: NO_2 O_3 BS TSP	Daily counts of adult respiratory admissions were not consistently associated with daily mean levels of SO_2. Heterogeneity between cities was likely due to the number of stations or temperature. Only hospital admissions for ≥ 65 yr olds were significantly associated with SO_2 in the warm season. Increment: 50 $\mu g/m^3$ All cities, yr round 15-64 yrs: RR 1.009 (0.992, 1.025) Warm RR 1.01 (0.98, 1.04) Cold RR 1.01 (0.97, 1.07) ≥ 65 yrs RR 1.02 (1.005, 1.046) Warm RR 1.06 (1.01, 1.11) Cold RR 1.02 (0.99, 1.04) APHEA protocol pooled result from ≥65 yrs old from Europe All respiratory RR 1.02 (1.00, 1.05)
Sunyer et al. (1997) Multicity, Europe (Barcelona, Helsinki, Paris, London) Period of Study: 1986-1992	Hospital admissions/ED Visits Outcome(s) (ICD 9): Asthma (493) Age groups analyzed: < 15, 15-64 Study design: Time-series Statistical analyses: APHEA protocol, Poisson regression, GEE; meta-analysis Covariates: Humidity, temperature, influenza, soybean, Long-term trend, season, day of wk Season: Cool, Oct-Mar; Warm: Apr-Sep Lag: 0,1,2,3 and cumulative 1-3	24-h median (range) ($\mu g/m^3$) Barcelona: 41 (2, 160) Helsinki: 16 (3, 95) London: 31 (9, 100) Paris: 23 (1, 219) # of stations: Barcelona: 3 London: 4 Paris: 4 Helsinki: 8 Copollutants: NO_2 BS O_3	SO_2 alone or as part of a mixture was a factor that exacerbated asthma admissions. In 2-pollutant models with SO_2 and BS, the association of BS with SO_2 was attenuated for < 15 yr olds, compared to single-pollutant model associations. In addition, the association of NO_2 was also attenuated by the inclusion of SO_2. Increment: 50 $\mu g/m^3$ of 24-h avg for all cities combined. Asthma: 15-64 yrs: 0.997 (0.961, 1.034) lag 2 1.003 (0.959, 1.050) lag 0-3, cum < 15 yrs: 1.075 (1.026, 1.126) lag 1 1.061 (0.996, 1.131) lag 2-3, cum 2-pollutant models SO_2/BS: < 15 yrs 1.092 (1.031, 1.156) lag 0-1 SO_2/NO_2 < 15 yrs 1.075 (1.019, 1.135)
Sunyer* et al. (2003) Multicity study (Birmingham (B), London (L), Milan (M), Netherlands (N), Paris (P), Rome (R) and Stockholm (S), Europe Period of Study: 1992 and 1997	Hospital admissions/ED Visits Outcome(s) (ICD 9): Asthma (493); COPD and Asthma (490-496); all respiratory (460-519) Age groups analyzed: All, 0-14 yrs; 16-64 yrs; ≥ 65 yrs Study design:Time-series Poisson regression with GAM following APHEA 2 protocol Covariates: temperature, humidity, Long-term trend, season Lag: 0, 1	SO_2 24-h avg and SD ($\mu g/m^3$) B 24.3 (12.7) L 23.6 (23.7) M 32.5 (37.5) N 8.5 (7.7) P 17.7 (12.5) R 9.8 (9.9) S 6.8 (6.2) Copollutants: PM_{10} (r = 0.64) CO (r = 0.53)	The magnitude of association with asthma across the seven cities was comparable to earlier studies of London, Helsinki and Paris. Exposure factors may be important. Children may spend greater time outdoors compared with adults. Pneumonia requires chronic exposure to produce inflammatory response and infection, whereas asthma is an acute response. Increment: 10 $\mu g/m^3$ Asthma : 0-14 yrs: 1.3% (0.4, 2.2) ; 15-64 yrs : 0.0% (−0.9, 1.00) COPD and Asthma: ≥ 65 yrs : 0.6% (0.0, 1.2) All Respiratory: ≥ 65 yrs 0.5% (0.1, 0.9) Asthma: 0-14 yrs: SO_2 + PM_{10}: −3.7% (p > 0.1) ; SO_2 + CO: −0.7% (p > 0.1)

Study	Methods	Pollutant Data	Findings
Sunyer et al. (1991) Barcelona, Spain Period of Study: 1985-1986	ED Visits Outcome(s) COPD (ICD 9): 490-496 Age groups analyzed: > 14 Study design: Time-series # of Hospitals: 4 Statistical analyses: multivariate linear regression Covariates: Meteorology, season, day of wk Statistical package: Lag: 0 to 2 days	24-h avg (SD): 56.5 (22.5) µg/m^3 98th: 114.3 Range: 17, 160 1-h max (SD): 141.9 (98.8) µg/m^3 98th: 461.3 Range: 14,720 Number of monitors: 17 Copollutants: BS, CO, NO_2, O_3	An incremental change of 25 µg/m^3 in SO_2 was correlated with an adjusted increase of 0.5 daily visits due to COPD. SO_2 and ER visits were more strongly correlated in warm weather. Even at 24-h avg levels less than 100 µg/m^3, effects of SO_2 were statistically significant for COPD admissions. Change in 24-h avg SO_2 daily ER µg/m^3 admissions P-value 150 0.55 < 0.01 100 0.7 < 0.01 72 0.7 0.04 52 0.41 > 0.05 39 −1.27 > 0.05 0.5 excess daily admissions per 25 µg/m^3 increment of SO_2.
Sunyer et al. (1993) Barcelona, Spain Period of Study: 1985-1989	ED Visits Outcome(s) (ICD 9): COPD (490-492; 494-496) Study design: Time-series Statistical analyses: Autoregressive linear regression Statistical package: Lag: 1,2	SO_2, 24-h Winter Tertiles (µg/m^3) < 40.4 40.4, 61 >61 Winter Tertiles (µg/m^3) < 28.1 28.1, 46.1 >46.1 Copollutants: BS	SO_2 concentrations were associated with the number of COPD ER admissions in the winter and summer. An increase of 25 µg/m^3 in SO_2 produced an adjusted change of ~6% and 9%, respectively, in the number of COPD emergencies in the winter and summer. Controlling for particulate matter resulted in a loss of significance. Co linearity of BS with SO_2 was observed. Effects were expressed as adjusted changes in daily COPD ER admissions based on an increment of 25 µg/m^3. Winter: 6% Summer: 9% Mean ER admissions for COPD (winter) were 15.8 (range 3, 34) and 8.3 (range 1, 24) in the summer.
Tenias et al. (1998) Valencia, Spain Period of Study: 1993-1995 Seasons: Cold: Nov-Apr Warm: May-Oct	ED Visits Outcome(s): Asthma ICD 9 Code(s): NR Age groups analyzed: > 14 Study design: Time-series N: 734 Statistical analyses: Poisson regression, APHEA protocol Covariates: seasonality, temperature, humidity, long-term trend, day of wk, holidays, influenza Season: Cold: Nov-Apr; Warm: May-Oct Dose-response investigated: Yes Statistical package: NR Lag: 0-3 days	24 h avg: 26.6 µg/m^3 25th: 17.9 50th: 26.2 75th: 34.3 95th: 42.6 Cold: 31.7 Warm: 21.7 1-h max: 56.3 µg/m^3 25th: 36.3 50th: 52.2 75th: 72.2 95th: 95.2 Cold: 64.6 Warm: 48.2 # of Stations: 2 Copollutants: 24 h avg: O_3 (r = −0.431) NO_2 (24 h av) (r = 0.265) NO_2 (1-h) (r = 0.199) 1-h: O_3 (r = −0.304) NO_2 (24 h avg) (r = 0.261) NO_2 (1-h) (r = 0.201)	SO_2 showed the strongest correlation to asthma admissions during the warm mos. Multipollutant models showed that O_3 and BS had a small effect on the association between SO_2 and asthma ER visits while NO_2 greatly depressed these effects. It is likely that NO_2 was the dominant pollutant for respiratory outcomes. SO_2 was the “most vulnerable pollutant” to the presence of other pollutants. Increment: 10 µg/m^3 SO_2 24-h avg: All yr 1.050 (0.973, 1.133) lag 0 Cold 1.032 (0.937, 1.138) lag 0 Warm 1.070 (0.936, 1.224) lag 0 SO_2 1-h max: All yr 1.027 (0.998, 1.057) lag 0 Cold 1.018 (0.980, 1.057) lag 0 Warm 1.038 (0.990, 1.090) lag 0

Study	Methods	Pollutant Data	Findings
Tenias et al. (2002) Valencia, Spain Period of Study: 1994-1995	ED Visits Outcome(s): COPD ICD 9 Code(s): NR Age groups analyzed: > 14 Study design: Time-series N: 1,298 # of Hospitals: 1 Statistical analyses: Poisson regression, APHEA protocol; basal models and GAM Covariates: Seasonality, annual cycles, temperature, humidity, day of wk, feast days Season: Cold, Nov-Apr; Warm, May-Oct Dose-response investigated: Yes Statistical package: NR Lag: 0-3 days	24 h avg: 26.6 µg/m^3 5th: 8.2 50th: 26.2 75th: 34.3 95th: 42.6 Cold: 31.7 Warm: 21.7 1-h max: 56.3 µg/m^3 5th: 16.8 50th: 52.2 75th: 72.2 95th: 95.2 Cold: 64.6 Warm: 48.2 Copollutants: BS (r = 0.687) NO_2 (r = 0.194) CO (r = 0.734) O_3 (r = −0.431)	SO_2 did not show any significant association with COPD ER visits for all seasons analyzed. SO_2 did not affect O_3 or CO association to ER admission for COPD when assessed together in the Multipollutant model. Possibility of a linear relationship between pollution and risk of emergency cases could not be ruled out. Increment: 10 µg/m^3. 24-h avg SO_2: All yr RR 0.971 (0.914, 1.031) lag 0 Cold, 24-h avg: RR 0.970 (0.905, 1.038) lag 0 Warm, 24-h avg: RR 0.982 (0.885, 1.090) lag 0 1-h max SO_2: All yr RR 0.981 (0.958, 1.027) lag 3 Cold, 24-h avg: RR 0.972 (0.945, 1.000) lag 3 Warm, 24-h avg: RR 1.003 (0.979, 1.056) lag 3
Thompson et al. (2001) Belfast, Northern Ireland Period of Study: 1993-1995	Hospital admissions/ED Visits Outcome(s): Asthma ICD 9 Code(s): NR Age groups analyzed: Children Study design: Time-series N: 1,044 Statistical analyses: Followed APHEA protocol, Poisson regression analysis Covariates: Season, long-term trend, temperature, day of wk, holiday Season: Warm (May-Oct); Cold (Nov-Apr) Statistical package: Stata Lag: 0-3	Warm Season SO_2 (ppb): Mean: 12.60; SD: 10.60; IQR: 6.0, 16.0 Cold Season SO_2 (ppb): Mean: 20.40; SD: 17.90; IQR: 11.0, 24.0 Copollutants: PM_{10} (r = 0.66) NO_2 (r = 0.82) NO_X (r = 0.83) NO (r = 0.76) O_3 (r = −0.58) CO (r = 0.64) Benzene (r = 0.80)	This study found weak, positive associations for SO_2 and adverse respiratory outcomes in asthmatic children. SO_2 Increment: Per doubling (ppb) Lag 0 RR 1.07 (1.03, 1.11) Lag 0-1 RR 1.09 (1.04, 1.15) Lag 0-2 RR 1.08 (1.02, 1.15) Lag 0-3 RR 1.08 (1.01, 1.15) Warm only Lag 0-1 RR 1.11 (1.04, 1.19) Cold only Lag 0-1 RR 1.07 (1.00, 1.15) Adjusted for Benzene Lag 0-1 RR 0.99 (0.90, 1.09)
Tobías et al. (1999) Barcelona, Spain Period of Study: 1986-1989	ED Visits Outcome(s): Asthma ICD9: NR Age groups analyzed: > 14 Study design: Time-series Statistical analyses: Poisson regression, followed APHEA protocol Covariates: Temperature, humidity, long-term trend, season, day of wk Statistical package: NR Lag: NR	24-h avg SO_2 µg/m^3 Non-epidemic Days: 85.8 (62.4) Epidemic Days: 116.3 (79.3) Copollutants: BS NO_2 O_3	The study failed to find a significant association between SO_2 and asthma ED visits. β x 104 (SE x 104) using Std Poisson Without modeling asthma epidemics: 3.99 (4.14) Modeling epidemics with 1 dummy variable: 1.64 (2.76) Modeling epidemics with 6 dummy variables: 1.53 (2.75) Modeling each epidemic with dummy variable: 2.20 (2.65) β x 104 (SE x 104) using Autoregressive Poisson Without modeling asthma epidemics: 6.99 (14.37) Modeling epidemics with 1 dummy variable: 1.68 (2.77) Modeling epidemics with 6 dummy variables: 1.72 (2.75) Modeling each epidemic with dummy variable: 2.85 (2.89)

Study	Methods	Pollutant Data	Findings
Vigotti et al. (1996) Milan, Italy Period of Study: 1980-1989	Hospital Admissions Outcomes (ICD 9 codes): Respiratory disease (460-519). Age groups analyzed: 15-64 yrs and >64 yrs Study design: Time-series N: >73,000 Statistical analyses: APHEA protocol Covariates: Season: Cold season (Oct. to Mar) and Warm season (Apr to Sep) Lag: 0, cumulative 4 day (0-3)	24-h avg: 117.7 μg/m^3 Range: 3.0, 827.8 5th: 15.0 25th: 34.0 50th: 65.5 75th: 162.5 95th: 376.3 Winter:248.6 Range: 30.6, 827.8 5th: 78.8 25th: 138.5 50th: 216.0 75th: 327.8 95th: 527.0 Summer:30.5 Range: 3.0, 113.8 5th: 9.1 25th: 18.5 50th: 27.8 75th: 39.2 95th: 62.7 # of monitors: 4; r = 0.89, 0.91 Copollutants: TSP (r = 0.63)	The effect of single day or cumulative day exposure to SO_2 was more pronounced during the cool mos. Interaction between seasons was not significant. SO_2 did not interact with TSP. No differences were noted between age groups. There were increased, but not significant (borderline), risks for increased hospital admissions based on an increment change in SO_2 of 125 μg/m^3 in the winter. Increment: 100 μg/m^3 All respiratory 15-64 yrs: All yr round: RR 1.05 (1.00, 1.10) lag 0 Warm: RR 1.04 (0.98, 1.11) lag 0 Cool: RR 1.06 (1.00, 1.13) lag 0 >64 yrs: All yr: RR 1.04 (1.00, 1.09) lag 0 Warm: RR 1.02 (0.96, 1.08) lag 0 Cool: RR 1.05 (1.00, 1.11) lag 0
Walters et al. (1994) Birmingham, United Kingdom Period of Study: 1988-1990	Hospital Admissions Outcome(s) (ICD9): Asthma (493) and acute respiratory conditions (466, 480-486, 490-496) Study design:Time-series Statistical analyses: Least squares regression Covariates: Temperature, pressure, humidity Lag: 3 day moving avg.	SO_2 24-h avg (μg/m^3) All yr: 39.06 Max: 126.3 Spring: 42.9 Summer: 37.8 Autumn: 40.9 Winter: 34.2 Copollutants: BS	In 2-pollutant models BS remained significant but SO_2 was no longer associated significantly with admission. A 100 μg/m^3 increment in SO_2 might result in four (0-7) more asthma admissions and 15.5 (6-25) move respiratory admissions/day. Spring and autumn did not show associations with admissions for asthma or respiratory. Increment of 100 μg/m^3 Asthma: Summer: 1.4% (−10, 39) lag 0 Winter: 2.7% (−0.8, 6.1) lag 0 All respiratory: Summer: 5.9% (1.1, 10.6) lag 0; ($p < 0.02$) Winter: 18% (8.8, 26.8) lag 0; ($p < 0.0002$)

Study	Methods	Pollutant Data	Findings
AUSTRALIA/NEW ZEALAND			
Barnett et al. (2005) Multicity, Australia/New Zealand; (Auckland, Brisbane, Canberra, Christchurch, Melbourne, Perth, Sydney) Period of Study: Jan 1998-Dec 2001	Hospital Admissions Outcomes (ICD 9/ICD 10): All respiratory (460-519/J00-J99 excluding J95.4-J95.9, RO9.1, RO9.8), asthma (493/J45, J46, J44.8), COPD (490-492, 494-496/J40-J44, J47, J67), pneumonia with bronchitis (466, 480-486/J12-17, J18.0 j18.1 J18.8 J18.9 J20 J21) Age groups analyzed: <1, 1-4, 5-14 Study design: Case-crossover Statistical analyses: Conditional logistic regression, random effects meta-analysis Covariates: Temperature, current-previous day temperature, relative humidity, pressure, extremes of hot and cold, day of wk, holiday, day after holiday Season: Cool, May-Oct; Warm, Nov-Apr Statistical package: SAS Lag: 0-1 days	24-h avg (ppb) (range): Auckland: 4.3 (0, 24.3) Brisbane: 1.8 (0, 8.2) Canberra: NA Christchurch: 2.8 (0, 11.9) Melbourne: NA Perth: NA Sydney: 0.9 (0, 3.9) Daily 1-h max (range): Auckland: NA Brisbane: 7.6 (0, 46.5) Canberra: NA Christchurch: 10.1 (0.1, 42.1) Melbourne: NA Perth: NA Sydney: 3.7 (0.1, 20.2)	Increased hospital admissions were significantly associated with SO_2 for acute bronchitis, pneumonia, and respiratory diseases. In multipollutant models the impacts of particulate matter and NO_2 were isolated. There were seasonal impacts on pneumonia and acute bronchitis admissions in the 1- to 4-yr-old age group for SO_2. Increment: 5.4 ppb (1-h max IQR) Pneumonia and acute bronchitis: 0 yrs: No analysis 1-4 yrs: 6.9% (2.3, 11.7) lag 0-1 Respiratory: 0 yrs: 3.2% (0.3, 6.3) lag 0-1 1-4 yrs: 2.7% (0.6, 4.8) lag 0-1 5-14 yrs: No analysis Asthma: 0 yrs: No analysis (poor diagnosis) 1-4 yrs: No analysis 5-14 yrs: No analysis
Lam (2007) Australia (New South Wales; Sydney) Period of Study: 2001-2002	ED Visits Outcome(s): Fever, gastroenteritis, asthma/other respiratory problems Study design: Time-series Statistical Analysis: Auto Regression Integrated Moving Average (ARIMA) statistical modeling Statistical package: SPSS Age groups analyzed: < 6 Covariates: NR Lag(s): NR	24-h avg (ppm): 0.35 (0.19) Range: 0.10, 0.90 1-h max (ppm): 0.38 (0.20) Range: 0.10, 1.80 Copollutants: PM_{10} $PM_{2.5}$ NO_2 O_3	Bivariate correlations resulted in ARIMA models for fever and NO_2 max, gastroenteritis and O_3 avg and NO_2 max; and respiratory problems and O_3 max. Neither NO_2 nor O_3 was significantly associated with any of the childhood illnesses analyzed. SO_2 was not significantly correlated with fever, gastroenteritis, or respiratory problems; therefore, SO_2 was not included in the ARIMA models.

Study	Methods	Pollutant Data	Findings
Petroeschevsky et al. (2001) Brisbane, Australia Period of Study: 1987-1994 Days: 2922	Hospital Admissions Outcome(s) (ICD 9): All respiratory (460-519); Asthma (493) Age groups analyzed: 0-4, 5-14, 15-64, 65+, all ages Study design: Time-series N: 33,710 (respiratory), 13,246 (asthma) Statistical analyses: APHEA protocol, Poisson regression, GEE Covariates: Temperature, humidity, season, infectious disease, day of wk, holiday Season: Summer, Autumn, Winter, Spring, All yr Dose-response investigated? Yes Statistical package: SAS Lag: Single: 1,2,3 day Cumulative: 0-2, 0-4	Mean: 24-h avg: Overall: 4.1 ppb Summer: 3.9 ppb Autumn: 4.2 ppb Winter: 4.8 ppb Spring: 3.7 ppb Mean: 1-h max Overall: 9.2 ppb Summer: 7.8 ppb Autumn: 9.3 ppb Winter: 11.3 ppb Spring: 8.4 ppb # of stations: 3 Copollutants: BSP O_3 NO_2	SO_2 was highly correlated with max daily ER admissions for respiratory conditions. The highest association was observed in the winter followed by autumn, spring, and summer. For asthma, the highest association was observed in the winter and autumn. No statistically significant contributions for respiratory admissions were reported for the age group 5-14 yr olds for any pollutant. Increment: 0 ppb Respiratory: 0-4 yrs 24-h avg 1.224 (1.087, 1.377) lag 0-4 5-14 yrs 1-h max 1.049 (0.986, 1.116) lag 0-4 15-64 yrs 24-h avg 1.033 (0.895, 1.118) lag 1 65+ yrs 24-h avg 1.121 (1.019, 1.234) lag 0 All ages 24-h avg 1.080 (1.030, 1.131) lag 1 Asthma: 0-14 yrs 24-h avg 1.080 (0.971, 1.201) lag 0 15-64 yrs 1-h max 0.941 (0.900, 0.984) lag 0 All ages 24-h avg 0.941 (0.876, 1.011) lag 2
LATIN AMERICA			
Braga* et al. (1999) São Paulo, Brazil Period of Study: 10/1992-10/1993	Hospital Admissions Outcome(s) (ICD9): All respiratory (466, 480-486, 491-492, 496) Age groups analyzed: <13 yrs Study design:Time-series N: 68,918 # of Hospitals: 112 Statistical analyses: Multiple linear regression models (least squares). Also used Poisson regression techniques. GLM and GAM using LOESS for smoothing. Covariates: Season, temperature, humidity, day of wk, Statistical package: SPSS, S-Plus Lag: 1,2,3,4,5,6,7 moving avgs	24-h avg 22.40 (9.90) µg/m^3 Min: 6.4 Max: 69.6 # of monitors: 13 Copollutants: PM_{10} (r = 0.73) CO (r = 0.62) NO_2 (r = 0.53) O_3	SO_2 did not show a correlation with respiratory hospital admissions with any lag structure. Increment: 22.4 µg/m^3 0.12 (−0.04, 0.28) lag 0 0.18 (−0.00, 0.37) lag 0-1 0.19 (−0.01, 0.39) lag 0-2 0.18 (−0.04, 0.40) lag 0-3 0.18 (−0.05, 0.42) lag 0-4 0.12 (−0.13, 0.36) lag 0-5 0.08 (−0.18, 0.35) lag 0-6

Study	Methods	Pollutant Data	Findings
Braga* et al. (2001) São Paulo, Brazil Period of Study: 1/93-11/97	Hospital Admissions Outcome(s) (ICD 9): All respiratory admissions (460-519) Age groups analyzed: 0-19, ≤ 2, 3-5, 6-13, 14-19 Study design: Time-series Statistical analyses: Poisson regression with GAM Covariates: Long-term trend, season, temperature, relative humidity, day of wk, holiday Statistical package: S-Plus 4.5 Lag: 0-6 moving avg	SO_2 Mean: 21.4 μg/m³; SD: 11.2 IQR: 14.4 μg/m³ Range: 1.6, 76.1 # of stations: 5-6 Copollutants: PM_{10} (r = 0.61) NO_2 (r = 0.54) CO (r = 0.47) O_3 (r = 0.17)	Children < 2 yrs were most susceptible to the effect of each pollutant. Pneumonia and bronchopneumonia were the main cause of hospital admissions (71%) in the < 2-yr-old group. Bronchitis/asthma were more important for the intermediate age groups. However, in all age groups the largest increase in admissions was caused by chronic disease in tonsils and adenoids. Multipollutant models rendered all pollutants except PM_{10} and SO_2 from significance. The effect of PM_{10} stayed relatively unchanged while SO_2 was reduced; however, it remained significant. Increment: μg/m³ (IQR) All respiratory admissions: < 2 yrs: 5.9% (4.5, 7.4); 3-5 yrs: 1.6% (−1.3, 4.4); 6-13 yrs: 0.6% (−2.2, 3.5); 14-19 yrs: 1.3% (−3.2, 5.8); All ages 4.5% (3.3, 5.8)
Farhat* et al. (2005) São Paulo, Brazil Period of Study: Aug 1996-Aug 1997	Hospital Admissions/ED Visits Outcome(s) (ICD9): Lower Respiratory Disease (466, 480-5) Age groups analyzed: < 13 Study design: Time-series N: 4,534 # of Hospitals: 1 Statistical analyses: 1) Poisson regression and 2) GAM – no mention of more stringent criteria Covariates: Long-term trends, seasonality, temperature, humidity Statistical package: S-Plus Lag: 0-7 days, 2,3,4 day moving avg	24-h avg: Mean: 23.7 μg/m³ SD: 10.0 Range: 3.4, 75.2 IQR: 12.5 # of Stations: 6 Copollutants: PM_{10} (r = 0.69) NO_2 (r = 0.66) CO (r = 0.49) O_3 (r = 0.28)	This study reports a significant effect of air pollution on respiratory morbidity, though several pollutants were associated with increased respiratory events, making it difficult to isolate a single agent as the main atmospheric contaminant. Increment: 12.5 μg/m³ (IQR) Single-pollutant models (estimated from graphs): Pneumonia: ~21% (4.8, 37) Asthma: ~12% (−10, 38) Pneumonia multipollutant models: Adjusted for: PM_{10} 13.3 (−5.7, 32.3) 6-day avg; NO_2 16.5 (−1.6, 34.6) 6-day avg; CO 18.4 (0.5, 36.2) 6-day avg; O_3 18.4 (0.5, 36.2) 6-day avg Multipollutant model: 13.3 (−5.9, 32.6) 6-day avg Asthma multipollutant models: Adjusted for: PM_{10} 3.8 (−23.3, 31.0) 2-day avg; NO_2 −1.2 (−27.4, 25.0) 2-day avg; CO 6.2 (−18.8, 31.2) 2-day avg; O_3 9.4 (−14.6, 33.5) 2-day avg Multipollutant model: −0.5 (−27.7, 26.6) 2-day avg
Gouveia and Fletcher (2000) São Paulo, Brazil Period of Study: 11/92-9/94	Hospital Admissions Outcome(s) (ICD 9): All respiratory; Pneumonia (480-486); asthma or bronchitis (466, 490, 491, 493) Age groups analyzed: < 1; < 5 yrs Study design: Time-series Statistical analyses: Poisson regression Covariates: Long-term trend, season, temperature, relative humidity, day of wk, holiday, strikes in public transport or health services Season: Cool (May-Oct), Warm (Nov-Apr) Statistical package: SAS Lag: 0, 1, 2 days	24-h avg: Mean: 18.3 μg/m³ SD: 9.0 Range: 3.2, 61.1 5th: 7.6 25th: 11.9 50th: 16.6 75th: 22.2 95th: 35.8 # of stations: 4 Copollutants: PM_{10} (r = 0.72) NO_2 (r = 0.37) CO (r = 0.65) O_3 (r = 0.08)	Current ambient air pollution concentrations have short-term adverse effects on children's respiratory morbidity assessed through admissions to hospitals. Increment: 27.1 μg/m³ (90th – 10th) All Respiratory: < 5 yrs RR 1.038 (0.983, 1.096) lag 1 < 5 yrs Cool RR 1.06 (0.99, 1.11) (estimated from graph) < 5 yrs Warm RR 0.98 (0.89, 1.07) (estimated from graph) Pneumonia: < 5 yrs RR 1.024 (0.961, 1.091) lag 1 < 1 yr RR 1.071 (0.998, 1.149) lag 0 Asthma: < 5 yrs RR 1.106 (0.981, 1.247) lag 2

Study	Methods	Pollutant Data	Findings
Ilabaca et al. (1999) Santiago, Chile Period of Study: 2/1/95–8/31/96 Days: 578	ED Visits Outcome(s) (ICD9): Upper respiratory illness (460-465, 487); Lower respiratory illness (466, 480-486, 490-494, 496, 519.1, 033.9); Pneumonia (480-486) Age groups analyzed: < 15 Study design: Time-series # of Hospitals: 1 Statistical analyses: Poisson regression Covariates: Long-term trend, season, day of wk, temperature, humidity, influenza epidemic Season: Warm (Sep-Apr), Cool (May-Aug) Lag: 0-3 days	24-h avg SO_2 ($\mu g/m^3$) Warm: Mean: 14.9 Median: 13.2 SD: 8.8 Range: 1.9, 60.2 5th: 5.6 95th: 32.0 Cool: Mean: 31.8 Median: 28.2 SD: 18.4 Range: 5.6, 92.1 5th: 9.4 95th: 75.2 # of stations: 4 Copollutants: Warm: NO_2 (r = 0.6556) O_3 (r = 0.1835) PM_{10} (r = 0.6687) $PM_{2.5}$ (r = 0.5764) Cool: NO_2 (r = 0.7440) O_3 (r = 0.1252) PM_{10} (r = 0.7337) $PM_{2.5}$ (r = 0.6874)	SO_2 was related to the number of respiratory ED visits, but because of the high correlation between contaminants, it is difficult to establish independent health effects. These results support the fact that exposure to air pollution mixtures may decrease immune functions and increase the risk for respiratory infections among children. Increment: IQR All respiratory: Cool: Lag 2 IQR: RR 1.0289 (1.0151, 1.0428); Lag 3 IQR: RR 1.0374 (1.0236, 1.0513); Lag avg 7 IQR: RR 1.0230 (1.0086, 1.0377) Warm: Lag 2 IQR: RR 1.0029 (0.9860, 1.0200) Lag 3 IQR: RR 1.0108 (0.9937, 1.0282) Lag avg 7 IQR: RR 1.0108 (0.9756, 1.0473) Upper respiratory: Cool: Lag 2 IQR: RR 1.0584 (1.0394, 1.0778) Lag 3 IQR: RR 1.0513 (1.0324, 1.0706) Lag avg 7 IQR: RR 1.0316 (1.0120, 1.0515) Warm: Lag 2 IQR: RR 1.0061 (0.9850, 1.0277) Lag 3 IQR: RR 1.0130 (0.9916, 1.0349) Lag avg 7 IQR: RR 0.9815 (0.9390, 1.0260) Pneumonia: Cool: Lag 2 IQR: RR 1.0164 (0.9757, 1.0587) Lag 3 IQR: RR 1.0342 (0.9938, 1.0762) Lag avg 7 IQR: RR 1.0291 (0.9850, 1.0751) Warm: Lag 2 IQR: RR 1.1010 (1.0404, 1.1653) Lag 3 IQR: RR 1.0248 (0.9669, 1.0862) Lag avg 7 IQR: RR 1.2151 (1.0771, 1.3709)
Lin et al. (1999) São Paulo, Brazil Period of Study: May 1991-Apr 1993 Days: 621	ED Visits Outcome(s): Respiratory disease, Upper respiratory illness, Lower respiratory illness, Wheezing ICD 9Code(s): NR Age groups analyzed: < 13 Study design: Time-series # of Hospitals: 1 Statistical analyses: Gaussian and Poisson regression Covariates: Long-term trend, seasonality, day of wk, temperature, humidity Statistical package: NR Lag: 5-day lagged moving avgs	SO_2 $\mu g/m^3$: Mean: 20 SD: 8 Range: 4, 60 Number of stations: 3 Copollutants: NO_2 (r = 0.38) CO (r = 0.56) PM_{10} (r = 0.73) O_3 (r = 0.21)	The results of this study demonstrate a significant association between the increase in emergency visits for all respiratory illness, especially URI, and SO_2 levels. Increment: 10 $\mu g/m^3$ All respiratory illness: SO_2 alone RR 1.079 (1.052, 1.107) 5-day moving avg $SO_2 + PM_{10} + O_3 + NO_2 + CO$ RR 0.938 (0.900, 0.977) Lower respiratory illness: SO_2 alone RR 1.052 (0.984, 1.125) 5-day moving avg $SO_2 + PM_{10} + O_3 + NO_2 + CO$ RR 0.872 (0.783, 0.971) Upper respiratory illness: SO_2 alone RR 1.075 (1.044, 1.107) 5-day moving avg $SO_2 + PM_{10} + O_3 + NO_2 + CO$ RR 0.951 (0.906, 0.999) Wheezing: SO_2 alone RR 1.034 (0.975, 1.096) 5-day moving avg $SO_2 + PM_{10} + O_3 + NO_2 + CO$ RR 0.908 (0.824, 1.002)

Study	Methods	Pollutant Data	Findings
Martins* et al. (2002) São Paulo, Brazil Period of Study: 5/96-9/98	ED Visits Outcome(s) (ICD10): Chronic Lower Respiratory Disease (CLRD) (J40-J47); includes chronic bronchitis, emphysema, other COPDs, asthma, bronchiectasia Age groups analyzed: >64 Study design: Time-series N: 712 # of Hospitals: 1 Catchment area: 13,163 total ER visits Statistical analyses: Poisson regression and GAM – no mention of more stringent criteria Covariates: Weekdays, time, min temperature, relative humidity, daily number of non-respiratory emergency room visits made by elderly Statistical package: S-Plus Lag: 2-7 days and 3 day moving avgs	SO_2 24-h avg ($\mu g/m^3$): 18.7, SD: 10.6 Range: 2.0, 75.2 IQR: 15.1 $\mu g/m^3$ # of stations: 13 Copollutants: O_3 (r = 0.28) NO_2 (r = 0.67) PM_{10} (r = 0.72) CO (r = 0.51)	The results of the study show a significant association between SO_2 and CLRD among the elderly. Increment: IQR of $\mu g/m^3$ Percent increase: 17.5 (5.0, 23.0) lag 3-day moving avg (estimated from graph) Single-pollutant model β = 0.0140 (0.0056) Multipollutant model (with O_3) β = 0.0104 (0.0059)
ASIA			
Agarwal et al. (2006) Safdarjung area of south Deli Period of Study: 2000-2003	Hospital Admissions Outcome(s) (ICD9): COPD, asthma and emphysema Study design: time-series Statistical Analysis: Performed Kruskal-Wallis one way analysis of variance by rank, chi-square analysis. Statistical package: SPSS Age groups analyzed: all Covariates: Temperature-min and maximum, relative humidity at 0830 and 1730 h and wind speed N: NR # Hospitals: 1 Lag: none	Mean, SD Quarter 1: 16.7, 5.5 Quarter 2: 13.6, 2.6 Quarter 3: 12.8, 3.1 Quarter 4: 14.3, 2.8 Copollutants: NO_2 SPM RSPM	SO_2 was found to be in "low" category the entire time, so no analysis could be performed

Study	Methods	Pollutant Data	Findings
Chew et al. (1999) Singapore Period of Study: 1990-1994	Hospital Admissions/ED Visits Outcome(s) (ICD 9): Asthma (493) Age groups analyzed: 3-12, 13-21 Study design: Time-series N: 23,000 # of Hospitals: 2 Statistical analyses: Linear regression, GLM Covariates: variables that were significantly associated with ER visits were retained in the model Statistical package: SAS/STAT, SAS/ETS 6.08 Lag: 1, 2 days avgs	24-h avg: 38.1 µg/m^3, SD: 21.8 Range: 3.0, 141.0 # of Stations: 15 Copollutants: NO_2 O_3 TSP	SO_2 was positively correlated to daily ER visits and hospitalization for asthma in children (3-12 yrs), but not adolescents. The association of ER visits with SO_2 persisted after standardization for meteorological and temporal variables. An adjusted increase in 2.9 ER visits for every 20 µg/m^3 increase in ambient SO_2 levels with a lag of 1 was observed. The increased number of ER visits/day for each quartile are listed below: Q1: < 9; Q2: 10-12; Q3: 13-16; Q4: > 16 Categorical analysis (via ANOVA) p-value and Pearson correlation coefficient (r) using continuous data comparing daily air pollutant levels and daily number of ER visits Age Group: 3-12 13-21 Lag 0 r = 0.04 r = 0.05; p < 0.001 p = 0.086 Lag 1 r = 0.10 r = 0.06; p < 0.001 p = 0.016 Lag 2 r = 0.08 r = 0.07; p < 0.001 p = 0.019
Hwang and Chan (2002) Taiwan Period of Study: 1998	ED Visits Outcome(s) (ICD 9): Lower Respiratory Disease (LRD) (466, 480-6) including acute bronchitis, acute bronchiolits, pneumonia Age groups analyzed: 0-14, 15-64, ≥ 65, all ages Study design: Time-series Catchment area: Clinic records from 50 communities Statistical analyses: Linear regression, GLM Covariates: temperature, dew point temperature, season, day of wk, holiday Lag: 0,1,2 days and avgs	24-h avg: 5.4 ppb, SD: 3.0 Range: 1.5, 16.9 Copollutants: NO_2 PM_{10} O_3 CO No correlations for individual-pollutants.	Colinearity of pollutants prevented use of multipollutant models Increment: 10% change in SO_2 (natural avg) which is equivalent to 2.4 ppb. NOTE: The percent change is for the rate of clinic use NOT for relative risk for adverse effect. Increased clinic visits for lower respiratory disease (LRD) by age group 0-14 yrs: Lag 0 0.5% (0.3, 0.6) 15-64 yrs: Lag 0 0.7% (0.5, 0.8) ≥65 yrs: Lag 0 0.8% (0.6, 1.1) All ages: Lag 0 0.5% (0.4, 0.7)
Ko et al. (2007b) Hong Kong Period of Study: 2000-2005	Hospital Admissions Outcome(s) (ICD9): Asthma Study design: Retrospective ecological study Statistical Analysis: Generalized additive models with Poisson distribution. Age groups analyzed: All Covariates: N: 69,716 # Hospitals: 15 Lag: 0-5 days	Mean, SD (µg/m^3) Whole yr: 18.8, 13.1 < 20 °C: 18.0, 10.0 ≥20 °C: 19.1, 14.1 Copollutants: NO_2 (r =0.573) PM_{10} (r =0.430) $PM_{2.5}$ (r =0.482) O_3 (r =0.123)	SO_2 had a non-significant effect on respiratory admissions. Relative Risk (95% CI) Lag 0: 1.004 (0.998, 1.011) Lag 1: 1.000 (0.994, 1.007) Lag 2: 0.999 (0.993, 1.006) Lag 3: 1.002 (0.998, 1.008) Lag 4: 1.004 (0.997, 1.010) Lag 5: 0.997 (0.990, 1.003) Lag 0,1: 1.003 (0.996, 1.011) Lag 0,2: 1.003 (0.994, 1.011) Lag 0,3: 1.004 (0.994, 1.014) Lag 0-4: 1.007 (0.996, 1.017) Lag 0-5: 1.004 (0.993, 1.016)

Study	Methods	Pollutant Data	Findings
Ko et al. (2007a) Hong Kong Period of Study: 2000-2004	Hospital Admissions Outcome(s) (ICD9): COPD Study design: Retrospective ecological study Statistical Analysis: Poisson distribution Age groups analyzed: All ages Covariates: Autocorrelation and overdispersion were corrected N: 119,225 # Hospitals: 15 Lag: 0-5 days	15.0 µg/m^3 SD: 11.6 Copollutants: NO_2 PM_{10} O_3 $PM_{2.5}$	Positive association with hospital admission for acute exacerbations of COPD. Relative Risk (95% CI) Lag 0: 1.007 (1.001, 1.014) Lag 1: 0.991 (0.981, 1.001) Lag 2: 0.992 (0.985, 1.000) Lag 3: 1.006 (0.999, 1.013) Lag 4: 1.004 (0.998, 1.011) Lag 5: 1.004 (0.997, 1.010) Lag 0-1: 0.998 (0.991, 1.006) Lag 0-2: 0.993 (0.985, 1.001) Lag 0-3: 0.998 (0.989, 1.007) Lag 0-4: 1.001 (0.991, 1.010) Lag 0-5: 1.004 (0.994, 1.014)
Lee* et al. (2002) Seoul, Korea Period of Study: 12/1/97-12/31/99 Days: 822	Hospital Admissions Outcomes (ICD 10): Asthma (J45–J46) Age groups analyzed: < 15 Study design: Time-series N: 6,436 Statistical analyses: Poisson regression, log link with GAM Covariates: Time, day of wk, temperature, humidity Season: Spring (Mar-May), Summer (Jun-Aug), Fall (Sep-Nov), Winter (Dec-Feb) Lag: 0-2 days cumulative	24-h avg SO_2 (ppb) Mean: 7.7 SD: 3.3 5th: 3.7 25th: 5.1 50th: 7.0 75th: 9.5 95th: 14.3 # of stations: 27 Copollutants: NO_2 (r = 0.723) O_3 (r = −0.301) CO (r = 0.812) PM_{10} (r = 0.585)	This study reinforces the possible role of SO_2 on asthma attacks, although it should be interpreted with caution because the effect estimates are close to the null and because results in the multipollutant models are inconsistent. Increment: 14.6 ppb (IQR) Asthma: SO_2 RR 1.11 (1.06, 1.17) lag 0-2 SO_2 + PM_{10} RR 1.08 (1.02, 1.14) lag 0-2 SO_2 + NO_2 RR 0.95 (0.88, 1.03) lag 0-2 SO_2 + O_3 RR 1.12 (1.06, 1.17) lag 0-2 SO_2 + CO RR 0.99 (0.92, 1.07) lag 0-2 SO_2 + O_3 + CO + PM_{10} + NO_2 RR 0.949 (0.868, 1.033)
Lee et al. (2006) Hong Kong, China Period of Study: 1997-2002 Days: 2,191	Hospital Admissions Outcome(s) (ICD 9): Asthma (493) Age groups analyzed: ≤18 Study design: Time-series N: 26,663 Statistical analyses: Semi-parametric Poisson regression with GAM (similar to APHEA 2) Covariates: Long-term trend, temperature, relative humidity, influenza, day of wk, holiday Statistical package: SAS 8.02 Lag: 0-5 days	SO_2 24-h avg: 17.7 µg/m^3, SD: 10.7 IQR: 11.1 µg/m^3 25th: 10.6 50th: 15.2 75th: 21.7 # of stations: 9-10 Copollutants: PM_{10} (r = 0.37) $PM_{2.5}$ (r = 0.47) NO_2 (r = 0.49) O_3 (r = −0.17)	Absence of an association of SO_2 with asthma admissions was attributed to low ambient SO_2 levels during the study period due to restrictions on sulfur content in fuel. Increment: 11.1 µg/m^3 (IQR) Asthma: Single-pollutant model Lag 0 −1.57% (−2.87, −0.26) Lag 1 −1.77% (−3.06, −0.46) Lag 2 −1.15% (−2.42, 0.14) Lag 3 0.82% (−0.45, 2.11) Lag 4 1.40% (0.13, 2.69) Lag 5 1.46% (0.19, 2.74) Multipollutant model–including PM, NO_2, and O_3: 0.81% (−0.75, 2.4) lag 5 Other lags NR

Study	Methods	Pollutant Data	Findings
Lee et al. (2007) Kaohsiung, Taiwan Period of Study: 1996-2003	Hospital Admissions Outcome(s) (ICD9): COPD (490-492, 494, and 496) identified by records from the National Health Insurance (NHI) program Study design: Case-crossover Statistical Analysis: Conditional logistic regression Statistical package: SAS Age groups analyzed: All ages Covariates: Adjustment for temperature and humidity N: 25,108 # Hospitals: 63 Lag: Cumulative lag up to 2 days	24-h avg (ppb): 9.49 Range: 0.92, 31.33 Copollutants: PM_{10} NO_2 CO O_3	All pollutants, except SO_2, were significantly associated with COPD hospital admissions on warm days, while on cold days all pollutants were found to be significantly associated. In two pollutant models, CO and O_3 were significantly associated with each of the other pollutants on warm days, and on cool days, only NO_2 was significantly associated with all pollutants. Odds Ratio (95% CI) Single-pollutant model (per 5.79 ppb SO_2): ≥ 25 °C: 1.024 (0.973, 1.077); < 25 °C: 1.190 (1.093, 1.295) Co-pollutant model (per 5.79 ppb SO_2): ≥ 25 °C: SO_2 + PM_{10}: 1.002 (0.951, 1.054) SO_2 + NO_2: 0.979 (0.926, 1.034) SO_2 + CO: 0.929 (0.876, 0.985) SO_2 + O_3: 1.057 (1.004, 1.113) < 25 °C: SO_2 + PM_{10}: 1.043 (0.952, 1.143) SO_2 + NO_2: 0.767 (0.689, 0.855) SO_2 + CO: 1.004 (0.915, 1.103) SO_2 + O_3: 1.198 (1.100, 1.304)
Tanaka et al. (1998) Kushiro, Japan Period of Study: 1992-1993	ED Visits Outcome(s): Asthma Age groups analyzed: 15-79 Study design: Time-series N: 102 # of Hospitals: 1 Statistical analyses: Poisson regression Covariates: temperature, vapor pressure, barometric pressure, relative humidity, wind velocity, wind direction at maximal velocity Statistical package: NR	SO_2 24-h avg 3.2 (2.4) ppb in fog 3.7 (1.9) ppb in fog free days Max SO_2 24-h avg < 11 ppb Copollutants: NO NO_2 SPM (TSP) O_3	The results reveal that ED visits by atopic subjects increased on low SO_2 days. This observation is inconsistent with most air pollution epidemiology, as high levels of air pollutants have conventionally been linked with asthma exacerbation. Increment: 5 ppb Nonatopic: OR 1.18 (0.96, 1.46) Atopic: OR 0.78 (0.66, 0.93)
Tsai et al. (2006) Kaohsiung, Taiwan Period of Study: 1996-2003 Days: 2922	Hospital Admissions Outcome(s) (ICD 9): Asthma (493) Study design: Case-crossover N: 17,682 Statistical analyses: conditional logistic regression Covariates: Temperature, humidity Season: Warm (≥ 25 °C); Cool (< 25 °C) Statistical package: SAS Lag: 0-2 days Cumulative	SO_2 24-h avg: 9.49 ppb Range: 0.92, 31.33 25th: 6.37 50th: 8.94 75th: 12.16 # of stations: 6 Copollutants: PM_{10} NO_2 O_3 CO	Positive associations were observed between air pollutants and hospital admissions for stroke. In single-pollutant models SO_2 was not associated with either PIH or IS. The season did not affect these associations. SO_2 was also not significant in 2-pollutant models. Increment: 5.79 ppb (IQR) Seasonality Single-pollutant model: >25 °C 1.018 (0.956, 1.083) lag 0-2; < 25 °C 1.187 (1.073, 1.314) lag 0-2 Dual-pollutant model: Adjusted for PM_{10}: >25 °C 0.993 (0.932, 1.058) lag 0-2; < 25 °C 1.027 (0.921, 1.146) lag 0-2 Adjusted for CO: >25 °C 0.910 (0.847, 0.978) lag 0-2; < 25 °C 1.036 (1.027, 1.046) lag 0-2 Adjusted for NO_2: >25 °C 0.967 (0.903, 1.035) lag 0-2; < 25 °C 0.735 (0.646, 0.835) lag 0-2 Adjusted for O_3: >25 °C 1.055 (0.990, 1.123) lag 0-2; < 25 °C 1.195 (1.080, 1.323) lag 0-2

Study	Methods	Pollutant Data	Findings
Wong et al. (1999) Hong Kong, China Period of Study: 1994-1995	Hospital Admissions Outcome(s) (ICD 9): All respiratory admissions (460-6, 471-8, 480-7, 490-6); Asthma (493), COPD (490-496), Pneumonia (480-7) Age groups analyzed: 0-4, 5-64, ≥ 65, all ages # of Hospitals: 12 Study design:Time-series Statistical analyses: Poisson regression (followed APHEA protocol) Covariates: Trend, season, day of wk, holiday, temperature, humidity Statistical package: SAS 8.02 Lag: days 0-3 cumulative	Median 24-h avg SO_2: 17.05 µg/m^3 Range: 2.74, 68.49 25th: 12.45 75th: 25.01 # of stations: 7 Copollutants: O_3 SO_2 PM_{10}	Adverse respiratory effects of SO_2 were noted at low concentrations. Results for respiratory outcomes were attributed to the elderly population. This was also true for the other pollutants. Therefore, it is difficult to be certain that the effects were due mainly to SO_2. Pair-wise comparisons in multipollutant models showed significant interactions of $PM_{2.5}$, NO_2, and O_3. Increment = 10 µg/m^3 Overall increase in admissions: 1.013 (1.004, 1.021) lag 0 Respiratory relative risks (RR): 0-4 yrs: 1.005 (0.991, 1.018) lag 0; 5-64 yrs: 1.008 (0.996, 1.021) lag 0; >65 yrs: 1.023 (1.012, 1.036) lag 0 Asthma: 1.017 (0.998, 1.036) lag 0 COPD: 1.023 (1.011, 1.035) lag 0 Pneumonia: 0.990 (0.977, 1.004) lag 4
Wong et al. (2001b) Hong Kong, China Period of Study: 1993-1994	Hospital Admissions Outcome(s) (ICD 9): Asthma (493) Age groups analyzed: ≤ 15 N: 1,217 # of Hospitals: 1 Study design: Time-series Statistical analyses: Poisson regression (followed APHEA protocol) Covariates: Season, temperature, humidity Season: Summer (Jun-Aug), Autumn (Sep-Nov), Winter (Dec-Feb), Spring (Mar-May) Lag: 0, 1, 2, 3, 4, 5 days; and cumulative 0-2 and 0-3 days.	24-h avg SO_2 Mean: 12.2 µg/m^3 SD: 12.9 Range: 0, 98 µg/m^3 Autumn: 10.6 (9.6) Winter: 10.0 (7.5) Spring: 9.6 (8.8) Summer: 18.5 (19.5) # of stations: 9 Copollutants: PM_{10} NO_2	SO_2 levels were found to be the highest during the summer. There were consistent and statistically significant associations between asthma admission and increased daily levels of SO_2. No associations were noted in the spring or winter. No significant associations were found between hospital admissions and day of the wk, humidity, temperature or atmospheric pressure. Total admissions were limited to one hospital. Increment: 10 µg/m^3 Asthma: All yr: RR 1.06 p = 0.004 Autumn: NR Winter: NR Spring: NR Summer: NR

Study	Methods	Pollutant Data	Findings
Wong* et al. (2002a) London England and Hong Kong Period of Study: London: 1992-1994 Hong Kong: 1995-1997 Days: 1,096	Hospital Admissions Outcome(s) (ICD 9): All respiratory admissions (460-519); asthma (493) Age groups analyzed: 15-64, 65+, all ages Study design: Time-series Statistical analyses: APHEA protocol, Poisson regression with GAM Covariates: Long-term trend, season, influenza, day of wk, holiday, temperature, humidity, thunderstorms Season: Cool, Oct-Mar; Warm: Apr-Sep Dose-Response Investigated?: Yes Statistical package: S-Plus Lag: 0, 1, 2, 3, 4 days, 0-1 cum. avg.	24-h avg SO_2 µg/m^3 Hong Kong: Mean: 17.7 Warm: 18.3 Cool: 17.2 SD: 12.3 Range: 1.1, 90.0 10th: 6.2 50th: 14.5 90th: 32.8 London: Mean: 23.7 Warm: 22.2 Cool: 25.3 SD: 12.3 Range: 6.2, 113.6 10th: 13.2 50th: 20.6 90th: 38.1 Copollutants: Hong Kong : PM_{10} (r = 0.30) NO_2 (r = 0.37) O_3 (r = −0.18) London: PM_{10} (r = 0.64) NO_2 (r = 0.71) O_3 (r = −0.25)	Similar non-statistically significant associations between asthma hospital admissions and SO_2 were found in both cities. The association between respiratory hospital admissions and SO_2 showed significance in the cold season in Hong Kong and on an all yr basis. Respiratory hospital admissions were not significantly associated with SO_2 in Britain. In the 2-pollutant model the association between respiratory hospital admission and SO_2 in London was insignificant, and remained insignificant after adjusted for the second pollutants. In Hong Kong, the positive association of SO_2 was most affected by NO_2, losing statistical significance. The positive association remained robust when adjusted for O_3, and a slight decrease in association after adjusted for $PM_{2.5}$. Increment: 10 µg/m^3 Asthma, 15-64 yrs Hong Kong: ER −0.1 (−2.4, 2.2) lag 0-1; ER −1.5 (−3.4, 0.5) lag; Warm: ER 1.5 (−1.5, 4.6) lag 0-1; Cool: ER −2.0 (−5.4, 1.4) lag 0-1 London: ER 0.7 (−1.0, 2.5) lag 0-1; ER 2.1 (0.7, 3.6) lag 3 Warm: ER −1.4 (−4.7, 1.9) lag 0-1; Cool: ER 1.6 (−0.5, 3.8) lag 0-1 Respiratory 65+ yrs Hong Kong: ER 1.8 (0.9, 2.6) lag 0-1; ER 1.7 (1.0, 2.4) lag 0 Warm: ER 1.1 (0.0, 2.2) lag 0-1; Cool: ER 2.7 (1.4, 4.0) lag 0-1 +O_3 ER 1.9 (1.1, 2.8) lag 0-1; +$PM_{2.5}$ ER 1.2 (0.3, 2.2) lag 0-1; +NO_2 ER 0.3 (−0.7, 1.4) lag 0-1 London: ER 0.2 (−0.6, 1.1) lag 0-1; ER 1.2 (0.5, 2.0) lag 3; Warm: ER 1.3 (−0.5, 3.1) lag 0-1; Cool: ER −0.3 (−1.3, 0.8) lag 0-1 +O_3 ER 0.5 (−0.4, 1.5) lag 0-1; +$PM_{2.5}$ ER 1.2 (0.3, 2.2) lag 0-1 +NO_2 ER 0.5 (−0.7, 1.7)lag 0-1
Yang and Chen (2007) Taipei, Taiwan Period of Study: 1996-2003	Hospital Admissions Outcome(s) (ICD9): COPD (490-492, 494, and 496) identified by records from the National Health Insurance (NHI) program Study design: Case-crossover Statistical Analysis: Conditional logistic regression Statistical package: SAS Age groups analyzed: All ages Covariates: Adjustments for weather variables, day of the wk, seasonality, and long-term time trends N: 46,491 # Hospitals: 47 Lag: Cumulative lag up to 2 days	24-h avg (ppb): 4.33 Range: 0.15, 17.82 25th: 2.67 50th: 3.90 75th: 5.46 Copollutants: PM_{10} NO_2 CO O_3	In single-pollutant models, all pollutants, except SO_2, significantly associated with COPD hospital admissions on warm days (≥20 °C). On cold days (< 20 °C), only SO_2 was significantly associated with COPD hospital admissions. In multi-pollutant models, NO_2 and O_3 were significantly associated with each pollutant on warm days. Odds Ratio (95% CI), Single-pollutant model (per 2.79 ppb SO_2): ≥ 20 °C: 1.006 (0.970, 1.043); < 20 °C: 1.071 (1.015, 1.129) Odds Ratio (95% CI), Co-pollutant model (per 2.79 ppb): ≥ 20 °C: SO_2 + PM_{10}: 0.909 (0.872, 0.949) SO_2 + NO_2: 0.835(0.798, 0.873) SO_2 + CO: 0.920(0.884, 0.958) SO_2 + O_3: 0.978(0.943, 1.015) < 20 °C: SO_2 + PM_{10}: 1.067 (0.997, 1.141) SO_2 + NO_2:1.147 (1.072, 1.227) SO_2 + CO: 1.140 (1.066, 1.219) SO_2 + O_3: 1.064 (1.009, 1.123)

*Default GAM

APHEA: Air Pollution and Health: a European Approach

Table F-3. Short-term exposure to SO_2 and cardiovascular morbidity in field/panel studies.

Study	Methods	Pollutant Data	Findings
UNITED STATES			
Dockery et al. (2005) Boston, MA Period of Study: Jul 1995-Jul 2002	Cohort study of 203 cardiac patients with implanted cardioverter defibrillators. Patients were followed for an avg of 3.1 yrs from 1995-2002 to assess the role of air pollution on the incidence of ventricular arrhythmias. The association of arrhythmic episode-days and air pollutions analyzed with logistic regression using GEE with random effects. Model adjusted for patient, season, min temperature, mean humidity, day of the wk, and previous arrhythmia within 3 days. Only effects of 2-day running mean of air pollution concentration reported.	48-h avg SO_2; Median: 4.9 ppb 25th%: 3.3 ppb 75%: 7.4 ppb 95%: 12.8 ppb Copollutants: $PM_{2.5}$ BC SO_4^{2-} PN NO_2 CO O_3	No statistically significant association between any of the air pollutant and ventricular arrhythmias when all events were considered. However, ventricular arrhythmias within 3 days of a prior event were statistically significant with SO_2, $PM_{2.5}$, BC, NO_2, CO, and marginally with SO_4^{2-} , but not with O_3 or PN. CO, NO_2, BC, and $PM_{2.5}$ correlated, thus it was impossible to differentiate the independent effects. Since the increased risk of ventricular tachyarrhythmia was associated with air pollution observed among patients with a recent tachyarrhythmia, it was suggested that air pollution acts in combination with cardiac electrical instability to increase risk of arrhythmia. For IQR (4.0 ppb) increase in 48-h mean SO_2 All events: OR = 1.04 (0.94, 1.14), p = 0.28 Prior arrhythmia event: < 3 Days: 1.30 (95% CI: 1.06, 1.61), p = 0.013 Prior arrhythmia event: >3 Days: 0.98 (0.87, 1.11) p = 0.78
Gold et al. (2000) Boston, MA Period of Study: June-Sep 1997	Panel study on 21 active Boston residents aged 53-87 yrs to investigate the association between short-term changes in ambient air pollution and short-term changes in cardiovascular function. Participants observed up to 12 times from June to Sep 1997 (163 observations made in total). Protocol involved 25 mins per wk of continuous ECG monitoring, that included 5 mins of rest, 5 mins of standing, 5 mins of exercise outdoors, 5 mins of recovery, and 20 cycles of slow breathing. Fixed effects models adjusted for time-varying covariates and individuals traits.	24-h avg 3.2 ppb Range: 0, 12.6 ppb IQR: 3.0 ppb Copollutants: $PM_{2.5}$ $PM_{10-2.5}$ O_3 NO_2 CO	In single-pollutant models, 24-h mean SO_2 associated with reduced heart rate in the first rest period but not overall. Associations weaker for shorter averaging periods. Association between SO_2 and heart rate not significant with the multipollutant model (SO_2 and $PM_{2.5}$). SO_2 not associated with r-MSSD. Heart rate, first rest period, mean 66.3 bpm Single-pollutant model: Estimated effect (SE) −1.0 (0.5); % mean 1.5, p = 0.03 Heart rate, first rest period, mean 66.3 bpm Multipollutant model ($PM_{2.5}$ and SO_2): SO_2 estimated effect (SE) −0.8 (0.5); % mean 1.2, p = 0.09 $PM_{2.5}$ estimated effect (SE) −1.6 (0.7); % mean 2.5, p = 0.03 Overall heart rate, mean 74.9 bpm Single-pollutant model: Estimated effect (SE) −0.5 (0.5), p = 0.30 Multipollutant model: SO_2 estimated effect (SE) −0.2 (0.5), p = 0.6 $PM_{2.5}$; Estimated effect (SE) −1.9 (0.7), p = 0.01% mean 2.6
Liao et al. (2004) Three locations in U.S.: Forsyth County, NC; Jackson, MS; Minneapolis, MN Period of Study: 1996-1998	Cross-sectional study of 6,784 cohort members of the Atherosclerosis Risk in Communities Study. Participants were 45-64 yrs of age; baseline clinical examinations conducted from 1987-1989. HRV data collected from 1996-1998. Air pollutants obtained form EPA AIRS for this same period. Resting, supine, 5-min beat-to-beat RR interval data were collected over a 4-h period. Multivariable linear regression models used to assess associations between pollutants measured 1-3 days prior to HRV measurements. Models controlled for age, ethnicity-center, sex, education, current smoking, BMI, heart rate, use of cardiovascular medication, hypertension, prevalent coronary heart disease, and diabetes.	Mean (SD) SO_2 measured 1 day prior to HRV measurement was 4 (4) ppb Copollutants: PM_{10} O_3 CO NO_2	Significant interaction between SO_2 and prevalence of coronary heart disease for low-frequency power analyses. SO_2 inversely associated with SD of normal R-R intervals and low-frequency power and positively associated with heart rate. SO_2 association with low-frequency power stronger among those with history of coronary heart disease. Effect size of PM_{10} larger than for gaseous pollutants. Log-transformed low-frequency power effect estimate and SE per 1 SD increment (4 ppb) SO_2 lag 1 day: Log transformed high-frequency power −0.024 (SE 0.016) Standard deviation of normal R-R intervals −0.532 (SE 0.270), p < 0.05 Heart rate: 0.295 (SE 0.130), p < 0.05 Prevalent CHD: −0.122 (SE 0.056), p < 0.01 No prevalent CHD −0.012 (SE 0.016)

Study	Methods	Pollutant Data	Findings
Liao et al. (2005) United States Period of Study: 1996-1998	Cross-sectional survey 10,208 participants (avg age 54 yrs) from Atherosclerosis Risk in Communities (ARIC) study cohort to assess the association between criteria air pollutants and hemostatic and inflammatory markers. 57% of participants were female and 66% male. Used hemostatis/ inflammation variables collected during the baseline examination and air pollution data 1-3 days prior to the event. Used multiple linear regression models that controlled for age, sex, ethnicity-center, education, smoking, drinking status, BMI, history of chronic respiratory disease, humidity, seasons, cloud cover, and temperature. Also history of CVD and diabetes if not effect modifier in a particular model.	SO_2 mean (SD) 0.0005 (0.004) ppm Q1-3: 0.005 (0.003) ppm Q4: 0.006 (0.005) ppm Copollutants: PM_{10} CO NO_2 O_3	Significant curvilinear association between SO_2 witfactor VIII-C, WBC, and serum albumin. Curvilinear association indicated threshold effect Results shown in graph.
Luttmann-Gibson et al. (2006) Steubenville, OH Period of Study: 2000	Conducted a panel study during the summer and fall of 2000, which consisted of 32 subjects 54-90 yrs old living in Steubenville, OH. Used linear mixed models, fixed effects of pollution, age, gender, race, obesity, season, time of day, apparent temperature, and a first order autoregressive process for within-subject residuals to examine the relation between air pollution and log-transformed HRV parameters and heart rate.	24-h avg (ppb): 4.1 Copollutants: $PM_{2.5}$ SO_4^{2-} EC NO_2 O_3	Increasing concentrations of $PM_{2.5}$ and SO_4^{2-} in the previous day were both found to be associated with reduced HRV. No association was observed between increasing SO_2 concentrations in the previous day and HRV. % Change (95% CI) (per 4.3 ppb SO_2) Standard Deviation of Normal RR Intervals: (SSDN) 0.7 (−1.0, 2.5) Differences Between Adjacent RR Intervals: (r-MSSD) 0.5 (−2.8, 4.0) High-Frequency Power (HF) 1.7 (−4.9, 8.7); Low-Frequency Power (LF) 4.9 (−1.4, 11.5); Heart Rate (HR) 0.3 (−0.2, 0.8)
Metzger et al. (2007) Atlanta, GA Period of Study: 1993-2002	Collected information on 518 patients (6287 event-days) for ventricular tachyarrhythemic events over 10-yr period. Used GEE analysis, a case-crossover analysis, and a sensitivity analysis stratified on subject	15.5 ppb (±16.4) Copollutants: PM_{10} O_3 NO_2 CO $PM_{2.5}$	Little evidence of associations between ambient air quality measurements and ventricular tachyarrhythmic events. Odds ratio (95% CI) All events: 1.002 (0.968-1.037) Events resulting in cardiac pacing or defibrillation: 0.988 (0.936-1.042) Events resulting in defibrillation: 1.004 (0.911-1.105) Primary GEE model: 1.002 (0.968-1.037) Controlling for min temperature: 1.010 (0.976-1.046) Using an unconstrained distributed Lag: 0.996 (0.952-1.083) Warm Season: 1.029 (0.989-1.116) Cold Season: 0.986 (0.956-1.023)
Park et al. (2005b) Greater Boston area, MA Period of Study: Nov 2000-Oct 2003	Cross-sectional study of effect of ambient air pollutants on heart rate variability (HRV) in 497 men who were in the Normative Aging Study and examined from Nov 2000 and Oct 2003. HRV measured between 0600 and 1300 h after resting for 5 mins. 4-h, 24-h, and 48-h moving avgs of air pollution matched to time of ECG measurement. Linear regression models included: age, BMI, fasting blood glucose, cigarette smoking, use of cardiac medications, room temp, season, and the lagged moving avg of apparent temp corresponding to the moving avg period for the air pollutant. Mean arterial blood pressure (MAP) and apparent temperature also included. Assessed modifying effects of hypertension, IHD, diabetes or use of cardiac/antihypertensive meds.	24-h avg SO_2 4.9 ppb SD: 3.4 Range: 0.95, 24.7 ppb Copollutants: $PM_{2.5}$ PNC BC NO_2 O_3 CO	No significant association between HRV and SO_2 for any of the averaging periods, but positive relationship. 4-h moving avg SO_2: (per 1 SD, 3.4 ppb SO_2) Log10 SDNN: 2.3 (−1.7, 6.4) Log10 HF:5.6 (−4.9, 17.3) Log10 LF: 2.2 (−5.9, 11.1) Log10 (LF:HF): −3.2 (−10.1, 4.2)

Study	Methods	Pollutant Data	Findings
Peters et al. (2000a) Eastern Massachusetts, U.S. Period of Study: 1995-1997	Pilot study to test hypothesis that patients with implanted cardioverter defibrillators would experience potentially life-threatening arrhythmias associated with air pollution episodes. Records detected arrhythmias and therapeutic interventions downloaded from the implanted defibrillator. Mean age of patients 62.2 yrs. 100 patients followed for over 3 yrs for 63,628 person-days. 33 patients with any discharges and 6 patients with 10 or more events. Data analyzed by logistic regression models using fixed effects models with individual intercepts for each patient. Model controlled for trend, season, meteorologic conditions, and day of week. Evaluated air pollutants on same day, lags 1, 2, and 3 days, and 5-day mean.	24-h avg SO_2: 7 ppb Median: 5 ppb Max: 87 ppb Copollutants: PM_{10} $PM_{2.5}$ BC CO O_3 NO_2	No association between increased defibrillator discharges and SO_2. 33 patients with at least 1 defibrillator discharge Odds Ratio (95% CI) Lag 0 0.76 (0.48, 1.21); Lag 1 0.91 (0.60, 1.37) Lag 2 0.89 (0.59, 1.34); Lag 3 1.09 (0.78, 1.52) 5-day mean 0.85 (0.50, 1.43) 6 patients with at least 10 discharges Odds Ratio (95% CI) Lag 0 0.72 (0.40, 1.31); Lag 1 0.77 (0.44, 1.37) Lag 2 1.01 (0.63, 1.61); Lag 3 1.08 (0.72, 1.62) 5-day mean 0.75 (0.38, 1.47)
Peters et al. (2001) Greater Boston area, MA Period of Study: Jan 1995-May 1996	Case cross over Study design used to investigate association between air pollution and risk of acute myocardial infarctions in 772 patients (mean age 61.6 yrs) with MI as part of the determinants of myocardial infarction onset study. For each subject, one case period was matched to 3 control periods, 24 h apart. Used conditional logistic regression models that controlled for season, day of wk, temperature, and relative humidity.	24-h avg SO_2: 7 ppb SD: 7 ppb 1-h avg SO_2: 7 ppb SD: 10 ppb Copollutants: $PM_{2.5}$, PM_{10}, $PM_{10-2.5}$, BC O_3, CO, NO_2	SO_2 not statistically associated with risk of onset of MI. Limitation of study is only 1 air pollution monitoring site available. OR for 2-h avg SO_2 and 24-h avg SO_2 estimated jointly: 2 h per 2 ppb increase SO_2 Unadjusted: 1.00 (0.87, 1.14) Adjusted: 0.96 (0.83, 1.12) 24 h per 2 ppb increase Unadjusted: 0.92 (0.71, 1.20) Adjusted: 0.91 (0.67, 1.23)
Rich et al. (2005) Boston, MA Period of Study: Jul 1995-Jul 2002	Case cross-over design used to evaluate association between ventricular arrhythmias detected by implantable cardioverter defibrillators and air pollution. Same study population as Dockery et al. (2005): 203 patients with ICD and residential zip codes within 40 km of central particle monitoring site. Analyses conducted on 84 subjects with confirmed ventricular arrhythmias during the follow-up. Case periods defined by time of each confirmed arrhythmic event. Control periods (3-4 per case) selected by matching on weekday and hour of the day within the same calendar mo. Used conditional logistic regression that controlled for temperature, dew point, barometric pressure, and a frailty term for each subject. ORs presented for IQR increase in mean concentration and averaging time. Moving avg of concentrations considered: lags 0-2, 0-6, 0-23, and 0-47 h.	1-h avg SO_2: Median: 4.3 ppb 25th %: 2.6 75th %: 7.5 Max: 71.6 24-h avg SO_2: Median: 4.8 25th %: 3.2 75th %: 7.3 Max: 31.4 Copollutants: $PM_{2.5}$ BC NO_2 CO O_3	An IQR increase in the 24-h moving avg SO_2 (4.1 ppb) marginally associated with a 9% increased risk of ventricular arrhythmia and an increased risk with 48-h moving avg. There was no risk associated with 24-h moving avg after controlling for $PM_{2.5}$ cases that had a prior ventricular arrhythmia within 72-h had greater risk associated with SO_2 compared to those without a recent event, suggesting that risk is greater among cases with more irritable or unstable myocardium. Odds ratios Single-pollutant model: 0-2-h lag (per 4.7 ppb) 1.07 (0.97, 1.18); 0-6-h lag (per 4.5 ppb) 1.09 (0.98, 1.20); 0-23-h lag (per 4.1 ppb) 1.09 (0.97, 1.22); 0-47-h lag (per 4.0 ppb) 1.17 (1.02, 1.34) 2-pollutant model: SO_2 and $PM_{2.5}$ per 4.1 ppb SO_2: 1.00 (0.84, 1.20); SO_2 and O_3 per 4.1 ppb SO_2: 1.12 (0.99, 1.27) Per 4.1 ppb increase SO_2 Prior arrhythmia event < 3 Days: 1.20 (1.01, 1.44) Prior arrhythmia event >3 Days: 0.96 (0.83, 1.10)
Rich et al. (2006b) Boston, MA Period of Study: June 1995-December 2002	Case-crossover study consisting of 203 individuals with implantable cardioverter defibrillators (ICDs) implanted between Jun 1995 and Dec 1999. Used conditional logistic regression, which included variables for mean pollutant concentration in the hour of the arrhythmia, and natural splines for mean temperature, dew point, and barometric pressure in the 24 h before the arrhythmia. The regression analyses were run for each pollutant individually to examine the association between increasing pollutant levels and paroxysmal atrial fibrillation episodes (PAF).	Max 24-h avg (ppb): 31.4 Max 1-h max (ppb): 71.6 Copollutants: $PM_{2.5}$ BC NO_2 CO O_3	O_3 was significantly associated with PAF in the hour preceding the arrhythmia, but the effect was not significant when analyzing the preceding 24-h. Increasing levels of $PM_{2.5}$, NO_2, and BC resulted in non-significant positive associations with PAF. SO_2 was not associated with PAF. Odds Ratio (per 4.9 ppb SO_2): 1.02 (0.81, 1.28) lag 0 h Odds Ratio (per 4.1 ppb SO_2): 0.99 (0.71, 1.39) lag 0-23-h

Study	Methods	Pollutant Data	Findings
Rich et al. (2006a) St. Louis, Missouri Period of Study: 5/9/2001-12/31/2002	Case-crossover design study of 56 patients with implantable cardioverter defibrillators. Subjects ranged from 20 to 88 yrs (mean 63). Case period defined by time of confirmed ventricular arrhythmia. Control periods matched on weekday and hour of the day within the same calendar mo. Used conditional logistic regression model that included mean of the previous 24-h temperature, relative humidity, barometric pressure, mean pollutant concentration in the 24 h before the arrhythmia. Model also included a frailty term for each subject.	599 days 25th %: 2 ppb 50th %: 4 ppb 75th %: 7 ppb Daily IQR: 5 ppb Case/control IQR: 5 ppb Copollutants: $PM_{2.5}$, EC, OC, NO_2 , CO, O_3	Statistically significant increase in risk of ventricular arrhythmias associated with each 5 ppm increase in 24-h moving avg SO_2. OR for ventricular arrhythmia associated with IQR increase 6-h moving avg SO_2 per 4 ppb: 1.04 (95% CI: 0.96, 1.12) 12-h moving avg SO_2 per 5 ppb: 1.17 (95% CI: 1.04, 1.30) 24-h moving avg SO_2 per 5 ppb: 1.24 (95% CI: 1.07, 1.44) 48-h moving avg SO_2 per 4 ppb: 1.15 (95% CI: 1.00, 1.34)
Sarnat et al. (2006) Steubenville, OH Period of Study: (June 4-Aug 18, Sep 25-Dec 15) 2000	Panel study consisting of 32, non-smoking older adults approximately 53-90 yrs old. Electrocardiograms (ECGs) and questionnaires regarding symptoms were administered on a weekly basis. Used a logistic mixed effects regression to examine the association between increasing air pollutant concentrations and supraventricular ectopy (SVE) and ventricular ectopy (VE).	1-day avg SO_2 24-h avg (ppb): 10.4 (8.3) Range: 1.8, 58.3 5-day moving avg 24-h avg (ppb): 10.7 (5.5) Range: 2.4, 31.3 Copollutants: $PM_{2.5}$, EC, O_3, NO_2, SO_4^{2-}, CO	$PM_{2.5}$ was significantly associated with SVE, whereas SO_4^{2-} and O_3 were marginally associated in models including 5-day moving avg pollutant concentrations. However, no pollutants were found to be associated with VE in similar models. Overall, subjects that reported previous cardiovascular conditions (e.g., myocardial infarction and hypertension) were found to be more susceptible to SVE due to increasing air pollutant concentrations. Odds Ratio (per 5.4 ppb SO_2) 5-day moving avg: SVE: 1.04 (0.78, 1.39) VE: 1.28 (0.85, 1.92)
Schwartz et al. (2005) Boston, MA Period of Study: 12 wks during the summer of 1999	Panel study of 28 subjects (aged 61-89 yrs) to examine association between summertime air pollution and HRV. Subjects examined once a wk up to 12 wks and HRV measured for approximately 30 mins. Analyses used hierarchical models that controlled for baseline medical condition, smoking history, day of wk and hour of day, indicator variable for whether subjects had taken their medication before they came, temperature and time trend.	24-h avg SO_2: 25th %: 0.017 ppm 50th %: 0.020 ppm 75th %: 0.54 ppm Copollutants: O_3 NO_2 CO $PM_{2.5}$ BC	No significant association with SO_2 Percentage change in HRV associated with IQR (0.523 ppm) increase in SO_2 1-h avg SO_2: SDNN (ms) 0.4 (−1.3 to 2.1); RMSSD (ms) 1.4 (−2.6 to 5.5); PNN50 (ms) 3.8 (−12.1 to 22.5) 24-h avg SO_2: SDNN (ms) 0.4 (−4.2 to 5.1); RMSSD (ms) −0.3 (−1.3 to 0.8); PNN50 (%) −0.2 (20.9 to 17.6); LFHFR 2.9 (−4.9 to 11.4)
Sullivan et al. (2005) King County, Washington Period of Study: 1988-1994	Case-crossover study of 5,793 confirmed cases of acute MI. Data was analyzed using simple descriptive analyses and Pearson's correlation coefficient.	9 ppb Range: 0-38 ppb Copollutants: $PM_{2.5}$ PM_{10} CO	Increases in SO_2 were not associated with MI after adjusting for relative humidity and temperature Odds Ratio (95% CI) (per 10 ppb SO_2) Averaging time: 1-h: 0.97 (0.94, 1.01); 2 h: 0.98 (0.95, 1.01); 4 h: 0.99 (0.96, 1.03); 24 h: 1.0 (0.95, 1.06)
Wheeler et al. (2006) Atlanta, Georgia Period of Study: 19992000	30 individuals with myocardial infarction or COPD were administered a questionnaire and an HRV protocol. Linear mixed-effect models were used to analyze the data.	Mean: 1.9 ppb Copollutants: $PM_{2.5}$, EC, O_3 CO, NO_2	No association with SO_2
CANADA			
Rich et al. (2004) Vancouver, British Columbia, Canada Period of Study: Feb-Dec 2000	Case-crossover analysis used to investigate association between air pollution and cardiac arrhythmia in 34 patients (aged 15-85 yrs, mean 62) with implantable cardioverter defibrillators. Study included only patients who experienced at least 1 ICD discharge during the study period. Control days were 7 days before and 7 days after day of ICD discharge. Conditional logistic regression analyses were stratified by individual.	24-h avg: 2.6 ppb SD: 1.3 ppb IQR: 1.6 ppb Copollutants: $PM_{2.5}$, EC, OC SO_4^{2-}, PM_{10}, CO NO_2, O_3	No statistically significant association between SO_2 and implantable cardioverter defibrillator discharges. However, when an analysis was stratified by season, OR for SO_2 were higher in the summer compared to winter. No quantitative results provided. Results shown in graph.

Study	Methods	Pollutant Data	Findings
Vedal et al. (2004) Vancouver, British Columbia, Canada Period of Study: 1997-2000	Retrospective, longitudinal panel study of 50 patients, aged 12-77 yrs with implantable cardioverter defibrillators. Total of 40,328 person-days over 4-yr period. GEE used to assess associations between short term increases in air pollutants and implantable cardioverter defibrillator discharges. Models controlled for temporal trends, meteorology, and serial autocorrelation.	24-h mean (SD) SO_2: 2.4 (1.2) ppb Range: 0.3, 8.1 ppb Median: 2.2 ppb 25th: 1.5 75th: 3.1 Copollutants: PM_{10} O_3 NO_2 CO	Concluded that in general no consistent effect of air pollution on cardiac arrhythmias in this population. There were no statistically significant associations between SO_2 and cardiac arrhythmias at any lag day, but positive associations at lag 2. When analysis was restricted to only patients who had at least 2 arrhythmias per yr over their period of observation (N: 16), a positive and significant association was seen with SO_2 at 2 days lag. When analysis was restricted to patients averaging 3 or more arrhythmias per yr (N: 13), there was no significant association, but a positive association was seen at 2 days lag. When stratified by season, SO_2 effects were in the in the positive direction in the winter, but in the negative direction in the summer. Authors noted results may be due to chance because of multiple comparisons or SO_2 may be surrogate for some other factor. Summer analysis: significant negative association with SO_2 at lag days 2 and 3 (data not shown). When stratified to patients with 2 or more arrhythmia event-days per yr, significant negative associations observed with SO_2 at lag of 3 days. Winter analysis: significant positive effect of SO_2 at 3 days lag (data not shown). If restricted to patients with at least 2 arrhythmias per yr, a significant positive association was seen at lags 2 and 3 days. When restricted to patients with 3 or more arrhythmia event days per yr, positive associations observed for SO_2 at lags of 2 and 3 days. No quantitative results, but % change in arrhythmia event-day rate for each SD increase in pollution concentration on log scale provided in figures.
EUROPE			
Berger et al. (2000) Erfurt, Germany Period of Study: Oct 2000-Apr 2001	Prospective panel study of 57 non-smoking men, of which 74% are ex-smokers, with coronary heart disease aged 52-76 yrs old. Subjects underwent 24-h electrocardiogram (ECG) recordings and analysis once every 4 wks. Associations analyzed using Poisson and linear regression modeling, for supraventricular and ventricular tachycardia, respectively, adjusting for trend, weekday, and meteorologic data.	24-h avg (SD) ($\mu g/m^3$): 4.1 (1.8) Range: 3.0, 11.7 Copollutants: Ultrafine Particles Accumulation Mode Particles $PM_{2.5}$ PM_{10} NO_2 CO NO	UFP, ACP, $PM_{2.5}$, and NO_2 associated with increased risk for supraventricular tachycardia and ventricular tachycardia at almost all lags. The majority of statistically significant associations was observed in the previous 24-71-h and with the 5-day moving avg. Associations were not observed for increasing concentrations of SO_2. Relative Risk (per 1.5 $\mu g/m^3$ SO_2) Supraventricular Extrasystoles: 0.92 (0.77, 1.09) lag 0. 0.98 (0.86, 1.12) lag 0-23-h 1.04 (0.93, 1.16) lag 24-47 h. 1.14 (0.98, 1.34) lag 48-71-h 0.95 (0.83, 1.09) lag 72-95-h. 1.01 (0.80, 1.27) lag 5-d avg Ventricular Extrasystoles: −2.1 (−6.1, 2.1) lag 0. −1.8 (−6.1, 2.7) lag 0 – 23-h −0.1 (−4.4, 4.4) lag 24 – 47 h. 4.5 (−0.4, 9.5) lag 48-71-h −2.2 (−6.4, 2.3) lag 72-95-h. −1.2 (−7.5, 5.5) lag 5-d avg
Henrotin et al. (2007) Dijon, France Period of Study : 1994-2004	Bi-directional case-crossover design to examine association between air pollutant and ischaemic stroke onset (2,078 cases).	Mean: 6.9 $\mu g/m^3$ SD: 7.5 Min: 0 Max: 65 Copollutants: SO_X, O_3, CO PM_{10}	SO_2 not significantly associated with occurrence of strokes Odds Ratio (95% CI) Ischaemic stroke: D0: 0.978 (0.868, 1.103). D-1: 0.978 (0.863, 1.108) D-2: 1.015 (0.902, 1.143). D-3: 1.003 (0.892, 1.127) Hemorrhagic stroke: D0: 1.099 (0.815, 1.483). D-1: 1.014 (0.747, 1.376) D-2: 0.961 (0.712, 1.297). D-3: 0.954 (0.729, 1.248)

Study	Methods	Pollutant Data	Findings
Ibald-Mulli et al. (2001) Augsburg, Germany Period of Study: 1984-85, 1987-88	Retrospective analysis of 2,607 subjects (25-64 yrs, subset of the participants of first and second MONICA survey who had valid electrocardiograms recordings in both surveys and blood pressure measurements). Used regression models for repeated measures that controlled for age, current smoking, and cardiovascular medication, BMI, total and high density lipoprotein cholesterol, temp, RH, and barometric pressure.	24-h avg SO_2 ($\mu g/m^3$) 1984-1985: Mean: 60.2 SD: 47.4 Range: 13.0, 238.2 follow up 1987-1988 Mean: 23.8 SD: 12.3 Range: 5.6, 71.1 Copollutants: TSP, CO	SO_2 and TSP associated with increases in systolic blood pressure. In the multipollutant model with TSP, the effect of TPS remained significant, but the SO_2 effect was substantially reduced. No clear association between SO_2 and CO and diastolic blood pressure was observed. Same day concentrations: mean change in systolic blood pressure per 5th to 95th percentile increase in SO_2 (per 80 $\mu g/m^3$) Same day concentrations (per 80 $\mu g/m^3$): Men (N: 1339): 0.96 (0.07, 1.85); Women (N: 1268): 0.96 (−0.46, 1.49); Men and women: 0.74 (0.08, 1.40) 5-day avgs; mean change in systolic blood pressure per 5th to 95th percentile increase in SO_2 (per 75 $\mu g/m^3$): Men: 0.97 (0.09, 1.85); Women: 1.23 (0.23, 2.22); Men and women: 1.07 (0.41, 1.73) 2-pollutant model: Men and women: 0.23 (−0.50, 0.96)
Peters et al. (1999) Augsburg, Germany Period of Study: Winter 1984-1985 Winter 1987-1988	Retrospective analysis on subsample of 2,681 subjects (25-64 yrs) of the MONICA cohort who had valid electrocardiogram readings from both surveys and no acute infections. GEE for clusters used to assess association between heart rate and air pollution. Analyses adjusted for temperature, relative humidity, and air pressure.	24-h avg SO_2 ($\mu g/m^3$) Winter 1984-85 Outside episode: Mean: 48.1 SD: 23.1 Range: 13, 103 Winter 1984-85 During episode: Mean: 200.3 SD: 26.6 Range: 160, 238 Winter: 1987-88 Mean: 23.6 SD: 12.2 Range: 6, 71 Copollutants: CO, TSP	Increases in SO_2 concentrations associated with increases in heart rate Mean change in heart rate per 5th to 95th percentile SO_2 Same day concentrations (per 80 $\mu g/m^3$ SO_2) Men: 1.02 (0.41, 1.63) Women: 1.07 (0.41, 1.73) Men and women: 1.04 (0.60, 1.49) 5-day avg (per 75 $\mu g/m^3$ SO_2) Men: 1.29 (0.68, 1.90) Women: 1.26 (0.57, 1.95) Men and women: 1.28 (0.82, 1.74)
Ruidavets et al. (2005) Toulouse, France Period of Study : 1995-1997	Cross-sectional survey of 863 randomly chosen adults (35-65 yrs) living in Toulouse (MONICA center) to examine the relationship between resting heart rate and air pollution. Resting heart rate was measured twice in a sitting position after a five minute rest. Used polytomous logistic regression models with quintiles of RHR. Final model controlled for sex, physical activity, systolic blood pressure, cardiovascular drug use, CRP, relative humidity, and season mos.	Mean SO_2: 13.3 (7.5) $\mu g/m^3$ Range: 1.3, 47.7 $\mu g/m^3$ Copollutants: NO_2, O_3	Marginally significant association between SO_2 and RHR in Q5 compared with Q1. No associations with SO_2 at 1, 2, or 3 days lag. OR based on daily levels of SO_2. OR for resting heart rate = 1.19 (95% CI: 1.02, 1.39) in 5th quintile (>75 bpm) compared to first quintile (< 60 bpm) for 5 $\mu g/m^3$ increase in SO_2 same day 0 am-12 pm. OR for resting heart rate 1.14 (95% CI: 1.01 to 1.30) in 5th quintile (>75 bpm) compared to first quintile (< 60 bpm) for 5$\mu g/m^3$ increase in SO_2 same day 12 am-12 pm Not-significant associations not listed
LATIN AMERICA			
Holguín et al. (2003) Mexico City, Mexico Period of Study: Feb 8 to Apr 30, 2000	Panel study of 34 nursing home residents (60-96 yrs) to assess association between heart rate variability and air pollution. Heart rate variability measured every alternate day for 3 mos. Thirteen of the subjects had hypertension. Used GEE models that controlled for age and avg heart rate during HRV measurement.	24-h avg SO_2 (ppb) Mean: 24 SD: 12 Range: 6, 85 Copollutants: Indoor $PM_{2.5}$ Outdoor $PM_{2.5}$ O_3, NO_2, CO	SO_2 not related to heart rate variability on the same day or lag 1 day Change in HRV per 10 ppb Beta Coefficient (95% CI) HRV-HF −0.003 (−0.035, 0.035) HRV-LF −0.004 (−0.004, 0.003) HRV-LF/HF 0.012 (−0.060, 0.082)

Table F-4. Short-term exposure to SO_2 and emergency department visits and hospital admissions for cardiovascular diseases.

Study	Methods	Pollutant Data	Findings
UNITED STATES			
Gwynn et al. (2000) New York (Buffalo; Rochester) Period of Study: May 1988-Oct 1990	Hospital Admissions Outcome(s) (ICD9): Respiratory (466, 480-486), Circulatory (401-405, 410-417), Total (minus 800) from Statewide Planning and Research Cooperative System (SPARCS) Study design: Time-series Statistical Analysis: Loess fits of temperature and relative humidity Age groups analyzed: all ages Covariates: adjustments for weather Lag(s): 0, 3	24-h avg (ppb): 12.2 Range: 1.63, 37.7 Copollutants: H^+ SO_4^{2-} PM_{10} Filled PM_{10} O_3 CO NO_2 CoH	β = 0.000245 (0.000917) t = 0.27 Relative Risk (per 7 ppb SO_2) 1.002
Koken et al. (2003) Denver, U.S. Period of Study: Jul and Aug, 1993-1997 N: 310 days	Outcome(s) (ICD9): Acute MI 410.00-410.92; Atherosclerosis 14.00-414.05; Pulmonary Heart Failure 416.0-416.9; Dysrhythmia 427.0-427.9; CHF 428.0. Discharge data from Agency for Healthcare Research and Quality (AHRQ) database. Age group analyzed: 65+ yrs Study population: 60,000 Covariates: seasonal adjustment not needed. Adjustment for temperature, dew point temperature made. Study design: Time-series Statistical analysis: GLMs to analyze frequency of admissions as a function of exposure. GEEs to estimate parameters in Poisson regression models, adjusting for overdispersion. Lag(s): 0-4 day	SO_2 24-h avg (ppb) Mean (SD): 5.7 (2.94) Min: 0.4 25th: 3.8 50th: 5.3 75th: 7.2 Max: 18.9 Copollutants: O_3 (r = −0.10) CO (r = 0.21) PM_{10} (r = 0.36) NO_2 (r = 0.46)	Effects were reported as percent change in hospitalizations based on an increment of 3.4 ppb. Single-pollutant model Dysrhythmia 8.9% (−0.34, 18.93) lag 0, adjusted for gender but not temperature SO_2 was found to be associated with cardiac dysrhythmia but not other outcomes. No association was observed for PM or NO_2 with the outcomes.
Low et al. (2006) New York City, NY Period of Study:1995-2003 N: 3,287 days	Outcome(s) (ICD): Ischemic stroke 433-434; Undetermined stroke 436; monitored intake in 11-hospitals (ER or clinic visits). Excluded stroke patients admitted for rehabilitation. Study design: Time-series Statistical Analysis: Autoregressive integrated moving avg (ARIMA) models Software package: SAS	SO_2 24-h avg (ppm) Mean (SD): 0.01098 (0.009124) Min: 0 25th: 0.005 Median: 0.009 75th: 0.014 Max: 0.096 Copollutants: : PM10 (0.042) NO2 (0.33) CO (0.303) Pollen (0.085)	At the highest concentration of SO_2 (96 ppb) in New York city over the study period the expected increase in strokes would be 0.857 visits on the day of the event. Each 1000 ppb (1 ppm) SO_2 would produce an additional 8.878 visits (SE 4.471) (p = 0.0471) for stroke.

Study	Methods	Pollutant Data	Findings
Metzger et al. (2004) Atlanta, GA Period of Study: Jan 1993-Aug 31 2000 N: 4 yrs	Outcome(s): IHD 410-414; AMI 410; Dysrhythmias 427; cardiac arrest 427.5; congestive heart failure 428; peripheral and cerebrovascular disease 433-437, 440, 443-444, 451-453; atherosclerosis 440; stroke 436. ED visits from billing records. N: 4,407,535 visits, 37 CVD visits/days # Hospitals: 31 Age groups analyzed: adults ≥ 19, elderly 56+ Statistical Analysis: Poisson regression, GLM. Sensitivity analyses using GEE and GAM (strict convergence criteria) Covariates: long-term trends, mean and dew point temp, relative humidity (cubic splines) Statistical Software: SAS Season: Warm (Apr 15-Oct 14), Cool (Oct 15-Apr 14) Lag(s): 0-3 days	SO_2 1-h max (ppb) Median: 11.0 10th-90th Range: 2.0 to 39 ppb Copollutants: PM_{10} (0.20) O_3 (0.19) NO_2 (0.34) CO (0.26) $PM_{2.5}$ (0.17) $PM_{10\text{-}2.5}$ (0.21) Ultrafine (0.24) Multipollutant models used. All models specified a priori.	Results presented for RR of an incremental increase in SO_2 of 20 ppb (a priori lag 3 day moving avg). All CVD: 1.007 (0.993, 1.022) Dysrhythmia: 1.001 (0.975, 1.028) CHF: 0.992 (0.961, 1.025) IHD: 1.007 (0.981, 1.033) PERI: 1.028 (0.999, 1.059) Finger wounds 1.007 (0.998, 1.026) Single day lag models presented graphically. No multipollutant models run for SO_2 since association was not observed in single-pollutant models.
Michaud et al. (2004) Hilo, Hawaii Period of Study: 1997-2001 N: 1385 days	Outcome(s) (ICD9): Cardiac 410-414, 425-429, Emergency visits, primary diagnosis. Study design: Time-series Statistical Analysis: Exponential regression, autocorrelation assessed by regressing square root of number of ED visits on covariates (Durbin-Watson statistic). Newey-West procedure also conducted for assessment of autocorrelation. Covariates: Temperature, humidity, interaction between SO_2 and PM Lag(s): 1-3 days	SO_2 (all hourly measurements) (ppb) Mean (SD): 1.92 (12.2) Min: 0 Max: 447 Daily SO_2 (12am-6am) (ppb) Mean (SD): 1.97 (7.12) Min: 0 Max: 108.5 Copollutants: PM	Effects were presented as relative risk based on an increment of 10 ppb and the 24-h avg SO_2 concentration. Cardiac 0.92 (0.85, 1.00) lag 3 No associations of cardiac ER visits with vog (SO_2-acidic aerosols) observed.
Moolgavkar (2000a) Cook County IL, Los Angeles County, CA, Maricopa County, AZ Period of Study: 1987-1995	Outcome(s) (ICD9): CVD 390-429; Cerebrovascular disease 430-448. Hospital admissions from CA department of health database. Age groups analyzed: 20-64, 65+ yrs Study design: Time-series N: 118 CVD admissions/days # Hospitals: NR Statistical analysis: Poisson regression, GAM Covariates: adjustment for day of wk, long-term temporal trends, relative humidity, temperature Statistical package: SPLUS Lag: 0-5 days	SO_2 24-h avg (ppb) Cook County: Min: 0.5; Q1: 4 Median: 6; Q3: 8 Max: 36 LA County: Min: 0; Q1: 1 Median: 2; Q3: 4 Max: 16 Maricopa County: Min: 0; Q1: 0.5 Median: 2; Q3: 4 Max: 14 Copollutants: PM_{10} (0.11, 0.42) $PM_{2.5}$ (0.42) (LA only) CO (0.35, 0.78) NO_2 (0.02, 0.74) O_3 (−0.37, 0.01)	Results reported for percent change in hospital admissions per 10 ppb increase in SO_2. T statistic in parentheses. CVD, 65+: Cook County: 4.0 (6.1), lag 0 3.1 (4.5), lag 0, 2-pollutant model (CO) 1.0 (1.4), lag 0, 2-pollutant model (NO_2) LA County: 14.4 (15.2), lag 0 −2.5 (−1.6), lag 0, 2-pollutant model (CO) 7.7 (5.7), lag 0, 2-pollutant model (NO_2) Maricopa County: 7.4 (4.5), lag 0 3.0 (1.8), lag 0, 2-pollutant model (CO) 3.9 (1.5), lag 0, 2-pollutant model (SO_2) Cerebrovascular Disease, 65+: Cook County: 3.1 (3.3) LA County: 6.5 (4.9) Lags 1-5 also presented. Effect size generally diminished with increasing lag time. Increase in hospital admissions (10.3 for CVD and 9.0 for cerebrovascular) also observed for the 20-64 age group.

Study	Methods	Pollutant Data	Findings
Moolgavkar (2003b) Cook County IL, Los Angeles County, CA, Maricopa County, AZ Period of Study: 1987-1995	Outcome(s) (ICD9): CVD 390-429; Cerebrovascular disease 430-448 was not considered in the reanalysis. Hospital admissions from CA department of health database. Age groups analyzed: 20-64, 65+ yrs Study design: Time-series N: 118 CVD admissions/day # Hospitals: NR Statistical analysis: Poisson regression, GAM with strict convergence criteria (10-8), GLM using natural splines Covariates: adjustment for day of wk, long-term temporal trends, relative humidity, temperature Statistical package: SPLUS Lag: 0-5 days	See original analysis (Moolgavkar, 2000) above.	Use of stringent criteria in GAM did not alter results substantially. However, increased smoothing of temporal trends attenuated results for all gases and effect size diminished with increasing lag. Results reported for incremental increase of 10 ppb SO_2. Estimated coefficient and T statistic in parentheses. GLM with 100 df (LA County) 13.67 (11.82), lag 0 6.44 (5.23), lag 1 0.23 (0.18), lag 2
Morris et al. (1995) U.S. (Chicago, Detroit, Houston, LA, Milwaukee, NYC, Philadelphia) Period of Study: 1986-1989 N: 4 yrs	Outcome(s) (ICD9): CHF 428. Daily Medicare hospital admission records. Study design: Time-series Statistical analyses: GLM, negative binomial distribution Age groups analyzed: ≥ 65 yrs Covariates: temperature, indicator variables for mo to adjust for weather effects and seasonal trends, day of wk, yr Statistical software: S-PLUS Lag(s): 0-7 days	SO_2 1-h max (ppm) Mean (SD): LA: 0.010 (0.005) Chicago: 0.025 (0.011) Philadelphia: 0.029 (0.015) New York: 0.032 (0.015) Detroit: 0.025 (0.013) Houston: 0.018 (0.009) Milwaukee: 0.017 (0.013) Copollutants: NO_2 O_3 CO Correlations of SO_2 with other pollutants strong. Multipollutant models run.	Results reported for RR of admission for CHF associated with an incremental increase in SO_2 of 0.05 ppm. CHF: LA: 1.60 (1.41, 1.82) Chicago: 1.05 (1.00, 1.10) Philadelphia: 1.01 (0.96, 1.06) New York: 1.04 (1.01, 1.08) Detroit: 1.00 (0.95, 1.06) Houston: 1.07 (0.97, 1.17) Milwaukee: 1.07 (0.99, 1.15) RR diminished in multipollutant (4 copollutants) models for all cities.
Peel et al. (2007) Atlanta, GA Period of Study: Jan 1993-Aug 2000	Outcome(s) (ICD9): IHD 410-414; dysrhythmia 427; CHF 428; peripheral vascular and cerebrovascular disease 433-437, 440, 443, 444, 451-453. Computerized billing records for ED visits. Comorbid conditions: Hypertension 401-405; diabetes 250; dysrhythmia 427, CHF 428; atherosclerosis 440; COPD 491, 492, 496; pneumonia 480-486; upper respiratory infection 460-465, 466.0; asthma 493, 786.09. # Hospitals: 31 N: 4,407,535 visits Study design: case-crossover and time-series. CVD outcomes among susceptible groups with comorbid conditions. Statistical analyses: Conditional logistic regression and Poisson GLM. Covariates: cubic splines for temperature and humidity included in models. Time independent variables controlled through design. Statistical Software: SAS Lag(s): 3 day avg, lagged 0-2 day	SO_2 1-h max (ppb) Mean (SD): 16.5 (17.1) 10th: 2 90th: 39 Copollutants: PM_{10} O_3 NO_2 CO	Results expressed as OR for association of CVD admissions with a 20 ppb incremental increase in SO_2. Case-Crossover: All CVD: 1.009 (0.995,1.024), 0-2 avg IHD: 1.013 (0.988, 1.039), 0-2 avg Dysrhythmia: 1.003 (0.975, 1.031), 0-2 avg Peripheral and Cerebrovascular: 1.024 (0.993, 1.055), 0-2 avg CHF: 0.993 (0.961, 1.026), 0-2 avg Time-series: Odds Ratio (95% CI) (per 20 ppb SO_2) All cardiovascular disease: 1.007 (0.993, 1.022) Ischemic heart disease: 1.007 (0.981, 1.003) Dysrhythmia: 1.001 (0.975, 1.028) Peripheral and cerebrovascular disease: 1.028 (0.999, 1.059) Congestive heart failure:0.992 (0.961, 1.025) Effect modification by comorbid conditions was not observed.

Study	Methods	Pollutant Data	Findings
Schwartz and Morris (1995) Detroit, MI Period of Study: 1986-1989	Outcome(s) (ICD9): IHD 410-414; CHF 428; Dysrhythmia 427. Medicare data, diagnosis at discharge. Study design: Time-series Statistical analysis: Poisson regression, GAM Age groups analyzed: 65+ yrs Covariates: adjustments for long-term patterns, temperature, humidity, days of the wk, holidays, viral infections, etc. Lag(s): 0-3, cumulative up to 3 days	SO_2 24-h avg (ppb): Mean: 25.4 IQR: 18 ppb Q2: 15 Q3: 33 # Stations: 6 Copollutants: PM_{10} (0.42) CO (0.23) O_3 (0.15)	Effects were expressed as relative risk based on an increment of 18 ppb. IHD 1.014 (1.003, 1.026) lag 0, single-pollutant 1.009 (0.994, 1.023), 2-pollutant model with PM_{10} CHF 1.002 (0.978, 1.017), single-pollutant model Risks for dysrhythmia were NR for SO_2.
Schwartz (1997) Tuscon, AZ Period of Study: Jan 1988-Dec 1990	Outcome(s) (ICD9): CVD 390-429. Ascertained from hospital discharge records. Study design: Time-series Statistical analysis: Poisson regression, GAM Age groups analyzed: 65+ Covariates: long-term and seasonal trends, day of the wk, temperature, dew point, Statistical software: S-PLUS	SO_2 24-h avg (ppb) Mean: 4.6 ppb IQR: 3.9 ppb 10th: 0.7 Q2: 2.0 Median: 3.4 Q3: 5.9 90th: 10.1 Copollutants: PM_{10} (0.095) NO_2 (0.482) CO (0.395) O_3 (−0.271)	Results were expressed as percent change based on an increment of 3.9 ppb. 0.14% (−1.3%, 1.6) No other statistically significant associations for cardiovascular outcomes were observed.
Tolbert et al. (2007) Atlanta, GA Period of Study: 1993-2004	ED Visits. Outcome(s) (ICD9): Cardiovascular (410-414, 427, 428, 433-437, 440, 443-445, 451-453); Respiratory (493, 786.07, 786.09, 491, 492, 496, 460-465, 477, 480-486, 466.1, 466.11, 466.19). Study design: Time-series Statistical Analysis: Poisson Generalized Linear Model (GLM). Statistical package: SAS Age groups analyzed: all ages Covariates: adjustment for day-of-wk, hospital entry, holidays, time, temperature, dew point temperature # Hospitals: 41 N: 238,360 (Cardiovascular); 1,072,429 (Respiratory) Lag(s): 3-day moving avg	1-h max (ppb): 14.9 Range: 1.0, 149.0 Copollutants: PM_{10} $PM_{2.5}$ O_3 NO_2 CO Sulfate Total Carbon Organic Carbon EC Water-Soluble Metals Oxygenated Hydrocarbons	Relative Risk (95% CI) (per 16.0 ppb SO_2) 1.003 (0.994, 1.011)

Study	Methods	Pollutant Data	Findings
Wellenius et al. (2005b) Birmingham, Chicago, Cleveland, Detroit, Minneapolis, New Haven, Pittsburgh, Seattle Period of Study: Jan 1986-Nov 1999 (varies slightly depending on city)	Outcome(s) IS, primary diagnosis of acute but ill-defined cerebrovascular disease or occlusion of the cerebral arteries; HS, primary diagnosis of intracerebral hemorrhage. ICD codes not provided. Hospital admissions ascertained from the Centers for Medicare and Medicaid Services. Cases determined from discharge data were admitted from the ER to the hospital. N IS: 155,503 N HS: 19,314 Study design: Time-stratified case-crossover. Control days chosen such that they fell in same mo and same day of wk. Design controls for seasonality, time trends, chronic and other slowly varying potential confounders. Statistical Analysis: 2-stage hierarchical model (random effects), conditional logistic regression for city effects in the first stage Software package: SAS Lag(s): 0-2, unconstrained distributed lags	SO_2 24 h avg (ppb) 10th: 2.17 25th: 3.57 Median: 6.22 75th: 10.26 90th: 16.17 SO_2 data not available for Birmingham, AL Copollutants: PM_{10} (0.39) CO NO_2	Results reported for percent increase in stroke admissions for an incremental increase in SO_2 equivalent to one IQR (6.69). Ischemic Stroke: 1.35 (0.43, 2.29), lag 0 Hemorrhagic Stroke: 0.68 (−1.77, 3.19) Multipollutant models not run.
Wellenius et al. (2005a) Allegheny County, PA (near Pittsburgh) Period of Study: Jan 1987-Nov 1999	Outcome(s): CHF 428. Cases are Medicare patients admitted from ER with discharge of CHF Study design: Case-crossover, control exposures same mo and day of wk, controlling for season by design. Statistical Analysis: Conditional logistic regression N: 55,019 admissions, including repeat admissions, 86% admitted ≤ 5 times Age groups analyzed: 65+ yrs (Medicare recipients) Covariates: Temperature and pressure. Effect modification by age, gender, secondary diagnosis arrhythmias, atrial fibrillation, COPD, hypertension, type 2 diabetes, AMI within 30 days, angina pectoris, IHD, acute respiratory infection. Statistical software: SAS Lag(s): 0-3	SO_2 24-h avg (ppb): Mean (SD): 14.78 (9.88) 5th: 3.98 25th: 7.70 Median: 12.24 75th: 18.98 95th: 33.93 # Stations: 10 Copollutants: PM_{10} (0.51) CO (0.54) NO_2 (0.52) O_3 (−0.19)	Effects were reported as percent change based on an increment of 11 ppb. CHF, single-pollutant models: 2.36 (1.05, 3.69) lag 0, or 2.14 (0.95, 3.35) lag 0 after adjusted to an increment of 10 ppb. CHF, 2-pollutant models: 1.35 (−0.27, 2.99), SO_2 with PM_{10} 0.10 (−1.35, 1.57), SO_2 with CO 0.68 (−0.82, 2.21), SO_2 with NO_2 2.02 (0.68, 3.37), SO_2 with O_3
CANADA			
Burnett et al. (1997b) Metropolitan Toronto (East York, Etobicoke, North York, Scarborough, Toronto, York), Canada Period of Study: 1992-1994, 388 days, summers only	Outcome(s) (ICD9): IHD 410-414; Cardiac Dysrhythmias 427; Heart failure 428. All Cardiac 410-414, 427, 428. Obtained from hospital discharge data. Population: 2.6 million residents Study design: Time-series Age groups analyzed: All # Hospitals: NR Statistical analysis: relative risk regression models, GAMs. Covariates: adjusted for long- term trends, seasonal and subseasonal variation, day of the wk, temperature, dew point Season: summer only Dose response: figures presented Lag: 1-4 days	SO_2 daily 1-h max (ppb): Mean: 7.9 CV: 64 Min: 0 25th percentile: 4 50th percentile: 7 75th percentile: 11 Max: 26 # of Stations: 4-6 (Results are reported for additional metrics including 24-h avg and daytime avg (day) Copollutants: H^+ (0.45) SO_4 (0.42) TP (0.55) FP (0.49) CP (0.44) COH (0.50) O_3 (0.18) NO_2 (0.46) CO (0.37)	Effects were expressed as relative risk based on an increment of 7.00 ppb (IQR). T ratio in parentheses. All cardiac disease Single-pollutant model 1.041 (2.66), daily max over 4 days, lag 0 Multipollutant model w/ SO_2, O_3, NO_2 Of 7.72 excess hospital admissions, 2.8% attributed to SO_2. Objective of study was to evaluate the role of particle size and chemistry on cardiac and respiratory diseases.

Study	Methods	Pollutant Data	Findings
Burnett et al. (1999) Metropolitan Toronto (East York, Etobicoke, North York, Scarborough, Toronto, York), Canada Period of Study: 1980-1994 N: 14 yrs	Outcome(s) (ICD9): IHD 410-414; Cardiac Dysrhythmias 427; Heart failure 428; All cardiac 410-414, 427, 428; Cerebrovascular Disease obtained from hospital discharge data 430-438; Peripheral Circulation Disease 440-459. Population: 2.13-2.42 million residents Study design: Time-series Statistical analysis: GAMs to estimate log RR per unit changes, stepwise regression used to select min number of air pollutants in multipollutant models. Covariates: long-term trends, seasonal variation, day of wk, temperature, and humidity. Statistical package: S-PLUS Lag(s): 0-2 days	SO_2 daily avg (ppb) Mean: 5.35 5th percentile: 0 25th percentile: 1 50th percentile: 4 75th percentile: 8 95th percentile: 17 Max: 57 Multiple day avgs used in models Copollutants: $PM_{2.5}$ (0.50) $PM_{10-2.5}$ (0.38) PM_{10} (0.52) CO (0.55) SO_2 (0.55) O_3 (−0.04)	Effects were reported as % change based on an increment of 5.35 ppb. Single-pollutant model Dysrhythmias 0.8% (−0.3, 1.9) Cerebrovascular 0.04% (−0.7, 0.8) CHF 1.93% (0.9, 2.9) IHD 2.32% (1.6, 3.1) Attributed percent increase in admissions for SO_2 was determined from multipollutant models. IHD Attributed percent increase: 0.95% Authors note SO_2 effects could be largely explained by other variables in the pollution mix as demonstrated by the multipollutant model.
Fung et al. (2005) Windsor, Ontario, Canada Period of Study: Apr 1995-Jan 2000	Outcome(s) (ICD9): CHF 428; IHD 410-414; dysrhythmias 427 and all cardiac. Hospital admissions from Ontario Health Insurance Plan records. Study design: Time-series Statistical analysis: GLM N: 11,632 cardiac admission, 4.4/day for 65+ age group Age groups analyzed: 65+, < 65 yrs Statistical Software: SPLUS Lag(s): lag 0, 2, 3 day avg	SO_2 1-h max (ppb) Mean (SD): 27.5 (16.5) Min: 0 Max: 129 IQR: 19.3 ppb Copollutants: CO (0.16) O_3 (−0.02) PM_{10} (0.22) NO_2 (0.22)	Effects were expressed as percent change of cardiac disease hospital admissions based on an increment of 19.3 ppb. Single-pollutant model: < 65 yrs: 2.3% (−1.8, 6.6) lag 0; 3.9% (−1.5, 9.6) lag 0-1; 3.4% (−3.0, 10.1) lag 0-2 ≥ 65 yrs: 2.6% (0.0, 5.3) lag 0; 4.0% (0.6, 1.6) lag 0-1; 5.6% (1.5, 9.9) lag 0-2 Inclusion of particulate matter and adjustment for meteorological variables did not change the association between SO_2 and cardiac hospitalization.
Stieb et al. (2000) Saint John, New Brunswick Canada Period of Study: July 1992-Mar 1996	Outcome(s): Angina pectoris; MI; dysrhythmia/conduction disturbance; CHF; All Cardiac. ED Visits collected prospectively. Study design: Time-series Statistical analyses: Poisson regression, GAM N: 19,821 ER visits # Hospitals: 2 Lag(s): 1-8 days	SO_2 24-h avg (ppb) Mean (SD): 6.7 (5.6) 95th: 18 Max: 60 SO_2 1-h max (ppb) Mean (SD): 23.8 (21.0) 95th: 62 Max: 161 Copollutants: CO (0.31) H_2S (−0.01) O_3 (−0.02) NO_2 (0.41) PM_{10} (0.36) $PM_{2.5}$ (0.31) H^+ (−0.24) SO_4 (0.26) COH (0.31)	Results reported for percent change in admissions based on a single-pollutant model for incremental increase in NO_2 equivalent to one IQR (8.9 ppb). Cardiac visits (p-value in parentheses): 4.9 (0.002), 1 day avg, lag 8, all yr 2.8 (0.067), 5 day avg, lag 6, May-Sept Multi-pollutant models: 4.9, (1.7, 8.2), 1 day avg, lag 8, all yr (O_3) Lags 0-10 presented graphically. All but lag 8 in single-pollutant model approximately null.

Study	Methods	Pollutant Data	Findings
Villeneuve et al. (2006a) Edmonton, Canada Period of Study: Apr 1992-Mar 2002	Outcome(s) (ICD9): Acute ischemic stroke 434, 436; hemorrhagic stroke 430, 432; transient ischemic attack (TIA) 435; Other 433, 437, 438. ED visits supplied by Capital Health. N: 12,422 Stroke Visits Catchment area: 1.5 million people Study design: Case-crossover, exposure index time compared to referent time. Time independent variables controlled in the design. Index and referent day matched by day of wk. Statistical analysis: conditional logistic regression, stratified by season and gender. Covariates: temperature and humidity Statistical software: SAS Season: Warm: Apr-Sep; Cool: Oct-Mar. Lag(s): 0, 1, 3 day avg	SO_2 24 h avg ppb: All yr Mean (SD): 2.6 (1.9) Median: 2.0 25th: 1.0 75th: 4.0 IQR: 3.0 Summer Mean (SD): 2.1 (1.6) Median: 2.0 25th: 1.0 75th: 3.0 IQR: 2 Winter Mean (SD): 3.1 (2.0) Median: 3.0 25th: 2.0 75th: 4.0 IQR: 2.0 Correlation between SO_2 and other pollutants (all yr): NO_2 (0.42) CO (0.41) O_3 (−0.25) $PM_{2.5}$ (0.22) PM_{10} (0.19)	Effects were reported as odds ratios based on an increment of 3 ppb. Acute Ischemic stroke, ≥ 65 yrs All yr OR 1.05 (0.99,1.11), lag 0 Warm OR 1.11 (1.01, 1.22), lag 0 Cold OR 1.00 (0.93, 1.09), lag 0 Effect stronger among males Hemorrhagic stroke, ≥ 65 yrs All yr: 0.98 (0.90, 1.06), lag 0 Cold: 0.94 (0.84, 1.05), lag 0 Warm: 1.03 (0.90, 1.17) Effect stronger among males Transient Cerebral Ischemic Attack, ≥ 65 yrs All yr: 1.06 (1.00, 1.12), lag 0 Cold: 1.03 (0.95, 1.11), lag 0 Warm OR 1.11 (1.02, 1.22), lag 0 2-pollutant models presented graphically. Association of SO_2 with Acute Ischemic stroke diminished with inclusion of CO and NO_2.
EUROPE			
Anderson et al. (2001) West Midlands conurbation, UK Period of Study: 1994-1996 N: 832 days	Outcome(s) (ICD9): All CVD 390-459; cardiac disease 390-429; IHD 410-414; stroke 430-438. Emergency admissions counted. Catchment area: 2.3 million Age groups analyzed: 0-14, 15-64, ≥ 65. Study design: Time-series, APHEA 2 methods Statistical analyses: GAMs for modeling non-liner dependence of some variables. Covariates: Adjusted for effects of seasonal patterns, temperature and humidity, influenza episodes, day of wk and holidays. Software package: S-PLUS Season: Interaction by warm and cool season investigated. Lag(s): 0-3 days	SO_2 24-h avg (ppb) Mean (SD): 7.2 (4.7) Min: 1.9 10th: 3.3 Median: 5.8 90th: 12.3 Max: 59.8 # of Stations: 5 sites Copollutants: PM_{10} (0.55) $PM_{2.5}$ (0.52) $PM_{2.5-10}$ (0.31) BS (0.50) SO_4 (0.19) NO_2 (0.52) O_3 (-0.22)	Results reported for % change in admissions, increment = 9 ppb (10th-90th). All CVD all ages −0.4 (−2.2, 1.5), mean lags 0 + 1 Cardiac all ages: 0.7 (−1.3, 2.8), mean lags 0 + 1 IHD ≥ 65 yrs 1.5 (−2.5, 5.6), mean lags 0 + 1 Stroke ≥ 65 yrs −5.1 (−9.6, −0.4), mean lags 0 + 1

Study	Methods	Pollutant Data	Findings
Atkinson et al. (1999b) London, England Period of Study: 1992-1994 N: 1,096 days	Outcome(s) (ICD9): All CVD 390-459; IHD 410-414. Emergency admissions obtained from the Hospital Episode Statistics (HES) database (complaints). Ages groups analyzed: 0-14 yrs, 15-64 yrs, 0-64 yrs, 65+ yrs, 65-74 yrs, 75+ yrs Study design: Time-series, hospital admission counts N: 189,109 CVD admissions Catchment area: 7 million residing in 1,600 Km^2 area of Thames basin. Statistical analyses: APHEA protocol, Poisson regression Covariates: adjusted long-term seasonal patterns, day of wk, influenza, temperature, humidity (compared alternative methods for modeling meteorological including linear, quadradic, piece-wise, spline) Season: warm season Apr-Sep, cool season remaining mos, interactions between season investigated Dose response investigated: yes, bubble charts presented Statistical package: SAS Lag: 0-3 Dose response: Bubble plots presented	SO_2 24 h avg (ppb): Mean: 21.2 SD: 7.8 Min: 7.4 10th: 13 Median: 19.8 90th: 31 Max: 82.2 10th-90th percentile: 11.2 # of Stations: 3, results averaged across stations Copollutants: PM_{10} CO SO_2 O_3 BS Correlations of SO_2 with CO, NO_2, O_3, BS ranged from 0.5-0.6 Correlation of SO_2 with O_3 negative	Results reported for % change in admissions, increment 10th-90th percentile (11.2 ppb). All CVD, all ages 1.57 (0.22, 2.93), lag 0 All CVD, 0-64 yrs 2.44 (0.3, 4.63), lag 0 All CVD, 65+ 1.72 (0.15, 3.32), lag 0 IHD, 0-64 yrs −2.03 (−5.35, 0.91), lag 2 IHD, 65+ 3.10 (0.61, 5.65), lag 0 Effect size and significance diminished in models containing SO_2 and BS.
Ballester et al. (2001) Valencia, Spain Period of Study: 1992-1996	Outcome(s) (ICD9): All CVD 390-459; heart diseases 410-414, 427, 428; cerebrovascular diseases 430-438. Admissions from city registry – discharge codes used. Study design: Time-series N: 1080 CVD admissions # of Hospitals: 2 Catchment area: 376,681 inhabitants of Urban Valencia Statistical analyses: Poisson regression, GAM, APHEA/ Spanish EMECAM protocol. Both linear and nonparametric model, including a loess term was fitted, departure from linearity assess by comparing deviance of both models. Covariates: long-term trend and seasonality, temperature and humidity, weekdays, flu, special events, air pollution. Season: Hot season May to Oct; Cold season Nov to Apr Statistical package: SAS Lag: 0-4	24 h avg ($\mu g/m^3$): Mean: 25.6 SD: NR Min: 4.4 Max: 68.4 Median: 25 # of Stations: 14 manual, 5 automatic Correlation among stations: 0.3-0.62 for BS, 0.46-0.78 for gaseous pollutants Copollutants: CO (0.74) NO_2 (0.22) O_3 (−0.35) BS (0.63) 2-pollutant models used to adjust for copollutants.	Results expressed as relative risk, increment of 10 $\mu g/m^3$. All CVD 1.0302 (1.0042, 1.0568), lag 2 Heart disease 1.0357 (1.0012, 1.0714), lag 2 Cerebrovascular disease 1.0378 (0.9844 to 1.0940), lag 5 Digestive diseases 1.0234 (0.9958, 1.0518), lag 1 All CVD, hottest semester 1.050 (1.010, 1.092), lag 2 Effect size for all CVD and cerebrovascular disease diminished in 2-pollutant models.

Study	Methods	Pollutant Data	Findings
Ballester et al. (2006) Multicity, Spain: (Barcelona, Bilbao, Castellon, Gijon, Granada, Huelva, Madrid, Oviedo, Seville, Valencia, Zaragoza) Period of Study: 1995/1996-1999 N: 1,096 days	Outcome(s) (ICD9): All CVD 390-459; Heart diseases 410-414,427,428. Emergency admission from hospital records. Discharge data used. Study design: Time-series, meta-analysis to pool cities N: Daily mean admissions reported by city. Statistical analyses: Poisson regression and GAM, with stringent convergence criteria, meta-analysis with random effect model. Tested linearity by modeling pollutant in linear and non-linear way (spline smoothing). Linear model provided best results 55% of time but used in all cases to facilitate comparability. Covariates: temperature, humidity and influenza, day of wk unusual events, seasonal variation and trend of the series Season: Hot: May to Oct; Cold: Nov to Apr Statistical package: S-PLUS Lag: 0-3	SO_2 24-h avg (μg/m^2) Mean, 10th, 90th Barcelona: 15.5, 6.6, 27.9 Bilbao: 18.6, 10.2, 29.3 Cartagena: 27.1, 14.6, 40.8 Castellon: 7.7, 3.8, 12.7 Gijon: 29.4, 10.3, 52.4 Granada: 19.1, 8.8, 31.5 Huelva: 11.9, 4.5, 22.6 Madrid: 21.8, 8.7, 41.8 Oviedo: 40.9, 16.3, 75.5 Pamplona: 7.6, 1.8, 17.0 Seville: 9.6, 5.6, 14.6 Valencia: 16.6, 9.4, 24.4 Vigo: 9.3, 2.6, 18.2 Zaragoza: 9.3, 2.0, 19.9 # of stations: depends on the city Correlation among stations: Correlations between SO_2 stations within cities poor. Copollutants: CO (0.58) O_3 (−0.03) NO_2 (0.46) BS (0.24) TSP (0.31) PM_{10} (0.46) Correlations reported are the median for all cities.	Results reported for % change in admissions, increment 10 (μg/m^3). All cardiovascular 1.33% (0.21, 2.46) lag 0-1 Heart diseases 1.72% (0.50, 2.95) lag 0-1 Single day lags presented graphically. Effect size decreased with increasing lag. Multi-pollutant results presented graphically. Control for CO and particulates diminished SO_2 effects.
D'Ippoliti et al. (2003) Rome, Italy Period of Study: Jan 1995- June 1997	Outcome(s) (ICD): AMI 410 (first episode). Computerized hospital admission data. Study design: case-crossover, time stratified, control days within same mo falling on the same day. Statistical analyses: conditional logistic regression, examined homogeneity across co-morbidity categories N: 6531 cases Age groups analyzed: 18-64 yrs, 65-74 yrd, ≥ 75 Season: Cool: Oct-Mar; Warm: Apr-Sep Lag(s): 0-4 day, 0-2 day cum avg Dose Response: OR for increasing quartiles presented and p-value for trend.	SO_2 24 h avg (μg/m^3) All yr: Mean (SD): 9.5 (6.0) 25th: 5.4 50th: 8.2 75th: 12.6 IQR: 7.2 Cold season: Mean (SD): 12.7 (6.5) Warm Season: Mean (SD): 88.3 (15.4) # Stations: 5 Copollutants: TSP (0.29) NO_2 (0.37) CO (0.56)	Results reported as odds ratios for increment equal to one IQR (7.2 μg/m^3). AMI Quartile I (referent) Quartile II: 0.987 (0.894, 1.089), lag 0-2 Quartile III: 1.008 (0.892, 1.140), lag 0-2 Quartile IV: 1.144 (0.991, 1.321), lag 0-2 Results at various lags NR for SO_2.
Llorca et al. (2005) Torrelavega, Spain Period of Study: 1992-1995	Outcome(s) (ICD): CVD (called cardiac in paper) 390-459. Emergency admissions, excluding nonresidents. Obtained admissions records from hospital admin office. Study design: Time-series Statistical analyses: Poisson regression, APHEA protocol Covariates: rainfall, temperature, wind speed direction N: 18,137 admissions Statistical software: STATA Lag(s): NR	SO_2 24 h avg μg/m^3: Mean (SD): 13.3 (16.7) Copollutants: TSP (−0.40) NO_2 (0.588) SH_2 (0.957) NO (0.544) Multipolutant models.	Results expressed as rate ratios. Increment = 100 μg/m^3. Cardiac admissions, single-pollutant model 0.94 (0.84, 1.05) Five-pollutant model 1.09 (0.83, 1.42) All cardiorespiratory admissions, single-pollutant model RR 0.98 (0.89, 1.07) Five-pollutant model 0.98 (0.80, 1.21)

Study	Methods	Pollutant Data	Findings
Poloniecki et al. (1997) London, UK Period of Study: Apr, 1987-Mar 1994, 7 yrs	Outcome(s): All CVD 390-459; MI 410; Angina pectoris 413; other IHD 414; ARR 427; congestive heart failure 428; cerebrovascular disease 430-438. Hospital Episode Statistics (HES) data on emergency hospital admissions. Study design: Time-series N: 373, 556 CVD admissions Statistical analyses: Poisson regression with GAM, APHEA protocol Covariates: long-term trends, seasonal variation, day of wk, influenza, temperature and humidity. Season: Warm, Apr-Sep; Cool, Oct-Mar Lag: 0-1	$SO_2$24 h avg ppb: Min: 0 10%: 2 Median: 6 90%: 21 Max: 1 Copollutants: BS CO 24 h avg NO_2 24 h avg O_3 8 h Correlations between pollutants high but not specified	Effects were expressed as relative risk based on an increment of 19 ppb (10th-90th percentile). Single-pollutant models (lag 0-1): MI: 1.0326 (1.0133, 1.0511) Angina: 1.0133 (0.9907, 1.0383) IHD: 0.9944 (0.9651, 1.0239) ARR: 1.0181 (1.0000, 1.0448) CHF: 1.0057 (0.9846, 1.0258) Cerebrovascular: 1.0019 (0.9837, 1.0189) All circulatory: 1.0248 (1.0062, 1.0444) MI, 2-pollutant models, cool season: 1.0399 (1.0171, 1.0628), SO_2 only 1.0285 (1.0019, 1.0571), SO_2 with NO_2 1.0380 (1.0057, 1.0704), SO_2/CO 1.0285 (1.0019, 1.0552), SO_2/BS 1.0476 (1.0209, 1.0742), SO_2 with O_3 In the warm season no significant associations were observed in 2-pollutant models.
Prescott et al. (1998) Edinburgh, UK Period of Study: Oct 1992-Jun 1995	Outcome(s) (ICD9): Cardiac and cerebral ischemia 410-414, 426-429, 434-440. Extracted from Scottish record linkage system. Study design: Time-series Statistical Analysis: Poisson, log linear regression models Age groups analyzed: < 65, 65+ yrs Covariates: Seasonal and weekday variation, temperature, and wind speed. Lag(s): 0, 1, 3 day moving avg	NO_2 24 h avg ppb Mean (SD): 8.3 (5.6) Range: 1-50 90th-10th Percentile = 12 ppb Copollutants: O_3, 24 h avg PM, 24 h avg NO_2, 24 h avg CO, 24 h avg Correlations NR.	Results reported as % increase in admissions, increment 10 ppb. All CVD, ≤ 65 yrs 4.9 (−1.0, 11.1), 3 day moving avg All CVD, ≥ 65 yrs −3.7 (−12.4, 5.9), 3 day moving avg
Sunyer et al. (2003) Europe (Birmingham, London, Milan, Paris, Rome, Stockholm, the Netherlands) Period of Study: 1990-1996	Hospital Admissions Outcome(s) (ICD9): Cardiovascular diseases (390-429); IHD (410-413); stroke (430-438) Study design: Time-series Statistical Analysis: Poisson autoregression with GAM Age groups analyzed: all ages Covariates: trend, seasonal patterns, meteorological factors Lag(s): 0 + 1	24-h median (µg/m^3): Birmingham: 19 London: 21 Milan: 18 Netherlands: 9 Paris: 15 Rome: 9 Stockholm: 5 Copollutants: PM_{10} BS NO_2 O_3	% increase in Hospital Admissions (95% CI) (per 10 µg/m^3 SO_2) Cardiovascular: All ages: 0.7 (0.3, 1.1); >65: 0.7 (0.3, 1.2) IHD: < 65: 0.6 (0.2, 1.1); >65: 1.2 (0.8, 1.6) IHD after adjustment for CO, NO_2, BS < PM_{10}: < 65: 0.7 (0.1, 1.3); >65: −1.4 (−8.0, 6.0) Stroke: >65: 0.0 (−0.5, 0.5)
Yallop et al. (2007) London, England Period of Study: Jan 1998-Oct 2001 N: >1400 days	Outcome(s): Acute pain in Sickle Cell Disease (HbSS, HbSC, HbS/∃0, thalassaemia, HbS/∃+). Admitted to hospital for at least one night. Study design: Time-series Statistical analyses: Cross-correlation function N: 1047 admissions Covariates: No adjustment made in analysis, discussion includes statement that the effects of weather variables and copollutants are inter-related. Statistical package: SPSS Lag(s): 0-2 days Dose response: quartile analysis, graphs presented, ANOVA comparing means across quartiles.	NR Copollutants: O_3 CO NO NO_2 PM_{10} Daily avg used for all copollutants.	No association for SO_2

Study	Methods	Pollutant Data	Findings
AUSTRALIA			
Jalaludin et al. (2006) Sydney, Australia Period of Study: Jan 1997-Dec 2001	Outcome(s) (ICD9): All CVD 390-459; cardiac disease 390-429; IHD 410-413; and cerebrovascular disease or stroke 430-438; Emergency room attendances obtained from health department data. Age groups included: 65+ Study design: Time-series, multicity APHEA2 Protocol. Statistical Analysis: GAM (with appropriate convergence criteria) and GLM Models. Only GLM presented. Lag: 0-3 Covariates: Daily avg temperature and daily relative, humidity, long-term trends, seasonality, weather, day of wk, public school holidays, outliers and influenza epidemics. Dose response: quartile analysis Season: Separate analyses for warm (Nov-Apr) and cool periods (May-Oct).	SO_2 24 h avg avg (ppb) Mean (SD): 1.07 (0.58) Min: 0.09 25th: 0.64 Median: 1.01 75th: 1.39 Max: 3.94 IQR: 0.75 # of Stations: 14 Copollutants: BS (0.21) PM_{10} (0.37) O_3 (0.454) NO_2 (0.52) CO (0.46)	Effects were presented as percent change based on an increment of 0.75 ppb. Single-pollutant model: All CVD, all yr: 1.33% (0.24, 2.43) lag 0 Cardiac: 1.62% (0.33, 2.93) lag 0 IHD: 1.12% (−0.84, 3.12) lag 0 Stroke: −1.41% (−3.67, 0.90) lag 0 Cool Season All cardiovascular: 2.15% (0.84, 3.46) lag 0 Cardiac: 2.48% (0.94, 4.04) lag 0 IHD: 2.49% (0.13, 4.91) lag 0 Stroke: −0.19% (−2.90, 2.60) lag 0 Warm Season All cardiovascular: 0.06% (−1.48, 1.62) lag 0 Cardiac: 0.38% (−1.37, 2.16) lag 0 IHD: −0.47% (−3.08, 2.22) lag 0 Stroke: −2.74% (−5.92, 0.55) lag 0 Results for lags 0-3 presented. In general, effect size diminished with increasing lag. Effects of SO_2 on all CVD were diminished with inclusion of PM and CO (graphically presented.)
Petroeschevsky et al. (2001) Brisbane, Australia Period of Study: Jan 1987-Dec 1994 N: 2,922 days	Outcome(s) (ICD9): CVD 390-459. Hospital admissions, non-residents excluded. Study design: Time-series Statistical analyses: Poisson regression, APHEA protocol, linear regression and GEEs Age groups analyzed: 15-64, 65+ Covariates: temperature, humidity, rainfall. Long-term trends, season, flu, day of wk, holidays. Dose response: quintile analysis. Statistical software: SAS Lag(s): lag 0-4, 3 day avg, 5 day avg	SO_2 24-h avg (pphm): Summer: mean, min, max 0.39, 0.0, 1.63 Fall: mean, min, max 0.42, 0.01, 3.55 Winter: mean, min, max 0.48, 0.0, 2.08 Spring: mean, min, max 0.37, 0.0, 6.02 Overall: mean, min, max 0.41, 0.0, 3.55 SO_2 1-h max (pphm): Summer: Mean, min, max 0.78, 0.0, 5.5 Fall: Mean, min, max 0.93, 0.05, 5.95 Winter: Mean, min, max 1.13, 0.0, 6.68 Spring: Mean, min, max 0.84, 0.0, 6.01 Overall: Mean, min, max 0.92, 0.0, 6.68 Copollutants:BSP O_3 NO_2 Correlation between pollutants NR.	Effects were expressed as relative risk based on an increment of 10 ppb and the 24-h avg SO_2 concentrations. All CVD 15 to ≥ 65 yrs: 1.028 (0.987, 1.070) lag 0 15 to 64 yrs: 1.081 (1.010, 1.158) lag 0 ≥ 65 yrs: 1.038 (0.988, 1.091) lag 1 Non-significant increasing risk for CVD in those 15-64 by quintile of SO_2 concentration observed.

Study	Methods	Pollutant Data	Findings
ASIA			
Chan et al. (2006) Taipai, Taiwan Period of Study: Apr 1997-Dec 2002 N: 2,090 days	Outcome(s) (ICD9): Cerebrovascular disease 430-437; stroke 430-434; hemorrhagic stroke 430-432; ischemic stroke 433-434. Emergency admission data collected from National Taiwan University Hospital. Ages groups analyzed: age >50 included in study Study design: Time-series N: 7341 Cerebrovascular admissions among those >50 yrs old Catchment area: Statistical analyses: Poisson regression, GAMs used to adjust for non-linear relation between confounders and ER admissions. Covariates: time trend variables: yr, mo, and day of wk, daily temperature difference, and dew point temperature. Linearity: investigated graphically by using the LOESS smoother. Lag: 0-3, cumulative lag up to 3 days	SO_2 24-h avg (ppb): Mean: 4.3 SD: 2.4 Min: 0.4 Max: 17.1 IQR: 3.1 ppb # of Stations: 16 Correlation among stations: NR. Copollutants: PM_{10} (0.59) $PM_{2.5}$ (0.51) CO (0.63) NO_2 (0.64) O_3 (0.51)	Results reported for OR for association of emergency department admissions with an IQR increase in SO_2 (3.1 ppb) Cerebrovascular: 1.008 (0.969, 1.047), lag 0 Stroke: 0.991 (0.916, 1.066), lag 0 Ischemic stroke: 1.044 (0.966, 1.125), lag 0 Hemorrhagic stroke: 0.918 (0.815, 1.021), lag 0 No significant associations for SO_2 reported. Lag 0 shown but similar null results were obtained for lags 0-3. 2-pollutant models to adjust for copollutants but not for SO_2, which was not associated with health outcomes.
Chang et al. (2005) Taipei, Taiwan Period of Study: 1997-2001 N: 5 yrs	Outcome(s) (ICD9): CVD 410-429. Daily clinic visits or hospital admission from computerized records of National Health Insurance. Discharge data. Source populatioN: 2.64 million N: 40.8 admissions/day; 74,509/5 yrs # Hospitals: 41 Study design: Case-crossover, referent day 1 wk before or after index day Statistical analyses: Conditional logistic regression. Covariates: same day temperature and humidity. Season: warm/cool (stratified by temperature cutpoint of 20 °C) Lag(s): 0-2 days	SO_2 24-h avg (ppb) Mean: 4.32 Min: 0.15 25th: 2.74 Median: 3.95 75th: 5.49 Max: 14.57 IQR: 2.75 # of Stations: 6 Copollutants: CO O_3 NO_2 PM_{10} Correlations NR. 2-pollutant models to adjust for copollutants.	Effects were expressed as odds ratios based on an increment of 2.75 ppb. Warm (≥ 20 °C) 0.967 (0.940, 0.995) Cool (< 20 °C) 1.015 (0.965, 1.069) In 2-pollutant models with (PM_{10}, NO_2, CO, or O_3) the effect of SO_2 was attenuated for both temperature ranges such that it was negatively associated with CVD. ≥ 20 °C: 0.874 (0.77, 0.880), w/ PM_{10} < 20 °C: 0.986 (0.928, 1.048), w/ PM_{10} ≥ 20 °C: 0.826 (0.798, 0.854), w/ NO_2 < 20 °C: 0.922 (0.865, 0.984), w/ NO_2 ≥ 20 °C: 0.903 (0.876, 0.931), w/ CO < 20 °C: 0.960 (0.901, 1.022), w/ CO ≥ 20 °C: 0.953 (0.926, 0.981), w/ O_3 < 20 °C: 1.014 (0.963, 1.067), w/ O_3
Lee et al. (2003b) Seoul, Korea Period of Study: Dec 1997-Dec 1999, 822-days, N: 184 days in summer	Outcome(s) (ICD10): IHD: Angina pectoris 120; Acute or subsequent MI 121-123; other acute IHD 124. Electronic medical insurance data used. Study design: Time-series Statistical methods: Poisson regression, GAM with strict convergence criteria. Age groups analyzed: all ages, 64+ Covariates: Long-term trends LOESS smooth, temperature, humidity, day of wk. Season: Presented results for summer (Jun, Jul, Aug) and entire period. Lag(s): 0-6	SO_2 24 h avg (ppb): 5th: 3.7 10th: 5.1 Median: 7.0 75th: 9.5 95th: 14.3 Mean (SD): 7.7 (3.3) IQR: 4.4 Copollutants: All yr NO_2 (0.72) O_3 (−0.30) CO (0.81) PM_{10} (0.59) Warm season NO_2 (0.79) O_3 (−0.56) CO (0.41) PM_{10} (0.61) 2-pollutant models.	Results reported for RR of IHD hospital admission for an incremental increase in SO_2 equivalent to one IQR (4.4 ppb). Single-pollutant model: Entire season- IHD All ages 0.96 (0.92, 0.99) lag 3 ≥ 64 yrs 0.95 (0.90, 1.01) lag 3 Summer- IHD All ages 1.09 (0.96, 1.24) lag 3 ≥ 64 yrs 1.32 (1.08, 1.62) lag 3 2-pollutant model: Entire season; SO_2 and PM_{10} ≥ 64 yrs 0.98 (0.94, 1.03) lag 3

Study	Methods	Pollutant Data	Findings
Tsai et al. (2003a) Kaohsiung, Taiwan Period of Study: 1997-2000	Outcome(s) (ICD9): All cerebrovascular 430-438; SHS 430;PIH 431-432; IS 433-435; Other 436-438. Ascertained from National Health Insurance Program computerized admissions records. Study design: Case-crossover Statistical Analysis: conditional logistic regression. N: 23,179 stroke admissions # Hospitals: 63 Statistical software: SAS Season: warm (≥ 20 °C); cool (< 20 °C) Lag(s): 0-2, cumulative lag up to 2 previous days	SO_2 (ppb) Min: 1.25 25th: 6.83 Median: 9.76 75th: 13.00 Max: 26.80 Mean: 10.08 # Station: 6 Copollutants: PM_{10} SO_2 CO O_3	Results reported as OR for the association of admissions with an incremental increase of SO_2 equivalent to the IQR of 6.2 ppb PIH admissions: Warm: 1.06 (0.95, 1.18), lag 0-2; Cool: 0.85 (0.58, 1.26), lag 0-2 IS admissions: Warm: 1.06 (1.00, 1.13), lag 0-2; Cool: 1.11 (0.83, 1.48), lag 0-2 2-pollutant models: PIH 0.91 (0.80, 1.03) w/ NO_2 IS 0.93 (0.87, 1.00) w/ NO_2; PIH 0.94 (0.83, 1.06), w/ CO IS 0.94 (0.88, 1.02), w/ CO PIH 1.08 (0.96, 1.20) w/ O_3 IS 1.08 (1.01, 1.15) w/ O_3 PIH 0.99 (0.88, 1.11) w/ PM IS 1.01 (0.95-1.08) w/ PM
Wong et al. (1999) Hong Kong, China Period of Study: 1994-1995	Outcome(s) (ICD9): CVD: 410-417, 420-438, 440-444; CHF 428; IHD 410-414; Cerebrovascular Disease 430-438. Hospital admissions through ER departments via Hospital Authority (discharge data). Study design: Time-series Statistical analyses: Poisson regression, APHEA protocol # Hospitals: 12 Covariates: daily temperature, relative humidity day of wk, holidays, influenza, long-term trends (yr and seasonality variables). Interaction of pollutants with cold season examined. Season: cold (Dec-Mar) Lag(s): 0-3 days	SO_2 24-h avg (µg/m^3) Mean: 20.2 IQR: 10 Copollutants: PM_{10} SO_2 O_3	Results reported for RR associated with incremental increase in NO_2 equal to 10 µg/m^3. All CVD, All ages 1.016 (1.006, 1.026) lag 0-1 All CVD, 5-65 yrs 1.004 (0.989, 1.020) lag 0-1 All CVD, >65 yrs 1.021 (1.010, 1.032) lag 0-1 CHF 1.036 (1.013, 1.059) lag 0 IHD 1.010 (0.995, 1.025) lag 0-1 Cerebrovascular 0.990 (0.978, 1.002) lag 3 2-pollutant model results not presented for SO_2
Wong et al. (2002a) Hong Kong, London Period of Study: 1995-1997 (Hong Kong), 1992-1994 (London)	Outcome(s) (ICD9): Cardiac disease 390-429; IHD 410-414. Patients admitted to hospitals from emergency departments, out patient departments or directly to inpatient wards. Statistical Analysis: Poisson regression, GAMs Covariates: smooth functions of time, temperature, humidity (up to 3 days before admission) day of wk, holidays and unusual events. Statistical software: S-PLUS Season: warm/cold Lag(s): 0-3, cumulative 0-1	SO_2 24-h avg (µg/m^3) Hong Kong Mean, all yr: 17.7 (12.3) Mean, warm: 18.3 Mean, cold: 17.2 Min: 1.1 10th: 6.2 50th: 14.5 90th: 32.8 Max: 90 London Mean, all yr: 23.7 (12.3) Mean, warm: 22.2 Mean, cold: 25.3 Min 6.2 10th: 13.2 50th: 20.6 90th: 38.1 Max: 113.6 Copollutants: Hong Kong NO_2 (0.37) PM_{10} (0.30) O_3 (−0.18) London NO_2 (0.71) PM_{10} (0.64) O_3 (−0.25)	Effects expressed as % change, increment was 10 µg/m^3 Cardiac (all ages) Hong Kong: All yr: 2.1% (1.3, 2.8) lag 0-1 Warm: 1.0% (0.0, 2.0) lag 0-1 Cold: 1.9% (1.2, 2.7) lag 0-1 London: All yr: 1.6% (1.0, 2.2) lag 0-1 Warm: 0.6% (−0.6, 1.7) lag 0-1 Cold: 1.9% (1.2, 2.7) lag 0-1 IHD (all ages) Hong Kong: All yr: 0.1% (−1.1, 1.2) lag 0-1 Warm: −0.6% (−2.0, 0.8) lag 0-1 Cold: 1.0% (−0.8, 2.8) lag 0-1 London: All yr: 1.7% (0.8, 2.6) lag 0-1 Warm: 1.0% (−0.6, 2.6) lag 0-1 Cold: 2.0% (0.9, 3.1) lag 0-1 Multipollutant model Cardiac (all ages) Hong Kong: SO_2 alone 2.1% (1.3, 2.8) SO_2 with NO_2 1.4% (0.4, 2.3) SO_2 with O_3 2.1% (1.4, 2.9) SO_2 with PM_{10} 2.0% (1.1, 2.8) London: SO_2 1.6% (1.0, 2.2) SO_2 with NO_2 1.4% (0.6, 2.3) SO_2 with O_3 1.6% (0.9, 2.2) SO_2 with PM_{10} 2.2% (1.2, 3.2)

Study	Methods	Pollutant Data	Findings
Yang et al. (2004b) Kaohsiung, Taiwan Period of Study: 1997-2000	Outcome(s) (ICD9): All CVD: 410-429 * (All CVD typically defined to include ICD9 codes 390-459) N: 29,661 Study design: Case-crossover Statistical Analysis: Poisson Time-series regression models, APHEA protocol # of Hospitals: 63 Season: Authors indicate not considered because the Taiwanese climate is tropical with no apparent seasonal cycle Covariates: Stratified by warm (≥ 25°) and cold (< 25°) days, temperature, and humidity measurements included in the model Statistical package: SAS Lag: 0-2 days	SO_2 24-h avg (ppb) Min: 1.25 25%: 6.83 50%: 9.76 75%: 13.00 Max: 26.80 Mean: 10.08 # of Stations: 6 Correlation among stations: NR Copollutants: PM_{10} CO SO_2 O_3 8 2-pollutant models used to adjust for copollutants Correlations NR	OR's for the association of one IQR (17.08 ppb) increase in SO_2 with daily counts of CVD hospital admissions are reported All CVD (ICD9: 410-429) One-pollutant model: ≥ 25°: 0.999 (0.954, 1.047); < 25°: 1.187 (1.092, 1.291) 2-pollutant models: Adjusted for PM_{10}: ≥ 25°: 0.961 (0.917, 1.008) < 25°: 1.048 (0.960, 1.145) Adjusted for NO_2:≥ 25°: 0.921 (0.875, 0.969) < 25°: 0.711 (0.641, 0.789) Adjusted for CO: ≥ 25°: 0.831 (0.785, 0.879) < 25°: 0.996 (0.910, 1.089) Adjusted for O_3: ≥ 25°: 1.034 (0.987, 1.084) < 25°: 1.194 (1.098, 1.299)
MIDDLE EAST			
Hosseinpoor et al. (2005) Tehran, Iran Period of Study: Mar 1996-Mar 2001, 5 yrs	Outcome(s) (ICD9): Angina pectoris 413. Primary discharge diagnosis from registry databases or records. Study design: Time-series Statistical methods: Poisson regression # Hospitals: 25 Covariates: Long-term trends, seasonality, temperature, humidity, holiday, post-holiday, day of wk. Lag(s): 0-3	SO_2 24-h avg (μg/m³) Mean (SD): 73.74 (33.30) Min: 0.30 25th: 48.23 Median: 74.05 75th: 98.64 Max: 499.26 Copollutants: NO_2 CO O_3 PM_{10} Correlations NR	Results reported for relative risk in hospital admissions per increment of 10 μg/m³ SO_2. Angina 0.99995 (0.99397, 1.00507), lag 1 In a multipollutant model only CO (lag 1) was significantly associated with angina pectoris related hospital admissions.

Table F-5. Short-term exposure to SO_2 and mortality.

Study	Methods	Pollutant Data	Outcome	Findings
META ANALYSIS				
Stieb et al. (2002), (reanalysis 2003) Meta-analysis of estimates from various countries.	The lags and multiday averaging used varied Meta-analysis of time-series study results.	24-h avg ranged from 0.7 ppb (San Bernardino) to 75 ppb (Shenyang) "Representative" concentration: 9.4 ppb Copollutants: PM_{10}, O_3, NO_2, CO	All cause	Single-pollutant model (29 estimates): 1.0% (0.6, 1.3) Multipollutant model estimates (10 estimates): 0.9% (0.3, 1.4)
UNITED STATES				
Chock et al. (2000) Pittsburgh, PA Period of Study: 1989-1991	Lags: 0, 1, 2, 3 Poisson GLM. Time-series study. Numerous results	Mean NR Copollutants: PM_{10}, O_3, NO_2, CO; 2-, 5-, and 6-pollutant models	All cause; age < 75 yrs; age 75+ yrs	All cause: Age 0-75 yrs: Lag 1: 0.7% (−0.7, 2.2) Age 75+ yrs: Lag 1: −0.2% (−1.6, 1.3)

Study	Methods	Pollutant Data	Outcome	Findings
De Leon et al. (2003) New York City Period of Study: 1985-1994	Lags: 0 or 1 Poisson GAM with Stringent convergence Criteria; Poisson GLM. Time-series study.	24-h avg: 14.64 ppb Copollutants: PM_{10}, O_3, NO_2, CO; 2-pollutant models	Circulatory and cancer with and without contributing respiratory causes	Gaseous pollutants results were given only in figures. Circulatory: Age < 75 yrs: ~2% Age 75+ yrs: ~2%
Dockery et al. (1992) St. Louis, MO and Eastern Tennessee Period of Study: 1985-1986	Lag: 1 Poisson with GEE. Time-series study.	24-h avg: St. Louis: 8.9 ppb Eastern Tennessee: 5.1 ppb Copollutants: PM_{10}, $PM_{2.5}$, SO_4^{2-}, H+, O_3, NO_2	All cause	All cause: St. Louis, MO: 0.8% (−1.7, 3.2) Eastern Tennessee: 0.4% (−0.4, 1.1)
Gamble (1998) Dallas, TX Period of Study: 1990-1994	Lag: 0 Poisson GLM. Time-series study.	24-h avg: 3 ppb Copollutants: PM_{10}, O_3, NO_2, CO; 2-pollutant models	All cause; respiratory; cardiovascular	All cause: −0.8% (−3.8, 2.4) Respiratory: −1.0% (−5.8, 4.1) Cardiovascular: −0.5% (−11.4, 11.8)
Gwynn et al. (2000) Buffalo, NY May 1998-Oct 1990	Lag: 0, 1, 2, 3 Poisson GAM with Default convergence criteria. Time-series study.	24-h avg: 12.2 ppb Copollutants: PM_{10}, CoH, SO_4^{2-} , O_3, NO_2, CO, H+	All cause; respiratory; circulatory	All cause: Lag 0: −0.1% (−1.8, 1.7) Circulatory: Lag 3: 1.3% (−2.9, 5.6) Respiratory: Lag 0: 6.4% (−2.5, 16.2)
Kelsall et al. (1997) Philadelphia, PA Period of Study: 1974-1988	Lag: 0 (AIC presented for 0 through 5) Poisson GAM.	24-h avg: 17.3 ppb Copollutants: TSP, CO, NO_2, O_3	All cause; respiratory; cardiovascular	All cause: Single-pollutant: 0.8% (0.3, 1.4) With all other pollutants: 0.8% (0.1, 1.6)
Kinney and Özkaynak (1991) Los Angeles County, CA Period of Study: 1970-1979	Lag: 1 OLS (ordinary least squares) on high-pass filtered variables. Time-series study.	24-h avg: 15 ppb Copollutants: KM (particle optical reflectance), Ox, NO_2, CO; multipollutant models	All cause; respiratory; circulatory	All cause: Exhaustive multipollutant model: 0.0% (−1.1, 1.2)
Klemm and Mason (2000) Atlanta, GA Period of Study: Aug 1998-Jul 1999	Lag: 0-1 Poisson GLM using quarterly, monthly, or biweekly knots for temporal smoothing. Time-series study.	1-h max: 18.7 ppb Copollutants: $PM_{2.5}$, $PM_{10-2.5}$, EC, OC, SO_4^{2-} , NO_3−, O_3, NO_2, CO	All cause; respiratory; cardiovascular; cancer; other; age < 65 yrs; age 65+ yrs	All cause - Age 65+ yrs: Quarterly knots: 4.7% (−2.6, 12.5) Monthly knots: 3.4% (−4.1, 11.5) Bi-weekly knots: 1.0% (−6.7, 9.3)
Klemm et al. (2004) Georgia (Fulton; DeKalb counties) Period of Study: 1998-2000	Lags: 2-day avg (avg of lag 0 and lag 1) Poisson with GLM. Time-series study.	1-h max (ppb): 19.4 (13.42) Copollutants: $PM_{2.5}$, Coarse mass, O_3, NO_2, CO, Acid, Ultrafine surface area, Ultrafine count, EC, Organic carbon, SO_4,Oxygenated hydrocarbons, Nonmethane hydrocarbons, NO_3	All-cause	≥ 65 yrs old Quarterly knots (SE) β = 0.00115 (0.00092) t = 1.24 Monthly knots (SE) β = 0.00084 (0.00096) t = 0.87 Biweekly knots (SE) β = 0.00024 (0.00101) t = 0.24
Lipfert et al. (2000a) Seven counties in Philadelphia, PA area Period of Study: May 1992-Sep 1995	Lag: 0-1 Linear with 19-day weighted avg Shumway filters. Time-series study. Numerous results.	24-h avg: ~8 ppb Copollutants: PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, SO_4^{2-}, other PM indices, O_3, NO_2, CO; 2-pollutant models	All cause; respiratory; cardiovascular; all ages; age 65+ yrs; age < 65 yrs; various subregional boundaries	All-cause: Philadelphia: 0.7% (p > 0.05)

Study	Methods	Pollutant Data	Outcome	Findings
Lippmann et al. (2000); reanalysis Ito, (2003) Detroit, MI Period of Study: 1985-1990 1992-1994	Lags: 0, 1, 2, 3, 0-1, 0-2, 0-3 Poisson GAM, reanalyzed with stringent convergence criteria; Poisson GLM. Numerical SO_2 risk estimates were not presented in the re-analysis. Time-series study.	24-h avg: 1985-1990: 9.8 ppb 1992-1994: 7 ppb Copollutants: PM_{10}, $PM_{2.5}$, PM_{10}-2.5, SO_4^{2-}, H+, O_3, NO_2, CO; 2-pollutant models	All cause; respiratory; circulatory; cause-specific	Poisson GAM: All cause: 1985-1990: Lag 1: 0.5% (−1.5, 2.4) 1992-1994: Lag 1: 1.1% (−1.4, 3.6)
Mar et al. (2000; 2003) Phoenix, AZ. Period of Study: 1995-1997	Lags: 0 for all cause; 0, 1, 2, 3, 4 for cardiovascular Poisson GAM with default convergence criteria (only cardiovascular deaths were reanalyzed in 2003). Time-series study.	24-h avg: 3.1 ppb Copollutants: $PM_{2.5}$, PM_{10}, PM_{10}-2.5, CO, NO_2, O_3, and selected trace elements, ions, EC, OC, TOC, and factor analysis components	All cause, cardiovascular	Poisson GAM: All cause: Lag 0: 11.2% (−1.5, 25.6) Poisson GLM: Cardiovascular: Lag 1: 7.4% (−13.1, 32.6)
Moolgavkar et al. (1995) Philadelphia, PA Period of Study: 1973-1988	Lag: 1 Poisson GLM. Time-series study.	24-h avg: Spring: 16.8 ppb Summer: 15.7 ppb Fall: 17.8 ppb Winter: 25.4 ppb Copollutants: TSP, O_3; 2-pollutant models	All cause	All yr: 1.3% (0.8, 1.8) Spring: 1.7% (0.6, 2.9) Summer: 0.9% (−0.7, 2.5) Fall: 1.3% (0.0, 2.6) Winter: 2.0% (0.9, 3.0)
Moolgavkar (2000b; 2003b) Cook County, IL; Los Angeles County, CA; and Maricopa County, AZ Period of Study: 1987-1995	Lags: 0, 1, 2, 3, 4, 5 Poisson GAM with default convergence criteria in the original Moolgavkar (2000); GAM with stringent convergence criteria and GLM with natural splines in the 2003 re-analysis. The 2000 analysis presented total death risk estimates only in figures.	24-h avg median: Cook County: 6 ppb Los Angeles: 2 ppb Maricopa County: 2 ppb Copollutants: $PM_{2.5}$, PM_{10}, O_3, NO_2, CO; 2- and 3-pollutant models	Cardiovascular; cerebrovascular; COPD	GLM (re-analysis): Cook County: All-cause: Lag 1: 2.6% (1.4, 3.8) Cardiovascular: Lag 1: 2.9% (1.0, 4.8) Los Angeles: Cardiovascular: Lag 1: 5.9% (3.0, 9.0)
Moolgavkar (2003a) Cook County, IL and Los Angeles County, CA Period of Study: 1987-1995	Lags: 0, 1, 2, 3, 4, 5 Poisson GAM with default convergence criteria. Time-series study.	24-h avg median: Cook County: 6 ppb Los Angeles: 2 ppb Copollutants: $PM_{2.5}$, PM_{10}, O_3, NO_2, CO; 2-pollutant models	All cause; cardiovascular	All cause: Cook County Single-pollutant: Lag 1: 2.6% (1.5, 3.7) With PM_{10}: Lag 1: 1.9% (0.6, 3.2) Los Angeles Single-pollutant: Lag 1: 6.9% (5.4, 8.4) With $PM_{2.5}$: Lag 1: 7.6% (3.4, 12.0)
Samet et al. (2000a; 2000b); reanalysis Dominici et al. (2003) 90 U.S. cities (58 U.S.cities with SO_2 data) Period of Study: 1987-1994	Lags: 0, 1, 2 Poisson GAM, reanalyzed with stringent convergence criteria; Poisson GLM. Time-series study.	24-h avg ranged from 0.4 ppb (Riverside) to 14.2 ppb (Pittsburgh) Copollutants: PM_{10}, O_3, NO_2, CO; multipollutant models	All cause; cardiopulmonary	Posterior means: All cause: Single-pollutant: Lag 1: 0.6% (0.3, 1.0) With PM_{10} and NO_2: Lag 1: 0.4% (−0.6, 1.4)
Schwartz (1991) Detroit, MI Period of Study: 1973-1982	Lags: 0, 1, 0-1 Poisson GEE. Time-series study.	24-h avg: 12 ppb Copollutants: TSP (predicted from extinction coefficient); 2-pollutant models	All cause	Poisson regression coefficient Single-pollutant: Lag 1: 0.863 (SE = 0.323) With TSP: Lag 1: 0.230 (SE = 0.489) (Though SO_2 levels were reported in ppb, these coefficients must have been for SO_2 in ppm.)

Study	Methods	Pollutant Data	Outcome	Findings
Schwartz (2000) Philadelphia, PA Period of Study: 1974-1988	Lag: 0 Poisson GAM model in 15 winter and 15 summer periods. The second stage regressed the TSP and SO_2 risk estimates on SO_2/TSP relationships.	24-h avg summer mean declined from 20 ppb in 1974 to 9 ppb in 1988; winter mean declined from 35 ppb in 1974 to 17 in 1988 Copollutants: TSP, extinction coefficient	All cause	Single-pollutant: 2.3% (1.6, 3.0) With TSP: 0.4% (−2.2, 3.1)
Schwartz (2004) 14 U.S. cities that had daily PM_{10} data Period of Study: 1986-1993	Lag: 1 Case-crossover design, estimating PM_{10} risks by matching by the levels of gaseous pollutants.	24-h avg median ranged from 2.2 ppb (Spokane, WA) to 39.4 ppb (Pittsburgh, PA) Copollutants: PM_{10} risk estimates computed, matched by the levels of SO_2, CO, NO_2, and O_3	All cause	SO_2 risk estimates not computed. PM_{10} risk estimates showed the largest risk estimate when matched for SO_2.
CANADA				
Burnett et al. (2004) 12 Canadian cities Period of Study: 1981-1999	Lag: 1 Poisson GLM. Time-series study.	24-h avg ranged from 1 ppb (Winnipeg) to 10 ppb (Halifax) Copollutants: $PM_{2.5}$, PM_{10}-2.5, O_3, NO_2, CO	All cause	Single-pollutant: 0.7% (0.3, 1.2) With NO_2: 0.4% (0.0, 0.8)
Burnett et al. (1998a) 11 Canadian cities Period of Study: 1980-1991	Lags: 0, 1, 2, 0-1, 0-2 examined but the best lag/averaging for each city chosen Poisson GAM with default convergence criteria. Time-series study.	24-h avg ranged from 1 ppb (Winnipeg) to 11 ppb (Hamilton) Copollutants: O_3, NO_2, CO	All cause	Single-pollutant: 3.4% (2.0, 4.7) With all gaseous pollutants: 2.6% (1.3, 3.9)
Burnett et al. (1998b) Toronto Period of Study : 1980-1994	Lags: 0, 1, 0-1 Poisson GAM with default convergence criteria. Time-series study.	24-h avg: 5 ppb Copollutants: O_3, NO_2, CO, TSP, COH, estimated PM_{10}, estimated $PM_{2.5}$	All cause	Single-pollutant: Lag 0: 1.0% (0.3, 1.8) With CO: Lag 0: 0.6% (−0.4, 1.5)
Goldberg et al. (2003) Montreal, Quebec Period of Study: 1984-1993	Lags: 0, 1, 0-2 Poisson GLM with natural splines. Time-series study.	24-h avg: 6 ppb Copollutants: $PM_{2.5}$, coefficient of haze, SO42−, O_3, NO_2, CO	Congestive heart failure (CHF) as underlying cause of death versus those classified as having CHF 1 yr prior to death	CHF as underlying cause of death: Lag 1: −0.1% (−8.9, 9.6) Having CHF 1 yr prior to death: Lag 1: 5.4% (1.3, 9.5)
Vedal et al. (2003) Vancouver, British Columbia Period of Study: 1994-1996	Lags: 0, 1, 2 Poisson GAM with stringent convergence criteria. Time-series study. By season.	24-h avg: 3 ppb Copollutants: PM_{10}, O_3, NO_2, CO	All cause; respiratory; cardiovascular	Results presented in figures only. All cause: Summer: Lag 0: ~3% Winter: Lag 1: ~1%
Villeneuve et al. (2003) Vancouver, British Columbia Period of Study: 1986-1999	Lags: 0, 1, 0-2 Poisson GLM with natural splines. Time-series study.	24-h avg: 5 ppb Copollutants: $PM_{2.5}$, PM_{10}, PM_{10}-2.5, TSP, coefficient of haze, SO42−, O_3, NO_2, CO	All cause; respiratory; cardiovascular; cancer; SES	All yr: All cause: Lag 1: 1.7% (−1.1, 4.5) Cardiovascular: Lag 1: 1.1% (−3.1, 5.4) Respiratory: Lag 1: 8.3% (0.6, 16.6)
EUROPE				
Anderson et al. (1996) London, England Period of Study: 1987-1992	Lag: 1 Poisson GLM. Time-series study.	24-h avg: 11 ppb Copollutants: BS, O_3, NO_2; 2-pollutant models	All cause; respiratory; cardiovascular	All cause: 1.0% (0.0, 2.0) Respiratory: 1.7% (−1.3, 4.9) Cardiovascular: 0.2% (−1.4, 1.8)

Study	Methods	Pollutant Data	Outcome	Findings
Anderson et al. (2001) West Midlands region, England Period of Study: 1994-1996	Lag: 0-1 Poisson GAM with default convergence criteria. Time-series study.	24-h avg: 7.2 ppb Copollutants: PM_{10}, $PM_{2.5}$, PM_{10}-2.5, BS, SO42−, O_3, NO_2, CO	All cause; respiratory; cardiovascular	All cause: −0.2% (−2.5, 2.1) Respiratory: −2.2% (−7.4, 3.2) Cardiovascular: −0.2% (−3.5, 3.1)
Ballester et al. (2002) 13 Spanish cities Period of Study: 1990-1996	Lags: 0-1 for 24-h avg SO_2; 0 for 1-h max SO_2 Poisson GAM with default convergence criteria. Time-series study.	24-h avg SO_2 ranged from 2.8 ppb (Sevilla) to 15.6 ppb (Oviedo) Copollutants: TSP, BS, PM_{10}	All cause, cardiovascular, respiratory	All cause: Lag 0-1: 1.4% (0.2, 2.7) Cardiovascular: Lag 0-1: 1.4% (−0.4, 3.3) Respiratory: Lag 0-1: 3.5% (1.0, 6.0)
Biggeri et al. (2005) 8 Italian cities Period of study variable between 1990-1999	Lag: 0-1 Poisson GLM. Time-series study.	24-h avg ranged from 2 ppb (Verona) to 14 ppb (Milan) Copollutants: O_3, NO_2, CO, PM_{10}	All cause; respiratory; cardiovascular	All cause: 4.1% (1.1, 7.3) Respiratory: 7.4% (−3.6, 19.6) Cardiovascular: 4.9% (0.4, 9.7)
Bremner et al. (1999) London, England Period of Study : 1992-1994	Lags: Selected best from 0, 1, 2, 3, (all cause); 0, 1, 2, 3, 0-1, 0-2, 0-3 (respiratory, cardiovascular) Poisson GLM. Time-series study.	24-h avg: 7 ppb Copollutants: BS, PM_{10}, O_3, NO_2, CO; 2-pollutant models	All cause; respiratory; cardiovascular; all cancer; all others; all ages; age specific (0-64, 65+, 65-74, 75+ yrs)	All cause: Lag 1: 1.6% (−0.5, 3.7) Respiratory: Lag 2: 4.8% (−0.2, 10.0) Cardiovascular Lag 1: 1.3% (−1.7, 4.3)
Clancy et al. (2002) Dublin, Ireland Period of Study:` 1984-1996	NA Comparing standardized mortality rates for 72 mos before and after the ban on coal sales in Sep 1990.	24-h avg: 1984-1990: 11.7 ppb 1990-1996: 7.7 ppb Copollutants: BS	All cause, cardiovascular, and respiratory	BS mean declined by a larger percentage (70%) than SO_2 (34%) between the two periods. All cause death rates reduced by 5.7% (4, 7); respiratory deaths by 15.5% (12, 19); cardiovascular deaths by 10.3% (8, 13).
Dab et al. (1996) Paris, France Period of Study : 1987-1992	Lag: 1 Poisson autoregressive. Time-series study.	24-h avg: 11.2 ppb 1-h max: 22.5 ppb Copollutants: BS, PM_{13}, O_3, NO_2, CO	Respiratory	Lag 1: 2.3% (−0.9, 5.5)
Díaz et al. (1999) Madrid, Spain Period of Study: 1990-1992	Lag: 1 Autoregressive OLS regression. Time-series study.	24-h avg: Levels NR. Copollutants: TSP, O_3, NO_2, CO	All cause; respiratory; cardiovascular	Only significant regression coefficients were shown, but description of the table was not clear enough to derive risk estimates.
Fischer et al. (2003) The Netherlands Period of Study: 1986-1994	Lags: 0-6 Poisson GAM with default convergence criteria. Time-series study.	24-h avg median: 3.5 ppb Copollutants: PM_{10}, BS, O_3, NO_2, CO	All-cause, cardiovascular, COPD, and pneumonia in age groups < 45, 45-64, 65-74, 75+	Cardiovascular: Age < 45 yrs: 4.3% (−4.6, 13.9); Age 45-64 yrs: −0.5% (−3.6, 2.7); Age 65-74 yrs: 1.6% (−0.8, 4.2); Age 75+ yrs: 2.8% (1.3, 4.3)

Study	Methods	Pollutant Data	Outcome	Findings
Garcia-Aymerich et al. (2000) Barcelona, Spain Period of Study: 1985-1989	Selected best averaged lag Poisson GLM. Time-series study.	Levels NR. Copollutants: BS, O_3, NO_2	All cause; respiratory; cardiovascular; general population; patients with COPD	All cause: General population: Lag 0-3: 4.4% (2.3, 6.5); COPD patients: Lag 0-2: 2.6% (−5.0, 10.7) Respiratory: General population: Lag 0-1: 3.5% (−0.6, 7.8) COPD patients: Lag 0-2: 2.3% (−8.9, 15.0) Cardiovascular: General population: Lag 0-3: 5.1% (2.3, 8.0) COPD patients: Lag 0-2: 2.0% (−11.5, 17.5)
Hoek et al. (1997) Rotterdam, the Netherlands Period of Study: 1983-1991	Lag: 1 Poisson GAM with default convergence criteria. Time-series study.	24-h avg median: 7.7 ppb Copollutants: TSP, BS, Fe, O_3, CO	All cause	Single-pollutant:1.5% (0.0, 3.0) With TSP and O_3: 0.5% (−1.2, 2.3)
Hoek et al. (2001; reanalysis 2003) The Netherlands: Entire country, four urban areas Period of Study: 1986-1994	Lag: 1, 0-6 Poisson GAM, reanalyzed with stringent convergence criteria; Poisson GLM. Time-series study.	24-h avg median: 3.5 ppb in the Netherlands; 5.6 ppb in the four major cities Copollutants: PM_{10}, BS, SO_4^{2-}, NO_3-, O_3, NO_2, CO; 2-pollutant models	All cause; COPD; pneumonia; cardiovascular	Poisson GLM: All cause: Lag 1: 1.3% (0.7, 1.9) Lag 0-6: 1.8% (0.9, 2.7) With BS: 1.1% (−0.3, 2.4) Cardiovascular: Lag 0-6: 2.7% (1.3, 4.1) COPD: Lag 0-6: 3.6% (−0.3, 7.7) Pneumonia: Lag 0-6: 6.6% (1.2, 12.2)
Hoek et al. (2001); reanalysis Hoek (2003) The Netherlands Period of Study: 1986-1994	Lag: 0-6 Poisson GAM, reanalyzed with stringent convergence criteria; Poisson GLM. Time-series study.	24-h avg median: 3.5 ppb in the Netherlands; 5.6 ppb in the four major cities Copollutants: PM_{10}, O_3, NO_2, CO	Total cardiovascular; myocardial infarction; arrhythmia; heart failure; cerebrovascular; thrombosis-related	Poisson GLM: Total cardiovascular: 2.7% (1.3, 4.1) Myocardial infarctioN: 0.8% (−1.2, 2.8) Arrhythmia: 2.3% (−3.9, 8.8) Heart failure: 7.1% (2.6, 11.7) Cerebrovascular: 4.4% (1.4, 7.5) Thrombosis-related: 9.6% (3.1, 16.6)
Katsouyanni et al. (1997) 12 European cities Period of Studys vary by city, ranging from 1977 to 1992	“Best” lag variable across cities from 0 to 3 Poisson autoregressive. Time-series study.	24-h avg median of the median across the cities was 14 ppb, ranging from 5 ppb (Bratislava) to 26 ppb (Cracow) Copollutants: BS, PM_{10}	All cause	All cities: 1.1% (0.9, 1.4) Western cities: 2.0% (1.2, 2.8) Central eastern cities: 0.5% (−0.4, 1.4)

Study	Methods	Pollutant Data	Outcome	Findings
Keatinge and Donaldson (2006) London, United Kingdom Period of Study: 1991-2002	Lags: Mean of 0, −1, −2 Graphic analysis and GAM. Time-series study.	24-h avg: Levels NR Copollutants: O_3, PM_{10}	All-cause	Relative Risk for a 10^6 Increase in Mortality (per 10 ppb SO_2) SO_2 + Temp: 3.1 (0.6, 5.5) SO_2 + Temp + Acclim.: 2.2 (−0.1, 4.6) SO_2 + Temp + Acclim. + Acclim. x Temp: 2.5 (0.2, 4.8) SO_2 + Temp + Acclim. + Acclim. x Temp + Sun: 2.3 (−0.03, 4.5) SO_2 + Temp + Acclim. + Acclim. x Temp + Sun + Wind: 1.6 (−0.7, 3.8) SO_2 + Temp + Acclim. + Acclim. x Temp + Sun + Wind + Abs. Humidity: 1.7 (−0.6, 3.9) SO_2+ Temp + Acclim. + Acclim. x Temp + Sun + Wind + Abs. Humidity + Rain: 1.8 (−0.4, 4.1) SO_2 + Temp. + Abs. Humidity: 2.5 (0.03, 4.9)
Kotesovec et al. (2000) Northern Bohemia, Czech Republic Period of Study: 1982-1994	Lags: 0, 1, 2, 3, 4, 5, 6, 0-6 Poisson GLM, time-series study	24-h avg: 34.9 ppb Copollutants: TSP	All cause, cardiovascular (only age = < 65 presented), cancer	All cause: Lag 1: 0.1% (−0.1, 0.4)
Le Tertre et al. (2002) Bordeaux , Le Havre, Lille, Lyon, Marseille, Paris, Rouen, Strasbourg, France Period of Study varies by city, ranging from 1990-1995	Lags: 0-1 Poisson GAM with default convergence criteria. Time-series study.	24-h avg ranged from 3 ppb (Bordeaux) to 9 ppb (Rouen) Copollutants: BS, O_3, NO_2	All cause; respiratory; cardiovascular	8-city pooled estimates: All cause: 2.0% (1.2, 2.9) Respiratory: 3.2% (0.1, 6.3) Cardiovascular: 3.0% (1.5, 4.5)
Michelozzi et al. (1998) Rome, Italy Period of Study: 1992-1995	Lags: 0, 1, 2, 3, 4 Poisson GAM with default convergence criteria. Time-series study.	24-h avg: 5.7 ppb Copollutants: PM_{13}, NO_2, O_3, CO	All-cause	Lag 1: −2.0% (−4.4, 0.5); (negative estimates at all lags examined)
Peters et al. (2000b) NE Bavaria, Germany 1982-1994 Coal basin in Czech Republic Period of Study: 1993-1994	Lags: 0, 1, 2, 3 Poisson GLM. Time-series study.	24-h avg: Czech Republic: 35 ppb Bavaria, Germany: 14 ppb Copollutants: TSP, PM_{10}, O_3, NO_2, CO	All cause; respiratory; cardiovascular; cancer	Czech Republic: All cause: Lag 1: 0.8% (−0.2, 1.8) Bavaria, Germany: All cause: Lag 1: 0.3% (−0.3, 0.9)
Pönkä et al. (1998) Helsinki, Finland Period of Study: 1987-1993	Lags: 0, 1, 2, 3, 4, 5, 6, 7 Poisson GLM. Time-series study.	24-h avg median: 3.5 ppb Copollutants: TSP, PM_{10}, O_3, NO_2	All cause; cardiovascular; age < 65 yrs, age 65+ yrs	No risk estimate presented for SO_2. PM_{10} and O_3 were reported to have stronger associations.

Study	Methods	Pollutant Data	Outcome	Findings
Prescott et al. (1998) Edinburgh, Scotland Period of Study: 1992-1995	Lag: 0 Poisson GLM. Time-series study.	24-h avg: 1981-1995: 15 ppb 1992-1995: 8 ppb Copollutants: BS, PM_{10}, O_3, NO_2, CO; 2-pollutant models	All cause; respiratory; cardiovascular; all ages; age < 65 yrs; age 65+ yrs	Results presented as figures only. Essentially no associations in all categories. Very wide confidence intervals.
Rahlenbeck and Kahl (1996) East Berlin, Germany Period of Study: 1981-1989	Lags: 0, 1, 2, 3, 4, 5 OLS, with log of SO_2, Time-series study.	24-h avg: 61.9 ppb "SP" (beta absorption)	All cause	Single-pollutant: Lag 1: 4.4% (0, 8.7); With SP: Lag 1: 2.9% (−2.7, 8.5)
Roemer and van Wijinen (2001) Amsterdam, the Netherlands Period of Study:` 1987-1998	Lags: 1, 2, 0-6 Poisson GAM with default convergence criteria (only one smoother). Time-series study.	24-h avg: Background sites: 3.1 ppb Traffic sites: 4.2 ppb Copollutants: BS, PM_{10}, O_3, NO_2, CO	All cause	Total population using background sites: Lag 1: 2.6% (−0.6, 5.8) Traffic population using background sites: Lag 1: 0.6% (−6.9, 8.6) Total population using traffic sites: Lag 1: 2.4% (−0.3, 5.1)
Saez et al. (1999) Barcelona, Spain Period of Study: 1986-1989	Lags: 0-1 Poisson with GEE. Time-series study.	Levels NR. Copollutants: BS, O_3, NO_2,	Asthma mortality; age 2-45 yrs	RR = 1.9 (0.7, 4.4)
Saez et al. (2002) Seven Spanish cities Variable periods of study between 1991 and 1996	Lags: 0-3 Poisson GAM with default convergence criteria. Time-series study.	Values for SO_2 NR. Copollutants: O_3, PM, NO_2, CO	All cause; respiratory; cardiovascular	Risk estimates for SO_2 was NR. Including SO_2 in regression model did not appear to reduce NO_2 risk estimates.
Spix and Wichman (1996) Koln, Germany Period of Study: 1977-1985	Lags: 0, 1, 0-3 Poisson GLM. Time-series study.	24-h avg: 15 ppb 1-h max: 32 ppb Copollutants: TSP, PM_7, NO_2	All-cause	Lag 1: 0.8% (0.2, 1.4)
Sunyer et al. (2002) Barcelona, Spain Period of Study:` 1986-1995	Lags: 0-2 Conditional logistic (case-crossover)	24-h avg median: 6.6 ppb Copollutants: PM_{10}, BS, NO_2, O_3, CO, pollen	All cause, respiratory, and cardiovascular mortality in a cohort of patients with severe asthma	Odds ratio: Patients with 1 asthma admission: All cause: 14.8% (−19.8, 64.4) Patients with more than 1 asthma adm: All cause: 50.4% (−48.6, 340.4) Patients with more than 1 asthma or COPDadm: All cause: 20.2% (−17.5, 75.0) NO_2 and O_3 were more strongly associated with outcomes than SO_2.
Sunyer et al. (1996) Barcelona, Spain Period of Study: 1985-1991	Selected best single-day lag Autoregressive Poisson. Time-series study.	24-h avg median: Summer: 13 ppb Winter: 16 ppb Copollutants: BS, NO_2, O_3	All cause; respiratory; cardiovascular; all ages; age 70+ yrs	All yr, all ages: All cause: Lag 1: 3.5% (1.9, 5.1) Respiratory: Lag 0: 3.5% (−0.2, 5.0) Cardiovascular: Lag 1: 2.2% (0.5, 3.9)
Verhoeff et al. (1996) Amsterdam, the Netherlands Period of Study: 1986-1992	Lags: 0, 1, 2 Poisson GLM. Time-series study.	24-h avg: 4.5 ppb Copollutants: BS, PM_{10}, O_3, CO; multipollutant models	All cause; all ages; age 65+ yrs	Single-pollutant: Lag 1: 1.4% (−1.4, 4.2) With BS: −3.7% (−8.1, 0.9)

Study	Methods	Pollutant Data	Outcome	Findings
Zeghnoun et al. (2001) Rouen and Le Havre, France Period of Study: 1990-1995	Lags: 0, 1, 2, 3, 0-3 Poisson GAM with default convergence criteria. Time-series study.	24-h avg: Rouen: 10 ppb Le Havre: 12 ppb Copollutants: NO_2, BS, $PM_{13,}$ O_3	All cause; respiratory; cardiovascular	All cause: Rouen: Lag 1: 2.3% (−1.1, 5.9) Le Havre: Lag 1: 1.1% (−0.3, 2.5)
Zmirou et al. (1996) Lyon, France Period of Study : 1985-1990	Lags: Selected best from 0, 1, 2, 3 Poisson GLM. Time-series study.	24-h avg: 16 ppb Copollutants: PM_{13}, NO_2, O_3	All cause; respiratory; cardiovascular; digestive	All cause: Lag 0: 3.4% (1.4, 5.4) Respiratory: Lag 3: 2.8% (0.9, 4.8) Cardiovascular: Lag 0-3: 4.5% (2.0, 7.0)
Zmirou et al. (1998) 10 European cities Period of Studys vary by city, ranging from 1985-1992	Lags: 0, 1, 2, 3, 0-1, 0-2, 0-3 (best lag selected for each city) Poisson GLM. Time-series study.	24-h avg: Cold Season: Ranged from 12 ppb (London) to 87 ppb (Milan) ppb Warm Season: Ranged from 5 ppb (Bratislava) to 21 ppb (Cracow) in warm season Copollutants: BS, TSP, NO_2, O_3	Respiratory; cardiovascular	Western cities: Respiratory: 2.8% (1.7, 4.0) Cardiovascular: 2.3% (0.9, 3.7) Central eastern cities: Respiratory: 0.6% (−1.1, 2.3) Cardiovascular: 0.6% (0.0, 1.1)
AUSTRALIA				
Simpson et al. (1997) Brisbane, Australia Period of Study: 1987-1993	Lag: 0 Autoregressive Poisson with GEE. Time-series study.	24-h avg: 4.2 ppb 1-h max: 9.6 ppb Copollutants: PM10, bsp, O3, NO2, CO	All cause; respiratory; cardiovascular	All cause: All yr: Lag 0: −2.8% (−2.7, 8.6) Summer: Lag 0: 2.8% (−8.3, 15.2) Winter: Lag 0: 2.8% (−3.9, 9.8)
LATIN AMERICA				
Borja-Aburto et al. (1998) SW Mexico City Period of Study: 1993-1995	Lags: 0, 1, 2, 3, 4, 5, and multiday avg. Poisson GAM with default convergence criteria (only one smoother). Time-series study.	24-h avg: 5.6 ppb Copollutants: $PM_{2.5}$, O_3, NO_2; 2-pollutant models	All cause; respiratory; cardiovascular; other; all ages; age >65 yrs	SO_2 risk estimates NR. $PM_{2.5}$ and O_3 were associated with mortality.
Borja-Aburto et al. (1997) Mexico City Period of Study: 1990-1992	Lags: 0, 1, 2 Poisson iteratively weighted and filtered least-squares method. Time-series study.	24-h avg median: 5.3 ppb Copollutants: TSP, O_3 CO; 2-pollutant models	All cause; respiratory; cardiovascular; all ages; age < 5 yrs; age >65 yrs	All-cause: Lag 0: 0.2% (−1.1, 1.5) Cardiovascular: Lag 0: 0.7% (−1.6, 3.0) Respiratory: Lag 0: −1.0% (−5.0, 3.2)
Cakmak et al. (2007b) 7 Chilean urban centers Period of Study: 1997-2003	Lags: 0, 1, 2, 3, 4, 5, 0-5 Poisson GLM with random effects between cities. Time-series study.	24-h avg ranged from 9.12 ppb (Las Condes) to 64.06 ppb (Independencia) Population-weighted avg concentration: 14.08 ppb Copollutants: PM_{10}, O_3, CO	All cause; respiratory; cardiovascular; all ages; age < 65 yrs; age 65-74 yrs; age 75-84 yrs; age 85+ yrs	All cause: All ages: Single-pollutant: Lag 1: 4.0% (2.4, 5.6) Lag 0-5: 6.5% (4.5, 8.5) Multipollutant: Lag 1: 3.2% (1.3, 5.1) < 65 yrs: Lag 0-5: 3.0% (0.6, 5.5) 65-74 yrs: Lag 0-5: 5.1% (1.2, 9.1 75-84 yrs: Lag 0-5: 7.8% (4.1, 11.6) 85+ yrs: 7.8% (4.2, 11.5) Warm Season: Lag 0-5: 7.2% (4.1, 10.3) Cool Season: Lag 0-5: 3.0% (-0.4, 6.5)

Study	Methods	Pollutant Data	Outcome	Findings
Cifuentes et al. (2000) Santiago, Chile Period of Study: 1988-1966	Lags: 1-2 Poisson GAM with default convergence criteria; Poisson GLM. Time-series study.	24-h avg: 18.1 ppb Copollutants: $PM_{2.5}$, PM_{10}-2.5, CO, NO_2, O_3	All cause	Poisson GLM: Single-pollutant: Lag 1-2: 0.2% (−0.9, 1.3) With other pollutants: Lag 1-2: −0.6% (−1.7, 0.5)
Conceição et al. (2001) São Paulo, Brazil Period of Study: 1994-1997	Lag: 2 Poisson GAM with default convergence criteria. Time-series study.	24-h avg: 7.4 ppb Copollutants: PM_{10}, CO, O_3	Child mortality (age under 5 yrs)	Single-pollutant: Lag 2: 17.0% (7.0, 28.0); With all other pollutants: Lag 2: 13.7% (−1.1, 30.8)
Loomis et al. (1999) Mexico City Period of Study: 1993-1995	Lags: 0, 1, 2, 3, 4, 5, 3-5 Poisson GAM with default convergence criteria. Time-series study.	24-h avg: 5.6 ppb Copollutants: $PM_{2.5}$, O_3	Infant mortality	SO_2 risk estimates NR. $PM_{2.5}$ and O_3 were associated with mortality.
Ostro et al. (1996) Santiago, Chile Period of Study: 1989-1991	Lag: 0 OLS, Poisson. Time-series study.	1-h max: 60 ppb Copollutants: PM_{10}, O_3, NO_2; 2-pollutant models	All cause	Lag 0: 0.7% (−0.3, 1.7)
Pereira et al. (1998) São Paulo, Brazil Period of Study: 1991-1992	Lag: 0 Poisson GLM. Time-series study.	24-h avg: 6.6 ppb Copollutants: PM_{10}, O_3, NO_2, CO	Intrauterine mortality	Single-pollutant model: 11.5% (−0.3, 24.7) With other pollutants: 8.6% (−8.7, 29.3)
Saldiva et al. (1994) São Paulo, Brazil Period of Study: 1990-1991	Lags: 0-2 OLS of raw or transformed data. Time-series study.	24-h avg: 6.0 ppb Copollutants: PM_{10}, O_3, NO_2, CO; multipollutant models	Respiratory; age < 5 yrs	−1.0% (−47.1, 45.1)
Saldiva et al. (1995) São Paulo, Brazil Period of Study: 1990-1991	Lag: 0-1 OLS; Poisson with GEE. Time-series study.	24-h avg: 6.5 ppb Copollutants: PM_{10}, O_3, NO_2, CO; 2-pollutant models	All cause; age 65+ yrs	Single-pollutant: 8.5% (1.3, 15.6) With other pollutants: −3.1% (−13.0, 6.9)
ASIA				
Ha et al. (2003) Seoul, Korea Period of Study: 1995-1999	Lag: 0 Poisson GAM with default convergence criteria. Time-series study.	24-h avg: 11.1 ppb Copollutants: PM_{10}, O_3, NO_2, CO	All cause; respiratory; postneonatal (1 mo to 1 yr); age 2-64 yrs; age 65+	All cause: Postneonates: 11.3% (4.0, 19.1) Age 65+ yrs: 3.2% (3.1, 3.3)
Hong et al. (2002) Seoul, Korea Period of Study: 1995-1998	Lag: 2 GAM with default convergence criteria. Time-series study.	24-h avg (ppb): 12.1 (7.4) Copollutants: $PM_{10,}$ NO_2 CO, O_3	Stroke	% increase (per 5.7 ppb SO_2) 2.9% (0.8, 5.0) lag 2 Stratified by PM_{10} (Median: 47.4 µg/m³) <Med: 1.3% ≥ Med: 3.8%
Hong et al. (2002) Seoul, Korea Period of Study: 1995-1998	Lag: 2 Poisson GAM with default convergence criteria. Time-series study.	24-h avg: 12.1 ppb Copollutants: PM_{10}, O_3, NO_2, CO	Acute stroke mortality	5.2% (1.4, 9.0)

Study	Methods	Pollutant Data	Outcome	Findings
Kwon et al. (2001) Seoul, Korea Period of Study: 1994-1998	Lag: 0 Poisson GAM with default convergence criteria; case-crossover analysis using conditional logistic regression.	24-h avg: 13.4 ppb Copollutants: PM_{10}, O_3, NO_2, CO	Mortality in a cohort of patients with congestive heart failure	Odds ratio in general population: 1.0% (−0.1, 2.1) Congestive heart failure cohort: 6.9% (−3.4, 18.3)
Lee et al. (2000) Seoul, Korea Period of Study: 2000-2004	Lag: 1 GAM with stringent convergence criteria. Time-series study.	24-h avg (ppb): 5.20 (2.17) Copollutants: PM_{10}, CO, NO_2, O_3	Non-accidental	% Increase (per 3.06 ppb SO_2) 2.7 (1.8, 3.5) lag 1
Lee et al. (1999) Seoul and Ulsan, Korea Period of Study: 1991-1995	Lags: 0-2 Poisson with GEE. Time-series study.	1-h max: Seoul: 26 ppb Ulsan: 31 ppb Copollutants: TSP, O_3	All cause	Seoul: 1.5% (1.1, 1.9) Ulsan: 1.0% (−0.2, 2.2)
Lee and Schwartz (1999) Seoul, Korea Period of Study: 1991-1995	Lags: 0-2 Conditional logistic regression. Case-crossover with bidirectional control sampling.	1-h max: 26 ppb Copollutants: TSP, O_3	All cause	Two controls, ± 1 wk: 0.3% (−0.5, 1.0) Four controls, ± 2 wks: 1.0% (0.3, 1.6)
Lee et al. (2007) 7 Korean cities Period of Study: 1991-1997	Lags: 0-1 Poisson GAM with default convergence criteria. Time-series study.	24-h avg SO_2 ranged from 12.1 ppb (Kwangju) to 31.4 ppb (Taegu) Copollutants: TSP, NO_2, O_3, CO	All cause	Single-pollutant : Lag 0-1 : 0.6% (0.3, 0.8) Multipollutant : Lag 0-1 : 0.6% (0.2, 0.9)
Qian et al. (2007) Wuhan, China Period of Study : 2000-2004	Lag: 0 Poisson GAM with stringent convergence criteria. Time-series study.	24-h avg (μg/m³): 44.1 (25.3) Copollutants: PM_{10} NO_2 O_3	Non-accidental, cardiovascular, stroke, cardiac, respiratory, cardiopulmonary	Mean % change (per 10 μg/m³ SO_2) Non-accidental: All Ages: 0.01 (−0.46, 0.47) < 65: −0.55 (−1.33, 0.23) ≥ 65: 0.22 (−0.32, 0.76) Cardiovascular: All Ages: 0.20 (−0.45, 0.86) < 65: −0.63 (−1.96, 0.72) ≥ 65: 0.41 (−0.31, 1.14) Stroke: All Ages: −0.27 (−1.04, 0.51) < 65: −1.35 (−3.01, 0.33) ≥ 65: 0.01 (−0.87, 0.88) Cardiac: All Ages: 0.88 (−0.22, 1.99) < 65: 0.29 (−2.11, 2.75) ≥ 65: 1.01 (−0.18, 2.21) Respiratory: All Ages: 1.13 (−0.28, 2.56) < 65: −0.59 (−4.24, 3.19) ≥ 65: 1.36 (−0.05, 2.80) Cardiopulmonary: All Ages: 0.29 (−0.33, 0.92) < 65: −0.80 (−2.07, 0.49) ≥ 65: 0.53 (−0.15, 1.20)
HEI (2004) East Asian cities	The lags and multi-day averaging used in varied Meta-analysis of time-series study results	The levels of SO_2 in these Asian cities were generally higher than those in the U.S. or Canadian cities, with more than half of these studies reporting the mean SO_2 levels higher than 10 ppb. Copollutants considered varied across studies.	All-cause	The estimates were found to be heterogeneous across 11 studies. Random-Effects Estimate: 1.49% (95% CI: 0.86, 2.13); Fixed-Effects Estimate: 1.01% (95% CI: 0.73, 1.28).

Study	Methods	Pollutant Data	Outcome	Findings
Tsai et al. (2003b) Kaohsiung, Taiwan Period of Study : 1994-2000	Lags: 0-2 Conditional logistic regression. Case-crossover analysis.	24-h avg: 11.2 ppb Copollutants: PM_{10}, NO_2, O_3, CO	All cause; respiratory; cardiovascular; tropical area	Odds ratios: All cause: 1.1% (−4.4, 6.8) Respiratory: 3.5% (−17.6, 29.9) Cardiovascular: 2.4% (−9.1, 15.4)
Venners et al. (2003) Chonqing, China Period of Study : 1995	Lags: 0, 1, 2, 3, 4, 5 Poisson GLM, time-series study	24-h avg: 74.5 ppb Copollutants:$PM_{2.5}$	All cause, cardiovascular, respiratory, cancer, and other	All cause: Lag 2: 1.1% (−0.1, 2.4) Cardiovascular: Lag 2: 2.8% (0.4, 5.2) Respiratory: Lag 2: 3.0% (0.4, 5.7)
Wong et al. (2001a) Hong Kong Period of Study : 1995-1997	Lags: 0, 1, 2 Poisson GAM with default convergence criteria. Time-series study.	24-h avg: Warm Season: 6.4 ppb Cool Season: 6.0 ppb Copollutants: PM_{10}, O_3, NO_2; 2-pollutant models	All cause; respiratory; cardiovascular	All cause: Lag 1: 3.2% (1.1, 5.3) Respiratory: Lag 0: 5.3% (2.2, 8.6) Cardiovascular: Lag 1: 4.3% (1.1, 7.5)
Wong et al. (2002b) Hong Kong Period of Study : 1995-1998	Lags: 0, 1, 2, 0-1, 0-2 Poisson GLM. Time-series study.	24-h avg: 29 ppb Copollutants: PM_{10}, O_3, NO_2; 2-pollutant models	Respiratory; cardiovascular; COPD; pneumonia and influenza; ischemic heart disease; cerebrovascular	Respiratory: Lag 0-1: 2.6% (0.2, 5.1) Cardiovascular: Lag 0-1: 1.2% (−1.0, 3.5)
Yang et al. (2004a) Taipei, Taiwan Period of Study: 1994-1998	Lags: 0-2 Conditional logistic regression. Case-crossover analysis.	24-h avg: 5.5 ppb Copollutants: PM_{10}, NO_2, O_3, CO	All cause; respiratory; cardiovascular; subtropical area	Odds ratios: All cause: −0.5% (−7.0, 6.6) Respiratory: −1.8% (−23.1, 25.3); Cardiovascular: −3.4% (−15.2, 10.0)

Table F-6. Long-term exposure to SO_2 and respiratory morbidity.

Study	Methods	Pollutant Data	Findings
UNITED STATES AND CANADA			
Dockery et al. (1989) Kingston-Harriman, TN; Portage, WI; St. Louis, MO; Steubenville, OH; Topeka, KS; Watertown, MA Period of Study: 1980-1981 school yr	Cross-sectional assessment of the association between air pollution and chronic respiratory health of 5,422 (10-12 yrs) white children examined in the 1980-1981 school yr. Children were part of the cohort of children in the Six Cities Study of Air pollution and Health. Symptoms were analyzed using logistic regression that included sex, age, indicators of parental education, maternal smoking, indicator for gas stove, and an indicator for city. Respiratory symptoms investigated were bronchitis, chronic cough, chest illness, persistent wheeze, asthma. The logarithm of pulmonary function was fitted to a multiple linear regression model that included sex, sex-specific log of height, age, indicators of parental education, maternal smoking, a gas stove indicator, and city indicator. Annual means of the 24 h avg air pollutant concentration for the 12 mos preceding the examination of each child was calculated for each city.	Daily mean concentrations, averaging hourly concentrations for each day with at least 18 hourly values Portage: 4.2 ppb Topeka: 3.5 Watertown: 10.5 Kingston: 6.5 St. Louis: 13.5 Steubenville: 27.8	No significant associations between SO_2 and any pulmonary function measurements. No significant association between SO_2 and symptoms. Relative odds and 95% CI between most/least polluted cities: Bronchitis: 1.5 (0.4, 5.8) Chronic cough: 1.8 (0.3, 12.5) Chest illness: 1.5 (0.4, 5.9) Persistent wheeze: 0.9 (0.4, 1.9) Asthma: 0.6 (0.3, 1.2) Reference symptoms: Hay fever: 0.6 (0.2, 1.7) Ear ache: 1.2 (0.3, 5.3) Nonrespiratory illness: 1.0 (0.6, 1.5) Analysis stratified by asthma or persistent wheeze bronchitis No wheeze or asthma 1.5 (0.5, 4.3) Yes wheeze or asthma 2.0 (0.3, 14.3) Chronic cough No wheeze or asthma 2.4 (0.5, 11.7) Yes wheeze or asthma 1.9 (0.1, 44.1) Chest illness No wheeze or asthma 1.5 (0.4, 5.6) Yes wheeze or asthma 1.9 (0.3, 13.0)
Dockery et al. (1996) 18 sites in U.S. 6 sites in Canada Period of Study: 1988-1991	Study of the respiratory health effects of acid aerosols in 13,369 white children aged 8 to 12 yrs old from 24 communities in the U.S. and Canada between 1988 and 1991. Information was gathered by questionnaire and a pulmonary function.	SO_2 avg 4.8 ppm SD 3.5 Range 0.2, 12.9	With the exception of the gaseous acids (nitrous and nitric acid), none of the particulate or gaseous pollutants, including SO_2, were associated with increased asthma or any asthmatic symptoms. Stronger associations with particulate pollutants were observed for bronchitis and bronchitic symptoms. Odds Ratio (95% CI) for 12.7 ppb range of SO_2 pollution Asthma 1.05 (057, 1.93) Attacks of Wheeze 1.07 (0.75, 1.55) Persistent Wheeze 1.19 (0.80, 1.79) Any asthmatic symptoms 1.16 (0.80, 1.68) Bronchitis 1.56 (0.95, 2.56) Chronic cough 1.02 (0.66, 1.58) Chronic phlegm 1.55 (1.01, 2.37) Any Bronchitic symptoms 1.29 (0.98, 1.71)

Study	Methods	Pollutant Data	Findings
Euler et al. (1987) California, USA	Cross-sectional study of 7,445 (25 yrs or older) Seventh-Day Adventists who lived in their 1977 residential areas (Los Angeles and it border counties, San Francisco, and San Diego) for at least 10 yrs to determine the effect of long-term cumulative exposure to ambient levels of TSP and SO_2 on COPD symptoms. Study population is subgroup of NCI-funded ASHMOG study that enrolled 36,805 Seventh-Day Adventists in 1974. Each participant's cumulative exposure to the pollutant exceeding 4 different threshold levels were estimated using moly residence ZIP code histories and interpolated dosages from state monitoring stations. Participants completed a questionnaire on respiratory symptoms, smoking history, occupational history, and residence history.	None provided	Study reported that SO_2 exposure was not associated with symptoms of COPD until concentrations exceeded 4 ppm. The correlation coefficient of SO_2 (above 4 ppm) with TSP (above 200 µg/m^3) the highest exposure levels for these two pollutants was 0.30; thus, the authors believed that it was possible to separate the effects of SO_2 from TSP. Multiple regressions used in the analysis. No significant effect at exposures levels below 4 ppm or above 8 ppm. Relative risk estimate (based on 1,003 cases) SO_2 exposure above 2 ppm during 11 yrs of study 2000 h/yr: 1.09 1000 h/yr : 1.04 500 h/yr: 1.03 SO_2 exposure above 4 ppm 500 h/yr : 1.18 250 h/yr: 1.09 100 h/yr: 1.03 SO_2 above 8 ppm 60 h/yr: 1.07 30 h/yr: 1.03 15 h/yr: 1.02 SO_2 above 14 ppm 10 h/yr: 1.03 5 h/yr: 1.01 1 h/yr: 1.00
Goss et al. (2004) U.S. nationwide Period of Study: 1999-2000	Cohort study of 18,491 cystic fibrosis patients over 6 yrs of age who were enrolled in the Cystic Fibrosis Foundation National Patient Registry in 1999 and 2000. Mean age of patients was 18.4 yrs; 92% had pancreatic insufficiency. Air pollution from the Aerometric Information Retrieval System linked with patient's home ZIP code. Air pollutants studied included O_3, NO_2, SO_2, CO, PM_{10}, and $PM_{2.5}$. Health endpoints of interest were pulmonary exacerbations, lung function, and mortality. However, study did not have enough power to assess the outcome of mortality. Logistic regression and polytomous regression models that adjusted for sex, age, weight, race, airway colonization, pancreatic function, and insurance status were used.	Mean (SD): 4.91 (2.6) ppb Median: 4.3 ppb IQR: 2.7-5.9 ppb	With the single-pollutant model, no significant association between SO_2 and pulmonary exacerbations. Odds ratio per 10 ppb increase in SO_2: 0.83 (95% CI: 0.71, 1.01), p = 0.068 No clear association between pulmonary function and SO_2. No effect estimates provided.
McDonnell et al. (1999) California, U.S. Period of Study: 1973-1992	Prospective study (over 15 yrs) of 3,091 nonsmokers aged 27-87 yrs that evaluated the association between long-term ambient O_3 exposure and the development of adult-onset asthma. Cohort consisted of nonsmoking, non-Hispanic white, California Seventh Day Adventists who were enrolled in 1977 in the AHSMOG study. Logistic regression used to assess the association between the 1973-1992 mean 8-h avg ambient O_3 concentration and the 1977-1992 incidence of doctor-told asthma. Levels of PM_{10}, NO_2, and SO_4 were measured but no effect estimates were given.	Mean: SO_2 6.8 µg/m^3 Range: 0.0-10.2 µg/m^3 Correlation coefficient r = 0.25 with O_3	No significant positive association between SO_2 and asthma for males or females. Addition of a second pollutant to the O_3 model for the male subjects, did not result in a decrease of more than 10% in the magnitude of the regression coefficient for O_3, and for the females addition did not cause the coefficient for O_3 to become significantly positive
Schwartz (1989) United States Period of Study: Feb 1976-Feb 1980	Cross-sectional study using data from the Second National Health and Nutrition Examination Survey (NHANES II) to examine the relation between air pollution and lung function growth in 4,300 children and youths 6-24 yrs old. A two-staged analysis was performed that consisted of (1) regression equations including factors known to affect lung function and (2) a regression of the residuals of the first regression on air pollution.	Annual percentiles (ppm): 10th: 0.0060 25th: 0.0106 50th: 0.0131 75th: 0.0159 90th: 0.0193	The study did not find an association between SO_2 and any of the lung function growth measurements (i.e., FVC, FEV_1, and Peak flow).

Study	Methods	Pollutant Data	Findings
EUROPE			
Ackermann-Liebrich et al. (1997) 8 communities in Switzerland Aarau, Basel, Davos, Geneva, Lugano, Montana, Payerne, and Wald Period of Study: 1991-1993	Cross-sectional population based study of 9,651 adults (18-60 yrs) in 8 areas in Switzerland (SAPALDIA), to evaluate the effect of long-term exposure of air pollutants on lung function. Examined the effects of SO_2, NO_2, O_3, TSP, and PM_{10}. Participants were given a medical exam that included questionnaire data, lung function tests, skin prick testing, and end-expiratory CO concentration. Subjects had to reside in the area for at least 3 yrs to be in the study.	Avg SO_2 in 1991 (µg/m^3) Mean: 11.7 SD: 7.1 Range: 2.5, 25.5	Mean values of SO_2, PM_{10}, and NO_2 were significantly associated with reduction in pulmonary function. SO_2 was correlated with Pm^3_0 (r = 0.78), PM_{10} (r = 0.93) and NO_2 (r = 0.86). Authors stated that the association with SO_2 disappeared after controlling for PM_{10} but no data was shown. Regression coefficients and 95% CI in healthy never smokers (per 10 µg/m^3 increase in annual avg SO_2) FVC: −0.0325 (−0.0390, −0.0260) FEV_1: −0.0125 (−0.0192,−0.0058)
Braun-Fahrlander et al. (1997) 10 communities in Switzerland Anieres, Bern, Biel, Geneva, Langnau, Lugano, Montana, Payerne, Rheintal, Zurich Period of Study: 1992-1993	Cross-sectional study of 4,470 children (6-15 yrs) living in 10 different communities in Switzerland to determine the effects of long term exposure to PM_{10}, NO_2, SO_2, and O_3 on respiratory and allergic symptoms and illnesses. Part of the Swiss Study on Childhood Allergy and Respiratory Symptoms with Respect to Air Pollution (SCARPOL).	Annual avg SO_2 (µg/m^3) Lugano: 23 Geneva: 13 Zurich: 16 BerN: 11 Anieres: 4 Biel: 15 Rheintal: 8 Langnau: NA Payerne: 3 MontaN: 2	This study reported that the annual mean SO_2, PM_{10}, and NO_2 were positively and significantly associated with prevalence rates of chronic cough, nocturnal dry cough, and bronchitis and conjunctivitis symptoms. Strongest association found with PM_{10}. However, there was no significant association between SO_2 and asthma or allergic rhinitis. Adjusted relative odds between the most/least polluted community 2-23 µg/m^2 (0.8, 8.8 ppb) Chronic cough: 1.57 (1.02, 2.42) Nocturnal dry cough: 1.66 (1.16, 2.38) Bronchitis: 1.48 (0.98, 2.24) Wheeze: 0.88 (0.54, 1.44) Asthma (ever): 0.74 (0.45, 1.21) Sneezing during pollen Season: 1.07 (0.67, 1.70) Hay fever: 0.84 (0.55, 1.29) Conjunctivitis symptoms: 1.74 (1.22, 2.46) Diarrhea: 1.02 (0.75, 1.39)
Charpin et al. (1999) Etang de Berre area of France: Arles, Istres, Port de Bouc, Rognac-Velaux, Salon de Provence, Sausset, Vitrolles Period of Study : Jan-Feb 1993	Cross-sectional cohort study of 2,073 children (10-11 yrs) from 7 communities in France (some with the highest photochemical exposures in France) to test the hypothesis that atopy is greater in towns with higher photochemical pollution levels. Mean levels of SO_2, NO_2, and O_3 were measured for 2 mos in 1993. Children tested for atopy based on skin prick test (house dust mite, cat dander, grass pollen, cypress pollen, and Alternaria). To be eligible for the study, subjects must have resided in current town for at least 3 yrs. Questionnaire filled out by parents that included questions on SES passive smoking at home. Two-mo mean level of air pollutants used in logistic regression analysis.	24-h avg (SD) SO_2 (µg/m^3) Arles: 29.7 (15.5) Istres: 23.8 (12.7) Port de Bouc: 32.3 (24.5) Rognanc-Velaux: 39.5 (21.8) Salon de Provence: 17.3 (11.6) Sausset: 29.0 (28.7) Vitrolles : 57.4 (32.0)	Study did not demonstrate any association between air pollution and atopic status of the children living in the seven communities, some with high photochemical exposures. A limitation of study is that authors did not consider short-term variation in air pollution and did not have any indoor air pollution measurements.
Frischer et al. (1999) Nine communities in Austria Period of Study: 1994-1996	Longitudinal cohort study of 1150 children (mean age 7.8 yrs) to investigate the long-term effects of O_3 on lung growth. Children were followed for 3 yrs and lung function was recorded biannually, before and after summertime. The dependant variables were change in FVC, FEV_1, and MEF_{50}. The 9 sites were selected to represent a broad range of O_3 exposures. GEE models adjusted for baseline function, atopy, gender, site, environmental tobacco smoke exposure, season, and change in height. Other pollutants studied included PM_{10}, SO_2, and NO_2.	Annual mean SO_2 (ppb) in 1994 Amstetten: 3.75 St. Valentin: 3.00 Krems: 3.75 Heidenreichstein: 4.13 Ganserndorf: 5.63 Mistelbach: 5.25 Wiesmath: 6.00 Bruck: 4.88 Pollau: 2.25	No consistent association observed between lung function and SO_2, NO_2 and PM_{10}. A negative effect estimate was observed during the summer and a positive estimate during the winter. Change in lung function (per ppb SO_2): FEV_1 (mL/day): Summer: −0.018 (0.004), p < 0.001 Winter : 0.003 (0.001), p < 0.001 FVC (mL/day): Summer: −0.009 (0.004), p = 0.02 Winter: 0.002 (0.001), p = 0.03 MEF_{50} (mL/s/day): Summer: −0.059 (0.010), p < 0.001 Winter: 0.003 (0.003), p = 0.26

Study	Methods	Pollutant Data	Findings
Frischer et al. (2001) Nine communities in Austria Period of Study: Sep-Oct 1997	Cross-sectional cohort study of 877 children (mean age 11.2 yrs) living in 9 sites with different O_3 exposures. Urinary eosinophil protein U-EPX) measured as a marker of eosinophil activation. U-EPX determined from a single spot urine sample analyzed with linear regression models.	½-h avg SO_2: 30-day mean 2.70 ppb IQR 2.1 ppb	No significant association between SO_2 and U-EPX Regression coefficient and SE −10.57 (0.25) per ppb SO_2
Frye et al. (2003) Zerbst, Hettstedt, Bitterfeld,East Germany Period of Study: 1992-93, 1995-1996, 1998-1999	Three consecutive cross-sectional surveys of children (11-14 yrs) from three communities in East Germany. Parents of 3,155 children completed a questionnaire on symptoms. Lung function tests performed on 2,493 children. Study excluded children if they lived for less than 2 yrs in current home and if their previous home was more than 2 km away. The log-transformed lung function parameters were used as the response variables in a linear regression analysis that controlled for sex, height, season of examination, lung function equipment, parental education, parental atopy, and environmental tobacco smoke. Used avg of annual means of pollutants 2 yrs preceding each survey.	Used avg of annual means of pollutants 2 yrs preceding health measurement High of 113 µg/m³ (in Bitterfeld) to a low of 6 µg/m³. (Pollution values only described in figure)	The annual mean TSP declined from 79 to 25 µg/m³ and SO_2 from 113 to 6 µg/m³ and the mean FVC and FEV_1 increased from 1992-1993 to 1998-1999. Study concluded that reduction of air pollution in a short time period may improve children's lung function. Percent change of lung function for a 100-µg/m³ decrease in SO_2 2 yrs before the investigation (N: 1,911) FVC: 4.9 (0.7, 9.3) FEV_1: 3.0 (−1.1, 7.2) FEV_1/FVC: −1.5 (−3.0, 0.1)
Garcia-Marcos et al. (1999) Cartagena, Spain Period of Study: winter 1992	A total of 340 children (10-11 yrs) living in and attending schools within a polluted and a relatively nonpolluted area were included in this study which aimed to establish the relative contribution socioeconomic status, parental smoking, and air pollution on asthma symptoms, spirometry, and bronchodilator response. Parents completed questionnaire on respiratory symptoms and risk factors including, living in polluted area, maternal smoking, paternal smoking, number of people living in the house, proximity to heavy traffic roads. Spirometry was performed before and after an inhaled 0.2 mg fenoterol was delivered to determine bronchodilator response. Bronchodilator response was considered positive if the FVC after fenoterol was increased by at least 10% or PEF by 12%. Logistic regression included as independent variables all the risk factors.	Annual mean SO_2 (µg/m³) Polluted areas 75 µg/m³ Nonpolluted areas: 20 µg/m³	This study found that living in the polluted areas reduced the risk of a positive bronchodilator response (RR = 0.61, p = 004).
Gokirmak et al. (2003) Malatya, Turkey	Study on occupational exposure to SO_2 in apricot sulfurization workers that investigated the role of oxidative stress resulting exposure to high concentrations of SO_2 on bronchoconstriction. Forty workers (mean age: 28 yrs, range 16-60 yrs) who have been working in apricot sulfurization for 20-25 days each yr and 20 controls (mean age: 29 yrs, range 17-42) who had no SO_2 exposure participated in the study. Activities of antioxidant enzymes (glutathione peroxidase (GSH-Px), superoxide dismutase (SOD) and catalase) malondialdehyde (MDA) concentrations (marker of lipid peroxidation), and pulmonary function test measured in subjects.	SO_2 conc ranged from 106.6 to 639.2 ppm in 9 apricot farms. Mean conc around sulfurization chamber: 324.1 (35.1) ppm	SOD, GSH-Px, and catalase activities were lower and malondialdehyde concentrations were higher in the apricot sulfurization workers compared to controls. Pulmonary function decreased after SO_2 exposure among the apricot sulfurization workers. Authors concluded that occupational exposure to high concentrations of SO_2 enhances oxidative stress and that lipid peroxidation may be a mechanism of SO_2 induced bronchoconstriction. Apricot sulfurization workers vs. controls Mean (SD) SOD (U/mL): 2.2 (0.6) vs. 3.2 (0.7) U/m, p < 0.0001 Glutathione peroxidase (U/mL): 0.6 (0.3) vs. 1.1 (0.3), p < 0.0001 Catalase (L/L): 107.6 (27.4) vs. 152.6 (14.3), p < 0.0001 MDA (nmol/L): 4.1 (0.9) vs. 1.9 (5.3) , p < 0.0001 Before vs. after SO_2 exposure among apricot sulfurization workers Mean (SD) FVC (% predicted) 88 (17) vs. 84 (16) , p < 0.001 FEV_1 (% predicted) 98 (14) vs. 87 (14), p < 0.001 FEV_1/FVC: 92 (7) vs. 86 (9), p < 0.001 FEF25-75% (% predicted) 108 (19) vs. 87 (23) , p < 0.001

Study	Methods	Pollutant Data	Findings
Heinrich et al. (2002) Reunified Germany Bitterfeld, Hettstedt, Zerbst Period of Study: 1992-1993, 1995-1996, 1998-1999	Three cross-sectional surveys of children (5-14 yrs) from 3 areas that were formerly part of East Germany to investigate the impact of declines in TSP and SO_2 on prevalence of nonallergic respiratory disorders in children. Study excluded children if they lived for less than 2 yrs in current home and if their previous home was more than 2 km away. GEE used for analysis.	SO_2 concentration in µg/m^3 Yr /Zerbst/Bitterf/ Hettst 1991/78/113/ 84 1992/ 58/ 75/ 46 1993/ 42/ 60/ 49 1994/ 29/ 35/ 38 1995/ 21/ 30/ 26 1996 25 24 25 1997/ 13/ 13/ 13 1998/ 8/ 9/ 6	Study found that SO_2 exposure was significantly associated with prevalence of bronchitis, frequent colds, and febrile infections. While results are reported as risk for an increase in air pollutant, the respiratory health of children improved with declines in TSP and SO_2. Authors concluded that exposure to combustion-derived air pollution is causally related to nonallergic respiratory health in children. Odds ratio and 95% CI: (per 100 µg/m^3 in 2 yr mean SO_2) All children: Bronchitis: 2.72 (1.74, 4.23) Otitis media: 1.42 (0.94, 2.15) Sinusitis: 2.26 (0.85, 6.04) Frequent colds: 1.81 (1.23, 2.68) Febrile infections: 1.76 (1.02, 3.03) Cough in morning: 1.10 (0.73, 1.64) Shortness of breath: 1.31 (0.84, 2.03) Children without indoor exposures (living in damp houses with visible molds, ETS in the home, gas cooking emissions, and contact with cats): Bronchitis: 4.26 (2.15, 8.46) Otitis media: 1.43 (0.73, 2.81) Sinusitis: 2.95 (0.52, 16.6) Frequent colds: 2.29 (1.15, 4.54) Febrile infections: 1.75 (0.78, 3.91) Cough in morning: 1.00 (0.38, 2.64) Shortness of breath: 2.07 (0.90, 4.75)
Herbarth et al. (2001) East Germany Period of Study: 1993-1997	Meta-analysis of three cross-sectional studies: (1) Study on Airway Diseases and Allergies among Kindergarten Children (KIGA), (2) the Leipzig Infection, Airway Disease and Allergy Study on School starters (LISS), and (3) KIGA-IND, which was based on the KIGA design but conducted in 3 differentially polluted industrial areas. A total of 3,816 children participated in the three studies. Analysis of data from parent-completed questionnaires to determine the effect of life time exposure to SO_2 and TSP on the occurrence of acute bronchitis. Total lifetime exposure burden corresponds to the exposure duration from birth to time of the study. The LISS study was divided in to LISS-U for the urban area and LISS-R for the rural area. Logistic regression analysis used that adjusted for predisposition in the family (mother or father with bronchitis), ETS, smoking during pregnancy or in the presence of the pregnant women.	Avg lifetime exposure burden of SO_2 (µg/m^3) KIGA: 142 LISS: 48 LIISS: R 47 KIGA-IND: 59	This study found the highest bronchitis prevalence in the KIGA cohort and the lowest in the LISS cohort, which is consistent with the SO_2 concentrations in these cohorts. Study found a correlative link between SO_2 and bronchitis ($R = 0.96$, $p < 0.001$) but not TSP ($R = 0.59$). Results of study suggest that SO_2 may be a more important factor than TSP in the occurrence of bronchitis in these study areas. Odds ratio for bronchitis adjusted for parental predisposition, smoking, and lifetime exposure to SO_2 and TSP (2-pollutant model). SO_2: 3.51 (2.56, 4.82) TSP: 0.72 (0.49, 1.04)
Hirsch et al. (1999) Dresden, Germany	Cross sectional study to relate the prevalence of respiratory and allergic diseases in childhood to measurements of outdoor air pollutants. 5,421 children ages 5-7 yrs and 9-11 yrs were evaluated by questionnaires, skin-prick testing, venipuncture for (Ig)E, lung function, and bronchial challenge test.	Mean (µg/m^3): 48.3 Range: 29.0-69.3 25-75 percentile 42.7-54.3	SO_X was positively associated with current morning cough but not with bronchitis. Prevalence odds ratio (95% CI) for symptoms within past 12 mos, +10 µg/m^3: Wheeze: Atopic 103 (0.79, 1.35) µg/m^3: Nonatopic 1.36 (1.01, 1.84) Morning Cough: Atopic 1.22 (0.92, 1.61) Nonatopic 1.32 (1.07, 1.63) Prevalence odds ratio (95% CI) for doctor's diagnosis, +10 µg/m^3: Asthma: Atopic 1.07 (0.79, 1.45) Nonatopic 1.35 (1.00, 1.82) Bronchitis: Atopic 1.04 (0.87, 1.25) Nonatopic 0.99 (0.88, 1.12)

Study	Methods	Pollutant Data	Findings
Horak et al. (2002) Eight communities in Austria Period of Study: 1994-1997	Longitudinal cohort study that continued the work of Frischer et al. (1999) by adding one more yr of data and analyzing the effects of PM_{10} in addition to SO_2, NO_2, and O_3. At the beginning of the study 975 children (mean age 8.11 yrs) were recruited for the study, but only 80.6% of the children performed all 6 lung function tests (twice a yr). The difference for each lung function parameter between two subsequent measures was divided by the days between measurements and presents as difference per day (dpd) for that parameter. 860 children were included in the GEE analysis that controlled for sex, atopy, passive smoking, initial height, height difference, site, and initial lung function.	Seasonal avg SO_2 $\mu g/m^3$: Winter: Mean: 16.8 Range: 7.5, 37.4 Summer: Mean : 6.9 $\mu g/m^3$ Range: 3.1, 11.7	Moderate correlation between PM_{10} and SO_2 in the winter (r = 0.52). In a one-pollutant model for SO_2, long term seasonal mean concentration of SO_2 was had a positive association with FVC dpd and FEV_1 dpd in the winter, but no effect on MEF_{25-75} dpd. In a two-pollutant model with PM_{10}, wintertime SO_2 had a positive association with FEV_1 dpd. Single-pollutant model FVC dpd: Summer: 0.009, p = .336; Winter: 0.006, p = .009 FEV_1 dpd: Summer : 0.005, p = 0.576; Winter: 0.005, p = 0.013 MEF_{25-75}: Summer: 0.015, p = 0.483; Winter: 0.003, p = 0.637 Two-pollutant model: SO_2 + PM_{10} FVC dpd: Summer: 0.008, p = 0.395; Winter: 0.004, p = 0.225 FEV_1 dpd: Summer : 0.010 (0.271); Winter: 0.007 (0.025) MEF_{25-75} dpd: Summer : 0.037, p = 0.086; Winter: 0.007, p = 0.429
Jedrychowski et al. (1999) Krakow, Poland Period of Study: 1995 (Mar-Jun) and 1997 (Mar-Jun)	Cohort prospective study consisting of 1,001 preadolescent children (9 yrs old) from two areas of Krakow, Poland. The study examined lung function growth using FVC and FEV_1 measurements taken in 1995 and then again two yrs later, 1997. Used a two-stage analysis that consisted of (1) multivariate linear regression analyses to determine body variables that are significant predictors of lung function growth, and then (2) multivariate logistic regression to examine the relation between air pollution and lung function growth.	Annual avg: City Center ($\mu g/m^3$): 43.87 (32.69) Control Area ($\mu g/m^3$): 31.77 (21.93)	The study did not provide individual estimates for SO_2.
Koksal et al. (2003) Malatya, Turkey	Study on occupational exposure to high concentrations of SO_2 on respiratory symptoms and pulmonary function on apricot sulfurization workers. Apricot sulfurization workers (N: 69) from 15 apricot farms who have been working in sulfurization of apricots for 20-25 days a yr during each summer were recruited for the study. Subjects rated symptoms (itchy eyes, runny nose, stuffy nose, itchy or scratchy throat, cough, shortness of breath, phlegm, chest pain, and fever) before during and 1-h after each exposure.	SO_2 conc ranged from 106.6 to 721.0 ppm	SO_2 exposure at high concentrations increased symptoms of itchy eyes, shortness of breath, cough, running and/or stuffy nose, and itchy or scratchy throat during exposure ($p < 0.05$). Inhalation of high concentrations of SO_2 for 1-h caused significant decreases in pulmonary function. Difference in pulmonary function measured before and after exposure: FVC (L) 0.16 (0.42), $p < 0.05$ FEV_1 (L) 0.39 (0.36), $p < 0.001$ FEV_1/FVC: 5.22 (6.75), $p < 0.001$ PEF (L/s) 1.39 (1.06), $p < 0.001$ $FEF_{25-75\%}$ (L/s) 0.82 (0.70), $p < 0.001$

Study	Methods	Pollutant Data	Findings
Kopp et al. (2000) Ten communities in Austria and SW Germany	Longitudinal cohort study of 797 children (mean age 8.2 yrs) from 2nd and 3rd grades of 10 schools in Austria and SW Germany to assess the effects of ambient O_3 on lung function in children over a 2-summer period. Study also examined the association between avg daily lung growth and SO_2, NO_2, and PM_{10}. Each child performed 4 lung function tests during spring 1994 and summer 1995. ISAAC questionnaire used for respiratory history. Linear regression models used to assess effect of air pollutants on FVC and FEV_1, which were surrogates of lung growth.	Mean SO_2 (95% CI) ppb Apr-Sep 1994 Amstetten: 3.7 (0.7, 3.9) St Valentin: 2.6 (1.5, 5.2) Krems: 3.7 (0.7, 7.5) Villingen: 0.7 (0 , 3.0) Heindenreichstein: 3.7, (0.7, 7.5) Ganserndorf: 3.7 (0.7, 11.2) Mistelbach: 3.7 (0.7, 7.5) Wiesmath: 6.3 (3.4, 9.4) Bruck: 1.5 (0.7, 4.1) Freudenstadt: 0.7 (0, 3.0) Oct 1994-Mar 1995 Amstetten: 3.7 (0.7, 7.5) St Valentin: 3.0 (1.1, 9.4) Krems: 3.7 (0.7, 11.0) Villingen: 1.9 (0 , 3.0) Heindenreichstein: 3.7 (0.7, 15.0) Ganserndorf: 3.7 (0.7, 22.5) Mistelbach: 3.7 (0.7, 22.5) Wiesmath: 2.23 (0.7, 10.1) Bruck: 15 (1.1, 7.9) Freudenstadt: 1.57 (0.4, 5.3) Apr-Sep 1995 Amstetten: 3.7 (0.7, 3.8) St Valentin: 2.6 (1.1, 6.8) Krems: 3.7 (0.5, 3.8) Villingen: 0.7 (0 , 2.6) Heindenreichstein: 0.7 (0.5, 0.9) Ganserndorf: 3.7 (0.7, 7.5) Mistelbach: 3.7 (0.7, 7.5) Wiesmath: 7.5 (0.7, 14.9) Bruck: 3.7 (0.4, 4.9) Freudenstadt: 0.7 (0, 3.4)	Lower FVC and FEV_1 increases observed in children exposed to high ambient O_3 levels vs. those exposed to lower levels in the summer. This study found no effect of SO_2 and PM_{10} on FVC increase during the summer of 1995 and winter 1994/1995, however, SO_2 was negatively associated with FVC during the summer of 1994. Change in FVC (per ppb SO_2) Summer 1994: −0.044, p = 0.006 Winter 1994/95: 0.007, p = 0.243 Summer 1995: 0.045, p = 0.028

Study	Methods	Pollutant Data	Findings
Kramer et al. (1999) East and West Germany Period of Study: 1991 to 1995	Repeated cross-sectional studies between 1991 and 1995 on 7-yr-old children in East Germany and between 1991 and 1994 in West Germany. Comparison of prevalence of airway diseases and allergies in East and West Germany during the first five yrs after reunification. A total of 19,090 children participated in the study. Logistic regression used to assess the effect of SO_2 and TSP on airway diseases and allergies. Analysis performed on 14,144 children with information on all covariates of interest.	East Germany 2-yr avg concentration ranged from 45 to 240 µg/m^3 West Germany 2-yr avg concentration ranged from 18-33	All infectious airway diseases and irritation of the airway was associated with either SO_2 or TSP in East Germany in 1991. The decrease of pollution between 1991 and 1995 had a favorable effect on the prevalence of these illnesses. SO_2 was significantly associated with more than 5 colds in the last 12 mos, tonsillitis, dry cough in the last 12 mos, and frequent cough in 1991-1995. Odds ratio and 95% CI: (per 200 µg/m^3 SO_2) in East Germany areas, 1991-1995 for children living at least 2 yrs in the areas, adjusted for time trend: Infectious airway diseases: Pneumonia ever diagnosed: 1.17 (0.85, 1.62) Bronchitis ever diagnosed: 0.85 (0.68, 1.05) ∃5 colds in last 12 mos: 1.55 (1.18, 2.04) Tonsillitis in the last 12 mos: 1.89 (1.49, 2.39) Dry cough in the last 12 mos: 1.46 (1.12, 1.91) Frequent cough ever: 2.51 (1.79. 3.53) Allergic diseases and symptoms: Irritated eyes in the last 12 mos: 1.06 (0.66, 1.70) Irritated nose in the last 12 mos: 1.26 (0.96, 1.66) Wheezing ever diagnosed: 0.68 (0.46, 1.01) Bronchial asthma ever diagnosed: 2.73 (1.24, 6.04) Hay fever ever diagnosed: 0.60 (0.24, 1.52) Eczema ever diagnosed: 0.87 (0.65, 1.18) Allergy ever diagnosed: 0.93 (0.67, 1.29)
Liebhart et al. (2007) Poland (Bialystok, Bydgoszcz, Gdansk, Krakow, Lublin, Lodz, Poznan, Rabka, Warszawa, Wroclaw, Zabrze) Period of Study: 1998-1999	The Polish Multicentre Study of Epidemiology of Allergic Diseases (PMSEAD), which consisted of a cohort of 16,238 individuals aged 3-80 yrs old from 33 areas in 11 regions of Poland. Asthma diagnosis was determined through household questionnaires. Conducted multivariate and univariate logistic regression analyses to examine the prevalence of and risk factors for asthma.	Range (µg/m^3): 4.0-35.0	In multivariate logistic regression models, BS was found to be a significant risk factor for asthma for both children and adults. SO_2 was found to be a significant risk factor for asthma in both children and adults, but only in a univariate logistic regression. Adjusted Odds Ratio (95% CI) Univariate logistic regression Children: 1.34 (1.04, 1.72) Adults: 1.19 (1.02, 1.38) Multivariate logistic regression Children: 1.20 (0.91, 1.59) Adults: 1.01 (0.85, 1.20)
Kohlhammer et al. (2007) Hettstedt, Germany Period of Study: 1992-1999	Three repeated cross-sectional studies of 5,360 children ages 5-14 examining health impacts (lifetime pneumonia) of social and environmental factors	---	No relationship between SO_2 and pneumonia was observed.

Study	Methods	Pollutant Data	Findings
Penard-Morand et al. (2006) Six communities in France: Bordeaux, Clermont-Ferrand, Creteil, Marseille, Strasbourg and Reims Period of Study: Mar 1999-Oct 2000	Cross-sectional study of 4,901 children (9-11 yrs) form 108 randomly selected schools in 6 cities to assess the association between long-term exposure to background air pollution (NO_2, SO_2, PM_{10}, O_3) and atopy and respiratory outcomes. Analysis restricted to children who had lived at least the last 3 yrs in their house at the time of the examination. Analysis used three yr avgd air pollutant concentrations at the children's schools. Parents completed questionnaire on respiratory and allergic disorders (asthma, allergic rhinitis (AR), and atopic dermatitis) and children underwent examination that included a skin prick test to assess allergic sensitization, evidence of visible flexural dermatitis and measure of exercise-induced bronchial reactivity (EIB).	Estimated 3-yr avg concentrations at 108 schools Low conc: 4.6 µg/m^3 (Range: 1.3, 7.4), High conc: 9.6 µg/m^3 (range 7.7, 13.7)	Increased concentrations of SO_2 were significantly associated with an increased risk of EIB, lifetime asthma and lifetime AR. Past yr wheeze and asthma were also associated with SO_2. In a two-pollutant model with PM_{10}, significant associations were observed between SO_2 and EIB and past yr wheeze. Odds ratio and 95% CI (per 5 µg/m^3 SO_2) EIB: 1.39 (1.15, 1.66), $p < 0.001$ Flexural dermatitis: 0.86 (0.73, 1.02), $p < 0.10$ Past yr wheeze: 1.23 (1.0, 1.51), $p < 0.05$ Past yr asthma: 1.28 (1.00, 1.65), $p < 0.01$ Past yr rhinoconjunctivitis: 1.05 (0.89, 1.24) Past yr atopic dermatitis: 1.01 (0.86, 1.18) Lifetime asthma: 1.19 (1.00, 1.41), $p < 0.10$ Lifetime allergic rhinitis: 1.16 (1.01, 1.32), $p < 0.05$ Lifetime atopic dermatitis: 0.93 (0.82, 1.05) Two-pollutant model with PM_{10} EIB: 1.46 (1.12, 1.90) Past yr wheeze: 1.45 (1.09, 1.93)
Pikhart et al. (2001) Czech Republic, Poland, Period of Study: 1993-1994	Part of the small-area variation in air pollution and health (SAVIAH) study to assess long-term effects of air pollution on respiratory outcomes. Analysis on data from two centers of the multicenter study: Prague, Czech Republic, and Poznan, Poland. Both cities had wide variation in air pollution levels. Parents/guardians of 6,959 children (7-10 yrs) completed a questionnaire about the socioeconomic situation of the family, type of housing, family history of atopy, parental smoking, family composition, and health of the child. SO_2 was measured at 80 sites in Poznan and 50 sites in Prague during 2-wk campaigns. From these data GIS was used to estimate pollutant concentrations at a small area level. Logistic regression used to assess effect of air pollution on the prevalence of respiratory outcomes.	Mean SO_2 (µg/m^3) Prague: 83.9 Range: 65.8-96.6 PoznaN: 79.7 Range: 44.2-140.2	SO_2 levels (mean of home and school) were associated with the prevalence of wheezing/whistling in the past 12 mos. There was a marginal association between SO_2 and lifetime prevalence of wheezing and physician diagnosed asthma. Fully adjusted model controlled for age, gender, maternal education, number of siblings, dampness at home, heating and cooking on gas, maternal smoking, and family history of atopy and center. Authors noted SO_2 is strongly spatially correlated with particles in the Czech Republic and probably Poland, so SO_2 may be proxy for exposure to other pollutants. Not other pollutants measured in study. Odds ratio (per 50 µg/m^3) SO_2 Wheezing/whistling in past 12 mos: 1.32 (1.10, 1.57) Wheezing/whistling ever: 1.13 (0.99, 1.30) Asthma ever diagnosed by doctor: 1.39 (1.01, 1.92) Dry cough at night: 1.06 (0.89, 1.27)
Ramadour et al. (2000) Seven towns in SE France Period of Study: Jan-Feb 1993	Cross-sectional cohort study of 2,445 children (age 13-14 yrs) who had lived for at least 3 yrs in their current residence to compare the levels of O_3, SO_2, and NO_2 to the prevalence rates of rhinitis, asthma, and asthmatic symptoms. Some of the communities had the heaviest photochemical exposure in France. Subjects completed ISAAC survey of asthma and respiratory symptoms. Analysis conducted with logistic regression models that controlled for family history of asthma, personal history of early -life respiratory diseases, and SES. Also performed simple univariate linear regressions.	Mean (SD) µg/m^3 of SO_2 during 2-mo period Port de Bouc: 32.3 (24.5) Istres: 23.8 (12.7) Sausset: 29.0 (28.7) Rognanc-Velaux: 39.5 (21.8) Vitrolles: 57.4 (32.0) Arles: 29.7 (15.5) SaloN: 17.3 (11.6)	Study found no relationship between mean levels of SO_2, NO_3, or O_3 and rhinitis ever, 12-mo rhinitis, rhinoconjunctivitis, and hay fever or asthmatic symptoms. Simple regression analyses of respiratory outcomes vs. mean SO_2 levels in the 7 towns indicated that nocturnal dry cough was associated with mean SO_2 levels (r = 0.891). Potential confounding across towns.
Soyseth et al. (1995b) Ardal and Laerdal, Norway Period of Study: winter seasons 1989-92	Cross-sectional study of 529 children (aged 7-13 yrs) to determine whether exposure to SO_2 during infancy is related to the prevalence of bronchial hyperresponsiveness (BHR). A sulfur dioxide emitting aluminum smelter is present in Ardal, but there is no air polluting industry in Laerdal. Parents filled out questionnaire regarding family history of asthma, type of housing, respiratory symptoms and parent's smoking habits. Spirometry was performed on each child and bronchial hyperactivity was determined by methacholine challenge or reversibility test. Skin prick test done to assess atopy. Also examined, the effects of fluoride.	Median SO_2 37.1 µg/m^3 at ages 0-12 mos 37.9 µg/m^3 at ages 13-36 mos	This study found that the risk of BHR was associated with SO_2 exposure at 0-12 mos Odds ratio for BHR (per 10 µg/m^3 SO_2) for various ages at exposure 0-12 mos: 1.62 (1.11, 2.35) 13-36 mos: 1.40 (0.90, 2.21) 37-72 mos: 1.19 (0.77, 1.82) 73-108 mos: 1.19 (0.63, 2.22)

Study	Methods	Pollutant Data	Findings
Studnicka et al. (1997) Austria (8 nonurban communities) Period of Study: 1991-1993	Longitudinal study of 843 children 7 yrs old from 8 nonurban Austrian communities. A logistic regression was used to examine the association between SO_2 concentrations and asthma and respiratory symptoms by comparing low, regular, and high SO_2 communities with very low SO_2 communities.	Range: Jan. 1991-Dec. 1993 (ppb): 6.0 (Krems), 12.0 (Mistel. and Gäns)	SO_2 was significantly associated with bronchial asthma in the last 12 mos and positively associated with parent-reported "ever asthma" when comparing low SO_2 concentration communities with very low SO_2 communities. Adjusted Prevalence Odds Ratio Wheeze last 12 mos: Low: 0.68. Regular: 0.88. High: 0.42 Cough apart from colds last 12 mos: Low: 0.75. Regular: 0.85. High: 0.72 Bronchitis last 12 mos: Low: 0.21. Regular: 0.45. High: 0.56 Bronchial asthma last 12 mos: Low: 2.35. Regular: 0.22. High: 0.33 Parent-reported "ever asthma": Low: 1.70. Regular: 0.23. High: 0.67
von Mutius et al. (1995) Leipzig, East Germany, Period of Study: Oct 1991-Jul 1992	The effects of high to moderate levels of air pollution (SO_2, NO_X, and PM) on the incidence of upper respiratory were investigated in 1,500 schoolchildren (9-11 yrs) in Leipzig, East Germany. Logistic regression models controlled for paternal education, passive smoke exposure, number of siblings, temperature, and humidity.	During winter mos, SO_2 daily max concentrations ranged from 40-1283 µg/m^3. During high pollution period, avg concentration of SO_2 was 188 µg/m^3 and during low pollution avg was 57 µg/m^3.	The daily mean values of SO_2 and NO_X were significantly associated with increased risk of developing upper respiratory illnesses during the high concentration period. In the low concentration period, only NO_X daily mean values were associated with increased risks. In a two-pollutant model with PM, similar estimates to the single-pollutant model were obtained, thus collinearity of data may not account for the effects of high mean concentrations of SO_2. Odds ratio and 95% CI: (did not indicate per what level of SO_2 increase) Daily mean SO_2 : High period: 1.72 (1.19, 2.49); Low period: 1.40 (0.95, 2.07) Daily max SO_2 : High period: 1.26 (0.80, 1.96); Low period: 0.99 (0.66, 1.47)

Study	Methods	Pollutant Data	Findings
LATIN AMERICA			
Solé et al. (2007) São Paulo, Brazil (São Paulo West (SPW), São Paulo South (SPS), Santo André (SA), Curitiba (CR), Porto Alegre (PoA)	Cohort of 16,209 adolescents (13-14 yrs old) from the 21 centers involved in the International Study of Asthma and Allergies in Childhood (ISAAC). Each participant was given a questionnaire to identify various allergy-related symptoms that occurred in the last 12 mos. The relationship between affirmative answer to a question, socioeconomic status, and air pollutants was analyzed by the Spearman correlation coefficient. The location with the lowest level of a specific air pollutant was defined as the reference and the risk of an affirmative answer to a question was presented as an odds ratio for each location.	NR	In the analysis of the risk of allergy-related symptoms due to SO_2 levels in relation to the center with the lowest annual mean SO_2 concentrations SPW was significantly associated with every symptom. Other significant associations were observed in SA for current wheezing; in CR for rhinitis and rhinoconjunctivitis; and in PoA for current wheezing, nighttime cough, rhinitis, and eczema. Odds Ratio (95% CI)-Reference Center: São Paulo South (SPS) Current Wheezing: SPW: 1.21 (1.08, 1.38); SA: 1.31 (1.16, 1.48); CR: 1.02 (0.90, 1.15) PoA: 1.68 (0.85, 1.10) Severe Asthma: SPW: 2.01 (1.56, 2.60); SA: 1.04 (0.78, 1.40); CR: 1.08 (0.81, 1.42); PoA: 1.01 (1.29, 2.20) Nighttime Cough: SPW: 1.14 (1.03, 1.26); SA: 0.94 (0.85, 1.04); CR: 0.93 (0.84, 1.02); PoA: 1.25 (0.91, 1.12) Rhinitis Last Yr: SPW: 1.14 (1.02, 1.27); SA: 1.05 (0.94, 1.18); CR: 1.71 (1.54, 1.90); PoA: 1.36 (1.12, 1.40) Rhinoconjunctivitis: SPW: 1.78 (1.55, 2.04); SA: 1.15 (0.99, 1.33); CR: 1.50 (1.31, 1.72); PoA: 1.48 (1.18, 1.57) Severe Rhinitis: SPW: 1.50 (1.32, 1.71); SA: 1.08 (0.94, 1.24); CR: 1.52 (1.34, 1.73); PoA: 0.97 (1.30, 1.69) Eczema: SPW: 1.40 (1.17, 1.68); SA: 1.00 (0.83, 1.21); CR: 0.88 (0.72, 1.06); PoA: 1.40 (0.80, 1.18) Flexural Eczema: SPW: 2.00 (1.58, 2.52); SA: 0.95 (0.73, 1.24); CR: 1.02 (0.79, 1.31); PoA: 2.41 (1.09, 1.80) Severe Eczema: SPW: 2.58 (1.94, 3.44); SA: 0.92 (0.65, 1.30); CR: 0.71 (0.50, 1.02); PoA: NR (1.80, 3.22)
ASIA			
Ho et al. (2007) Taiwan Period of Study: 1995-1996	Survey of 69,367 children ages 12-15 by questionnaire. The max likelihood estimation was carried out with Fisher's scoring algorithm and GEE.	NR	SO_2 not significant in both genders. However, SO_2 showed a reversal effect on monthly asthma attack rate. (Authors state that this reversal effect could be caused by the interaction of sulfur dioxide with the lowest 5% monthly temperature avg)
Hwang et al. (2005) Taiwan Period of Study: 2001	A cross-sectional study consisting of 32,672 Taiwanese school children aged 6-15 yrs old. Using a modified Chinese version of the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire collected information on each participant's health, environmental exposures, and other variables. A two-stage hierarchical model consisting of logistic and linear regression analyses was used to account for, in the first stage, variation among subjects, and, in the second stage, variation among municipalities.	2000 (ppb): 3.53 (2.00)	Increased annual levels of NO_X, CO, and O_3 were associated with an increased risk of childhood asthma levels. In both single- and co-pollutant models SO_2 was not found to be associated with the risk of asthma. Odds Ratio (95% CI) (per 10 ppb SO_2) Single-pollutant model 0.874 (0.729, 1.054) Two-pollutant model NO_X + SO_2: 0.724 (0.545, 0.963) CO + SO_2: 0.689 (0.542, 0.875) SO_2 + O_3: 0.826 (0.674, 1.014)

Study	Methods	Pollutant Data	Findings
Peters et al. (1996) Hong Kong (Kwai Tsing; Southern) Period of Study: 1989-1991	Cohort of 3,521 children from two districts in Hong Kong with good and poor air quality prior to the 1990 legislation to reduce fuel sulfur levels. Analyses consisted of multivariate methods using logistic regression along with generalized estimating equations (GEE) to examine the effect of legislation implemented to reduce fuel sulfur levels on respiratory health.	Annual avg ($\mu g/m^3$) Southern 1989: 11 1990: 8 1991: 7 Kwai Tsing 1989: 111 1990: 67 1991: 23	SO_2 emissions were reduced by 80% after institution of the legislation. The study does not provide effect estimates for individual pollutants.
Wang et al. (1999) Taiwan (Kaohsiung; Pintong) Period of Study: 1995-1996	A cross-sectional study consisting of 165,173 high school students aged 11-16 yrs old residing in the communities of Kaohsiung and Pintong in Taiwan from Oct 1995 to Jun 1996. Used a video and questionnaire developed by the International Study of Asthma and Allergies in Childhood (ISAAC). The association between air pollution and asthma was examined using logistic regression. In addition, the study performed a multiple logistic regression to examine the independent effects of risk factors of asthma after adjusting for age, sex, parents' education, and area of residence. The multiple logistic regression included pollutant concentrations to examine the combined effect.	Median: 1996 (ppm): 0.013	In the univariate analysis, increasing concentrations of TSP, SO_2, NO_2, CO, O_3, and airborne dust were all found to be significantly associated with asthma. These univariate estimates are associated with concentrations above a cutoff (i.e., the median concentrations of each pollutant). In the multivariate analysis increasing concentrations of TSP, NO2, CO, O3, and airborne dust were significantly associated with asthma. Odds Ratio (95% CI) (per 0.013 ppm SO_2) Univariate analysis ≥ 0.013 ppm: 1.05 (1.02, 1.09) Adjusted Odds Ratio (95% CI) Multivariate analysis 0.98 (0.95, 1.02)
MIDDLE EAST			
Dubnov et al. (2007) Israel (Hadera, Pardes-Hanna) Period of Study: 1996 and 1999	Cohort of 1,492 schoolchildren (7-14 yrs old) living near a major coal-fired power station. Subjects underwent pulmonary function tests (PFT) for forced vital capacity (FVC) and forced expiratory volume during the first second (FEV_1) to examine the association between pulmonary function and long-term exposure to air pollution. Using stepwise multiple regression (SMR) and ordinary leas squares regression (OLS) examined the multiplicative effect of NO_X and SO_2 on pulmonary function.	1996 and 1999 avg (SD) (ppm): 12.9 (11.3)	Using an integrated concentration value (ICV), which equals the product of NO_X concentration and SO_2 concentration when both concentrations individually exceed the half-hour reference level, found significant associations between exposure to air pollution and decrements in pulmonary function. All Children: NOX x SO_2 ΔFVC (%) $\beta = -0.004$, $p < 0.001$ ΔFEV_1 (%) $\beta = -0.004$, $p < 0.001$ Children in zone of highest concentration of air pollution: NOX x SO_2 ΔFVC (%) $\beta = -0.005$, $p < 0.001$ ΔFEV_1(%) $\beta = -0.005$, $p < 0.001$
AFRICA			
Houssaini et al. (2007) Morocco	Cross-sectional study of 1,318 children with a mean age of 12 yrs. Used a questionnaire and medical diagnosis/reporting for asthma, and evaluated using Student's t-test, Chi-square, odds ratios, and Cochran-Armitage tests.	Annual Avg: 2000-2001: 60.2 $\mu g/m^3$ 2001-2002: 50.2 $\mu g/m^3$ 2002-2003: 49.6 $\mu g/m^3$ 2003-2004: 36.8 $\mu g/m^3$	Significant prevalence for respiratory diseases, asthma, and infectious disease, when combined with TSP.

Table F-7. Long-term exposure to SO_2 and lung cancer incidence and mortality.

Study	Methods	Pollutant Data	Findings
UNITED STATES			
Abbey et al. (1999) Three California air basins: San Francisco, South Coast (Los Angeles and eastward), San Diego Period of Study: 1977-1992	Prospective cohort study of 6,338 nonsmoking non-Hispanic white adult members of the Adventist Health Study followed for all cause, cardiopulmonary, nonmalignant respiratory, and lung cancer mortality. Participants were aged 27-95 yrs at enrollment in 1977. 1,628 (989 females, 639 males) mortality events followed through 1992. All results were stratified by gender. Used Cox proportional hazards analysis, adjusting for age at enrollment, past smoking, environmental tobacco smoke exposure, alcohol use, education, occupation, and body mass index. Analyzed mortality from all natural causes, cardiopulmonary, nonmalignant respiratory, and lung cancer.	Mean SO_2 Levels: 24-h avg SO_2: 5.6 ppb Copollutants: PM_{10} SO_4 O_3 NO_2	Lung cancer mortality showed large risk estimates for most of the pollutants in either or both sexes, but the number of lung cancer deaths in this cohort was very small (12 for female and 18 for male) Generally wide confidence intervals (relative to other U.S. cohort studies). Adjusted Mortality Relative Risk (95% CI) (per 3.72 ppb SO_2) Lung Cancer Males: 1.99 (1.24, 3.20) Females: 3.01 (1.88, 4.84)
Beeson et al. (1998) Three California air basins: San Diego, San Francisco, South Coast (Los Angeles and eastward) Period of Study: 1977-1992	Prospective cohort study of 6,338 nonsmoking non-Hispanic white adult members of the Adventist Health Study aged 27-95 yrs at time of enrollment. 36 (20 females, 16 males) histologically confirmed lung cancers were diagnosed through 1992. Extensive exposure assessment, with assignment of individual long-term exposures to O_3, PM_{10}, SO_4^{2-}, and SO_2, was a unique strength of this study. All results were stratified by gender. Used Cox proportional hazards analysis, adjusting for age at enrollment, past smoking, education, and alcohol use.	24-h avg SO_2: 5.6 ppb	Lung cancer incidence relative risk: Male: RR = 3.72 (95%CI: 1.91, 7.28); Female: RR = 2.78 (95%CI: 1.51, 5.12) per 5 ppb increase in SO_2 Case number very small (16 for male, 20 for female).
Krewski et al. (2000)	Re-analysis and sensitivity analysis of Dockery et al. (1993) Harvard Six Cities study.	Mean SO_2 Levels: 24-h avg SO_2 ranged from 1.6 (Topeka) to 24.0 (Steubenville) ppb Copollutants: Fine Particles, Sulfates	SO_2 showed positive associations with lung cancer deaths (1.03 (95% CI: 0.91, 1.16), but in this dataset, SO_2 was highly correlated with $PM_{2.5}$ (r = 0.85), sulfate (r = 0.85), and NO_2 (r = 0.84)
EUROPE			
Beelen et al. (2008) The Netherlands Period of Study: 1987-1996.	Cohort study on diet and cancer with 120,852 subjects who were followed from 1987 to 1996. BS, NO_2, SO_2, and $PM_{2.5}$ and traffic-exposure estimates were analyzed. Cox regression model adjusted for age, sex, smoking, and area-level socioeconomic status.	Mean SO_2 Levels: Mean: 4.8 ppb, with a range of 1.5 to 11.8 ppb. Copollutants: $PM_{2.5}$ BS NO_2	Traffic intensity on the nearest road was not associated with exposure SO_2. Background SO_2 levels were not associated with lung cancer mortality. Adjusted RR (per 20 µg/m³ SO_2) 1.00 (0.79, 1.26)
Filleul et al. (2005) Seven French cities Period of Study: 1975-2001	Cohort study of 14,284 adults who resided in 24 areas from seven French cities when enrolled in the PAARC survey (air pollution and chronic respiratory diseases) in 1974. Daily measurements of SO_2, TSP, BS, NO_2, and NO were made in 24 areas for three yrs (1974-1976). Cox proportional hazards models adjusted for smoking, educational level, BMI, and occupational exposure. Models were run before and after exclusion of six area monitors influenced by local traffic as determined by the NO/NO_2 ratio >3.	Mean SO_2 Levels: 24-h avg SO_2 ranged from 17 mg/m³ ("Area 3" in Lille) to 85 mg/m³ ("Area 3" in Marseille) in the 24 areas in seven cities during 1974-1976. Median levels during 1990-1997 ranged from 8.5 mg/m³ (Bordeaux) to 23.4 mg/m³ (Rouen) in the five cities where data were available. Copollutants: TSP BS NO_2 NO	The authors noted that inclusion of air monitoring data from stations directly influenced by local traffic could overestimate the mean population exposure and bias the results. It should be noted that the table describing air pollution levels in Filleul et al.'s report indicates that the SO_2 levels in these French cities declined markedly from 1974-1976 and 1990-1997 period, by a factor of 2 to 3, depending on the city, whereas NO_2 levels between the two periods were variable, increased in some cities, and decreased in others. These changes in air pollution levels over the study period complicate interpretation of reported risk estimates. Relative Risk (95% CI) for lung cancer mortality (per 10 mg/m³ multi-year average) All 24 areas: 0.99 (0.92, 1.07) 18 areas:1.00 (0.91, 1.11)

Study	Methods	Pollutant Data	Findings
Nafstad et al. (2003) Oslo, Norway Period of Study: 1972-1998	Retrospective study associating cardiovascular risk factors to a national cancer register among 16,209 men ages 10-49 yrs. Survival analyses and Cox proportional hazards regression were used to estimate associations.	Estimated for each person each yr from 1974 to 1998 Five-yr median avg levels SO_2 participants home address, 1974-1978: 9.4 µg/m^3 (range 0.2 to 55.8) Median levels within the quartiles: 2.5 µg/m^3. 6.2 µg/m^3 14.7 µg/m^3. 31.3 µg/m^3 Copollutants: NO_X	Adjusted risk ratios (95% CI) of developing lung cancer: Model 1: 0-9.99 µg/m^3: Ref 10-19.99 µg/m^3: 1.05 (0.81, 1.35) 20-29.99 µg/m^3: 0.95 (0.72, 1.27) 30+ µg/m^3: 1.06 (0.79, 1.43) Model 2: Per 10 µg/m^3: 1.01 (0.94, 1.08) Adjusted risk ratios (95% CI) of developing non-lung cancer: Model 1: 0-9.99 µg/m^3: Ref. 10-19.99 µg/m^3: 1.07 (0.96, 1.19) 20-29.99 µg/m^3: 0.90 (0.80, 1.02) 30+ µg/m^3: 0.98 (0.86, 1.10) Model 2: Per 10 µg/m^3: 0.99 (0.96, 1.02)
Nafstad et al. (2004) Oslo, Norway Period of Study: 1972-1998	Cohort study of 16,209 Norwegian men 40-49 yrs of age living in Oslo, Norway, in 1972-1973. Data from the Norwegian Death Register were linked with estimates of avg yearly air pollution levels at the participants' home addresses from 1974 to 1998. NO_X, rather than NO_2 was used. Exposure estimates for NO_X and SO_2 were constructed using models based on the subject's address, emission data for industry, heating, and traffic, and measured concentrations. Addresses linked to 50 of the busiest streets were given an additional exposure based on estimates of annual avg daily traffic. Cox proportional-hazards regression was used to estimate associations between exposure and total and cause-specific mortality, adjusting for age strata, education, occupation, smoking, physical activity level, and risk groups for cardiovascular diseases	Mean SO_2 Levels: The yearly avg of 24-h avg SO_2 were reduced with a factor of 7 during the study period from 5.6 ppb in 1974 to 0.8 ppb in 1995. Copollutants: NO_X	SO_2 did not show any associations with lung cancer, e.g., 1.00 (0.93, 1.08) per 10 µg/m^3 increase mortality in SO_2. No association was also observed when including SO_2 in the model as a categorical variable. Note the very low levels of SO_2.
Nyberg et al. (2000) Stockholm County, Sweden Period of Study: Jan 1, 1985-Dec 31, 1990	Case-control study of men 40-70 yrs, with 1,042 cases of lung cancer and 1,274 controls, to evaluate the suitability of an indicator of air pollution from heating.	Annual levels computed for each yr between 1950 and 1990, but not provided herein NO_X/NO_2	Little effect of SO_x in any time window, but highest correlations in early yrs. SO_X RR (CI 95%) from heating (per 10 µg/m^3) for 30-yr avg < 41.30 µg/m^3: 1 ≥ 41.30 to < 52.75: 1.06 (0.83, 1.35) ≥ 52.75 to < 67.14: 0.98 (0.77, 1.24) ≥ 67.14 to < 78.20: 0.90 (0.68, 1.19) ≥ 78.20: 1.00 (0.73, 1.37) SO_X RR (CI 95%) from heating (per 10 µg/m^3) for 10-yr avg < 66.20 µg/m^3: 1 ≥ 66.20 to < 87.60: 1.16 (0.91, 1.47) ≥ 87.60 to < 110.30: 1.00 (0.79, 1.27) ≥ 110.30 to < 129.10: 0.92 (0.70, 1.21) ≥ 129.10: 1.21 (0.89, 1.66)

Table F-8. Long-term exposure to SO_2 and prenatal and neonatal outcomes.

Study	Methods	Pollutant Data	Findings
UNITED STATES			
Bell et al. (2007) Connecticut and Massachusetts Period of Study: 1999-2002	Outcome(s): LBW Study design: Case-control N: 358,504 live singleton births Statistical Analysis: Linear models and logistic regression Covariates: Gestational length, prenatal care, type of delivery, child's sex, birth order, weather, yr, and mother's race, education, marital status, age, and tobacco use.	Gestational exposure (ppb) Mean: 4.7 SD: 1.2 IQR: 1.6 Copollutants: NO_2 CO PM_{10} $PM_{2.5}$	No relationship between gestational exposure to SO_2 and birth weight. First trimester exposure to SO_2 was associated with low birth weight. No statistical difference n the effect estimates of SO_2 for infants of black and white mothers. Increment: 1.6 ppb (IQR) Change in birth weight: Entire pregnancy: −0.9 g (−4.4, 2.6) Black mother: 1.2 (−6.5, 8.8) White mother: −1.4 (−5.1, 2.3) 1st trimester: −3.7 to −3.3 grams LBW: OR 1.003 (0.961, 1.046)
Gilboa et al. (2005) Seven Texas Counties Period of Study: 1997-2000	Outcome(s): Selected birth defects Study design: Case-control N: 4,570 cases and 3,667 controls Statistical Analysis: Logistic regression Covariates: Maternal education, maternal race/ethnicity, season of conception, plurality, maternal age, maternal illness Statistical package: SAS vs. 8.2	Levels NR Copollutants PM_{10} O_3 NO_2 CO	When the fourth quartile of exposure was compared with the first, SO_2 was associated with increased risk of isolated ventricular septal defects. Inverse associations were noted for SO_2 and risk of isolated atrial septal defects and multiple endocardial cushion defects. Aortic artery and valve defects: < 1.3 ppb: 1.00; 1.3 to < 1.9: NA; 1.9 to < 2.7: 1.06 (0.34, 3.29); ≥ 2.7: 0.83 (0.26, 2.68) Atrial septal defects: < 1.3 ppb: 1.00; 1.3 to < 1.9: 1.22 (0.79, 1.88); 1.9 to < 2.7: 0.76 (0.47, 1.23); ≥ 2.7: 0.42 (0.22, 0.78) Pulmonary artery and valve defects: < 1.3 ppb: 1.00; .3 to < 1.9: 0.63 (0.23, 1.74); 1.9 to < 2.7: 0.93 (0.36, 2.38); ≥ 2.7: 1.07 (0.43, 2.69) Ventricular septal defects: < 1.3 ppb: 1.00; 1.3 to < 1.9: 1.02 (0.68, 1.53); 1.9 to < 2.7: 1.13 (0.76, 1.68); ≥ 2.7: 2.16 (1.51, 3.09) Conotruncal defects: < 1.3 ppb: 1.00; 1.3 to < 1.9: 0.71 (0.46, 1.09); 1.9 to < 2.7: 0.71 (0.46, 1.09); ≥ 2.7: 0.58 (0.37, 0.91) Endocardial cushion and mitral valve defects: < 1.3 ppb: 1.00; 1.3 to < 1.9: 0.89 (0.50, 1.61); 1.9 to < 2.7: 0.89 (0.49, 1.62); ≥ 2.7: 1.18 (0.68, 2.06) Cleft lip with or without cleft palate: < 1.3 ppb: 1.00; 1.3 to < 1.9: 0.79 (0.52, 1.20); 1.9 to < 2.7: 0.95 (0.64, 1.43); ≥ 2.7: 0.75 (0.49, 1.15) Cleft palate: < 1.3 ppb: 1.00; 1.3 to < 1.9: 0.89 (0.40, 1.97); 1.9 to < 2.7: 1.49 (0.72, 3.06); ≥ 2.7: 1.22 (0.56, 2.66)

Study	Methods	Pollutant Data	Findings
Lipfert et al. (2000c) United States Period of Study: 1990	Mortality Outcome(s): SIDS Study design: Cohort Statistical Analysis: Three logistic regression analyses to examine the relation between annual avg air pollutant values and various infant mortality endpoints (i.e., all causes, SIDS, respiratory, and other causes Statistical package: NR Age groups analyzed: 0-1 Covariates: Altitude, degree days (°F), median income (U.S. $), population density Lag(s): N/A	Mean (SD) SO_2: 4.57 (2.6) ppb Range: 0.3, 9.9 Copollutants: PM_{10} (r = 0.04) CO (r = -0.15) SO_4^{2-} (r = 0.36) $NSPM_{10}$ (r = -0.13)	In a model that included states that lacked data on maternal education and smoking along with various personal and ecological variables, SO_2 was not found to be a significant predictor of SIDS mortality in infants with birth weights >2,500 g. β = −0.0118 (0.0094) Mean Risk (95% CI) 0.95 (0.87, 1.03)
Maisonet et al. (2001) 6 Northeastern cities of U.S. Period of Study: 1994-1996	Outcome(s): Term LBW Study design: Case-control N: 89,557 live singleton births Statistical Analysis: Logistic regression models linear regression models Covariates: Maternal age, race, season of the yr, smoking and alcohol use during pregnancy, firstborn, gender, marital status, and previous terminations, prenatal care (ordinal variable), weight gain, and gestational age Stratified by race/ethnicity Statistical package: STATA	Exposure distribution (< 25th, 25th to < 50th, 50th to < 75th, 75th to < 95th, ≥ 95th) First trimester: < 7.09, 7.090 to 8.906, 8.907 to 11.969, 11.970 to 18.447, ≥18.448 Second trimester: < 6.596, 6.596 to 8.896, 8.897 to 11.959, 11.960 to 18.275, ≥ 18.276 Third trimester: < 5.810, 5.810 to 8.453, 8.454 to 11.777, 11.778 to 18.134, ≥ 18.135 Copollutants: CO PM_{10}	This study provides evidence of an increased risk for term LBW in relation to increased ambient air levels of SO_2 at concentrations well below the established standards. Higher risk estimates among whites when stratified by race/ethnicity First trimester: < 25th: Referent 25th-50th: 1.04 (0.88, 1.23) 50th-75th: 1.04 (0.94, 1.15) 75th-95th: 0.98 (0.81, 1.17) > 95th: 0.88 (0.73, 1.07) Increment (10 ppm): 0.98 (0.93, 1.03) Second trimester: 25th-50th: 1.18 (1.12, 1.25) 50th-75th: 1.12 (1.07, 1.17) 75th-95th: 1.13 (1.05, 1.22) > 95th: 0.87 (0.80, 0.95) Increment (10 ppm): 1.01 (0.93, 1.10) Third trimester: 25th-50th: 1.04 (0.92, 1.18) 50th-75th: 1.02 (0.87, 1.18) 75th-95th: 1.04 (0.84, 1.28) > 95th: 1.06 (0.76, 1.47) Increment (10 ppm): 1.01 (0.86, 1.20)
Sagiv et al. (2005) 4 Pennsylvania counties Period of Study: 1997-2001	Outcome(s): Pre-term birth Study design: Time-series N: 187,997 births Study design: Poisson-regression models Covariates: Long-term trends, copollutants, temperature, dew point temperature, and day of wk. Lag: Daily lags ranging from 1-7 days	Mean SO_2 Levels: 6-wk Mean: 7.9 ± 3.5 ppb Range: 0.8, 17 Median: 8.1 Daily Mean: 7.9 ± 6.2 Range: 0, 54.1 Median: 6.4 Copollutants: PM_{10}; r = 0.46 CO NO_2	This study found an increased risk for preterm delivery during the last 6 wks of pregnancy with exposure to SO_2. Increment: 15 ppb Mean: 6-wk SO_2: RR = 1.15 (1.00, 1.32) < 4.9 ppb: Referent 4.9 to 8.1 ppb: 1.02 (0.97, 1.06) 8.1 to 10.6 ppb: 1.04 (0.98, 1.10) 10.6 to 17.0 ppb: 1.06 (0.99, 1.14) Mean: Daily SO_2: RR = 1.07 (0.99, 1.15) lag 3
CANADA			
Dales et al. (2004) 12 Canadian cities Period of Study: 1984-1999	Outcome(s): SIDS Study design: Time-series N: 1556 SIDS deaths Statistical Analysis: Random effects regression model Covariates: Temperature, humidity, barometric pressure, season Lag: 0-5 days	Mean SO_2 Levels: 24-h avg: 5.51 ppb IQR: 4.92 Copollutants: CO NO_2 O_3 PM_{10} $PM_{2.5}$ $PM_{10-2.5}$	SIDS was associated with air pollution, with the effects of SO_2 seeming to be independent of sociodemographic factors, temporal trends, and weather. Increment: 4.92 ppb (IQR) Increase in SIDS incidence: 8.49%; p = 0.0079 lag 1

Study	Methods	Pollutant Data	Findings
Dales et al. (2006) 11 Canadian cities Period of Study: 1986-2000	Outcome(s): Hospitalization for respiratory disease in the neonatal period Study design: Time-series N: 9,542 Statistical Analysis: Random effects regression model; Poisson using fixed- or random-effects model Covariates: Fay of wk, temperature, humidity, pressure Lag: 0-5 days Statistical package: S-PLUS vs. 6.2	Mean SO_2 Levels: 24-h avg: 4.3 ppb IQR: 3.8 Copollutants: NO_2 (r = 0.20, 0.67) CO (r = 0.19, 0.66) O_3 (r = −0.41, 0.13) PM_{10} (r = −0.09, 0.61) SO_4	This study detected a significant association for respiratory disease among neonates and gaseous air pollutants. Increment: 3.8 ppb (IQR) Increase in neonatal respiratory hospital admissions: SO_2 alone: 2.06% (1.04, 3.08) Multipollutant model: 1.66% (0.63, 2.69) Multipollutant model restricted to days with PM10 measures: 1.41% (0.35, 2.47)
Dugandzic et al. (2006) Nova Scotia, Canada Period of Study: 1988-2000	Outcome(s): Term LBW Study design: Retrospective cohort study N: 74,284 term, singleton births Statistical Analysis: Logistic regression models Covariates: Maternal age, parity, prior fetal death, prior neonatal death, and prior low birth weight infant, smoking during pregnancy, neighborhood family income, infant gender, gestational age, weight change, and yr of birth. Statistical package: SAS vs. 8.0	Mean: SO_2 10 ppb Median: 10 25th%: 7 75th%: 14 Max: 38 Copollutants: O_3 PM_{10}	In the analyses unadjusted for birth yr, first trimester exposures in the highest quartile for SO_2 associated with increased risk of LBW. After adjusting for birth yr, RR attenuated and not statistically significant. There was a linear concentration-response effect with increasing levels of SO_2 during the first trimester. First Trimester 25th-50th: 0.96 (0.73, 1.28) 51st-75th: 1.18 (0.88, 1.58) >75th: 1.36 (1.04, 1.78) Increment (7 ppb): 1.20 (1.05, 1.38) Second Trimester 25th-50th: 1.12 (0.86, 1.46) 51st-75th: 1.13 (0.85, 1.50) >75th: 1.04 (0.79, 1.37) Increment (7 ppb): 0.99 (0.87, 1.13) Third Trimester 25th-50th: 1.04 (0.80, 1.34) 51st-75th: 0.85 (0.63, 1.15) >75th: 0.88 (0.67, 1.15) Increment (7 ppb): 0.93 (0.81, 1.06)
Liu et al. (2003) Vancouver, Canada Period of Study: 1985-1998	Outcomes: Preterm birth, LBW, IUGR Study design: Case-control N: 229,085 singleton live births Statistical Analysis: Multiple logistic regressions Covariates: Maternal age, parity, infant sex, gestational age or birth weight and season of birth	24-h avg: 4.9 ppb, 5th: 1.5 25th: 2.8 50th: 4.3 75th: 6.3 95th: 10.5 100th: 30.5 1-h max: 13.4 ppb, 5th: 4.3 25th: 7.8 50th: 11.7 75th: 16.8 95th: 28.3 100th: 128.5 Copollutants: NO_2 (r = 0.61) CO (r = 0.64) O_3 (r = −0.35)	LBW and IUGR were associated with maternal exposure to SO_2 during the first mo of pregnancy and preterm birth was associated with SO_2 during the last mo. These results were robust to adjustment for copollutants. Increment: 5 ppb Low birth weight First mo: OR 1.11 (1.01, 1.22) Last mo: OR 0.98 (0.89, 1.08) Preterm birth First mo: OR 0.95 (0.88, 1.03) Last mo: OR 1.09 (1.01, 1.19) IUGR First mo: OR 1.07 (1.01, 1.13) Last mo: OR 1.00 (0.94, 1.06) First trimester: OR 1.07 (1.00, 1.14) Second trimester: 0.98 (0.91, 1.04) Third trimester: 1.03 (0.96, 1.10)

Study	Methods	Pollutant Data	Findings
Liu et al. (2006) Calgary, Edmonton and Montreal, Canada Period of Study: 1986-2000	Outcome(s): IUGR Study design: Case-control N: 386,202 singleton live births Statistical Analysis: Multiple logistic regression Covariates: Maternal age, parity, infant sex, season of birth, city of residence	24-h avg: 3.9 ppb, 25% 2.0 ppb 50% 3.0 ppb 75% 5.0 ppb 95% 10.0 ppb 1-h max: 10.8 ppb, 25% 5.0 ppb 50% 8.6 ppb 75% 14.0 ppb 95% 28.0 ppb Copolllutants: NO_2 (r = 0.34) CO (r = 0.21) O_3 (r = −0.30) $PM_{2.5}$ (r = 0.44)	IUGR did not increase with maternal exposure to SO_2. Risk decreased during first 3 mos. Increment: 3.0 ppb ORs estimated from graph: 1st mo: OR ~0.966 (0.94, 0.99) 2nd mo: OR ~0.97 (0.95, 0.995) 3rd mo: OR ~0.97 (0.95, 0.995) 1st trimester: OR ~0 .96 (0.93, 0.99)
Bobak (2000) Czech Republic Period of Study: 1991	Outcomes: LBW, preterm birth Study design: Case-control N: 108,173 live singleton births Statistical Analysis: Logistic regression Covariates: Temperature, humidity, day of wk, season, residential area, maternal age, gender Statistical package: STATA	Mean trimester exposures 25th: 17.5 µg/m^3 50th: 32.0 µg/m^3 75th: 55.5 µg/m^3 Copollutants: TSP; r = 0.68 0.73 NO_X; r = 0.53, 0.63	LBW and preterm birth were associated with maternal exposure to SO_2, though the association between SO_2 and LBW was explained to a large extent by low gestational age. Increment: 50 µg/m^3 LBW (adjusted for sex, parity, maternal age group, education, marital status, and nationality, and mo of birth): 1st trimester: 1.20 (1.11, 1.30) 2nd trimester: 1.14 (1.06, 1.22) 3rd trimester: 1.14 (1.06, 1.23) LBW (also adjusted for gestational age): 1st trimester: 1.01 (0.88, 1.17) 2nd trimester: 0.95 (0.82, 1.10) 3rd trimester: 0.97 (0.85, 1.10) Preterm birth (AOR): 1st trimester: 1.27 (1.16, 1.39) 2nd trimester: 1.25 (1.14, 1.38) 3rd trimester: 1.24 (1.13, 1.36) Reduction in mean birth weight: 1st trimester: 11.4 g (5.9, 16.9)
EUROPE			
Mohorovic (2004) Labin, Istra, Croatia Period of Study: 1987-1989	Outcomes: LBW and preterm delivery Study design: Cross-sectional N: 704 births Statistical Analysis: Multiple correlation analyses, factor analyses, chi-square Statistical package: DBASE IV, SPSS	Monthly ground levels of SO_2: Range: 34.1, 252.9 µg/m3	The results show an association between SO_2 exposure at the end of the first and second mo of pregnancy and a negative correlation between length of gestations and lower birth weight of newborns. Correlation coefficients: 1st mo: Gestation length: −0.09, p = 0.008 Birthweight: −0.08, p = 0.016 2nd mo: Gestation length: −0.08, p = 0.016 Birthweight: −0.07, p = 0.026 3rd mo: Gestation length: −0.04, p = 0.147 Birthweight: −0.04, p = 0.135 6th mo: Gestation length: −0.02, p = 0.266 Birthweight: −0.04, p = 0.151 Whole pregnancy: Gestation length: −0.09, p = 0.007 Birthweight: −0.04, p = 0.153 Weekly avg during whole pregnancy: Gestation length: −0.05, p = 0.086 Birthweight: −0.06, p = 0.069

Study	Methods	Pollutant Data	Findings
Pereira et al. (1998) São Paulo, Brazil Period of Study: 1991-1992	Outcome(s): Intrauterine mortality Study design: Time-series Statistical Analysis: Poisson regression models Covariates: Mo, day of wk, min daily temperature, relative humidity Lag: 2 to 14 days	24-h avg SO_2: 18.90 (8.53) mg/m3 Range: 3.80, 59.70 Copollutants: PM_{10} (r = 0.45) NO_2 (r = 0.41) O_3 (r = 0.17) CO (r = 0.24)	SO_2 exhibited a marginal association with intrauterine mortality, but only when Poisson regression was employed. A concentration-response relationship was found. Estimated regression coefficients and standard errors: SO_2 alone: 0.0038 (0.0020) $SO_2 + NO_2 + CO + PM_{10} + O_3$: 0.0029 (0.0031)
LATIN AMERICA			
Gouveia et al. (2004) São Paulo, Brazil Period of Study: 1997	Outcome(s): LBW Study design: Time-series N: 179,460 live singleton births Statistical Analysis: Logistic and linear regression with GAM Covariates: Gender, gestational age, maternal age, maternal education, antenatal care, parity, delivery method Statistical package: S-Plus 2000	Annual Mean: SO_2 (μg/m^3) Mean: 19.6 SD: 10.3 Range: 3.4, 56.9 Jan-Mar: 22.3 (7.7) Apr-June: 28.1 (10.1) Jul-Aug: 17.9 (8.7) Oct-Dec: 10.3 (3.9) Copollutants: PM_{10} CO NO_2 O_3	First and second trimester exposures to SO_2 had a significant association with birth weight, though in different directions. When air pollutants were divided into quartiles and the lowest quartile was used as the referent exposure category, SO_2 during the second trimester was marginally associated with low birth weight. Increment: 10 μg/m^3 Reduction in birth weight First trimester: −24.2 g (−55.5, 7.1) Second trimester: 33.7 g (1.6, 65.8) Third trimester: 9.7 g (−25.6, 44.9) First trimester: 2nd: 0.902 (0.843, 0.966) 3rd: 0.911 (0.819, 1.013) 4th: 0.906 (0.793, 1.036) Second trimester: 2nd: 0.986 (0.922, 1.053) 3rd: 1.005 (0.904, 1.117) 4th: 1.017 (0.883, 1.173) Third trimester: 2nd: 1.203 (0.861, 1.68) 3rd: 1.225 (0.872, 1.722) 4th: 1.145 (0.749, 1.752)
ASIA			
Ha et al. (2001) Seoul, Korea Period of Study: 1996-1997	Outcome(s): LBW Study design: Time-series N: 276,763 Statistical Analysis: Multiple regression, GAM Covariates: Gestational age, maternal age, parental education level, infant's birth order, gender	24-h avg: 1st trimester: 25th: 10.0 ppb 50th: 13.2 ppb 75th: 16.2 ppb 3rd trimester: 25th: 8.4 ppb 50th: 12.2 ppb 75th: 16.3 ppb Copollutants: CO (r = 0.83) NO_2 (r = 0.70) TSP (r = 0.67) O_3 (r = −0.29)	Ambient SO_2 concentrations during the first trimester of pregnancy were associated with LBW Increment: 1st trimester: 6.2 ppb; 3rd trimester: 7.9 ppb 1st trimester: RR 1.06 (1.02, 1.10) 3rd trimester: RR 0.93 (0.88, 0.98) Reduction in birth weight (1st trimester): 8.06 g (5.59, 10.53)
Lee et al. (2003a) Seoul, Korea Period of Study: 1996-1998	Outcome(s): Term LBW Study design: Time series N: 388,105 full-term singleton births Statistical Analysis: GAM Covariates: Infant sex, birth order, maternal age, parental education level, time trend, and gestational age.	Avg concentration (ppb) Mean: 12.1 SD: 7.4 Range: 3, 46 25th: 6.8 50th: 9.8 75th: 15.6 Copollutants: PM_{10}; r = 0.78, 0.85 CO; r = 0.79, 0.86 NO_2; r = 0.75, 0.76	Second trimester exposures to SO_2 as well as during the entire pregnancy were associated with LBW. Reduction in birth weight was 14.6 g for IQR increase in SO_2 in the second trimester. When the exposure for each mo of pregnancy was evaluated separately, SO_2 exposure during 3 to 5 mos of pregnancy associated with LBW. Increment: 8.8 ppb (IQR) First trimester: 1.02 (0.99, 1.06) Second trimester: 1.06 (1.02, 1.11) Third trimester: 0.96 (0.91, 1.00) All trimesters: 1.14 (1.04, 1.24)

Study	Methods	Pollutant Data	Findings
Leem et al. (2006) Incheon, Korea Period of Study: 2001-2002	Outcome(s): Preterm delivery Study design: Time series N: 52,113 singleton births Statistical Analysis: Log-binomial regression Covariates: Maternal age, parity, sex, season, maternal education, paternal education	Mean: SO_2 concentrations by trimester: 1st trimester: Min: 7.86 µg/m^3 25th: 17.61. 50th: 22.74 75th: 45.85. Max: 103.96 3rd trimester: Min: 6.55 µg/m^3 25th: 17.03. 50th: 25.62 75th: 46.53. Max: 103.15 Copollutants: NO_2 (r = 0.54) CO (r = 0.31) PM_{10} (r = 0.13)	This study found the highest SO_2 concentrations during the first trimester to be significantly associated with elevated risks of preterm delivery. 1st trimester: 7.86 to 17.61 µg/m^3: referent 17.62 to 22.74: 1.13 (0.99, 1.28) 22.75 to 45.85: 1.13 (0.98, 1.30) 45.86 to 103.96: 1.21 (1.04, 1.42) 3rd trimester: 6.55 to 17.03 µg/m^3: referent 17.04 to 25.62: 0.87 (0.76, 1.01) 25.63 to 46.53: 0.97 (0.83, 1.13) 46.54 to 103.15: 1.11 (0.94, 1.31)
Lin et al. (2004a) Kaohsiung and Taipei, Taiwan Period of Study: 1995-1997	Outcome(s): LBW Study design: Case-control N: 92,288 live births Statistical Analysis: Multiple logisistic regression Covariates: Gestational period, gender, birth order, maternal age, maternal education, season of birth	24-h avg: Kaohsiung: Range: 10.07, 25.36 ppb Taipei: Range: 5.65, 9.33 ppb Copollutants: CO NO_2 O_3 PM_{10}	Few women living in Taipei were exposed to high levels of SO_2. In Kaohsiung, almost all women were exposed to high levels of SO_2. Women living in Kaohsiung had significantly higher risk of term LBW compared with women living in Taipei. OR for Kaoshiung births (compared to Taipei births) All births: OR: 1.13 (1.03, 1.24) Female births only: OR: 1.14 (1.01, 1.28)
Lin et al. (2004b) Kaohsiung and Taipei, Taiwan Period of Study: 1995-1997	Outcome(s): Term LBW Study design: Cohort N: 92,288 live births Statistical Analysis: Multiple logisistic regression Covariates: Gestational period, gender, birth order, maternal age, maternal education, season of birth	24-h avg: Kaohsiung: Range: 10.07, 25.36 ppb Taipei: Range: 5.65, 9.33 ppb Copollutants: CO NO_2 O_3 PM_{10}	This study found a 26% higher risk of term LBW delivery for mothers exposed to mean SO_2 concentrations exceeding 11.4 ppb during the entire pregnancy, as compared with mothers exposed to mean concentrations less than 7.1 ppb. Trimester specific analysis showed a significant association only for the third trimester. Lowest quartile of exposure = referent Entire pregnancy: 25th-75th: 1.16 (1.02, 1.33) >75th: 1.26 (1.04, 1.53) 1st trimester: 25th-75th: 1.02 (0.90, 1.16) >75th: 1.11 (0.94, 1.33) 2nd trimester: 25th-75th: 1.09 (0.96, 1.24) >75th: 1.17 (0.99, 1.37) 3rd trimester:25th-75th: 1.13 (0.99, 1.28) >75th: 1.20 (1.01, 1.41)
Wang et al. (1997) Four residential areas: Congwen, Dongcheng, Xicheng, Xuanwu Beijing, China Period of Study: 1988-1991	Outcome(s): Term LBW Study design: Cohort study N: 74,671 first parity live births Statistical Analysis: Multiple linear regression and logistic regression Covariates: Gestational age, residence, yr of birth, maternal age, and infant gender.	Mean pollution concentrations provided in graph TSP; r = 0.92	Exposure-response relationship between SO_2 during the third trimester of pregnancy and low birth weight. 3rd trimester: 9 to 18 µg/m^3 (reference) 18 to 55: 1.09 (0.94, 1.26) 55 to 146: 1.12 (0.97, 1.29) 146 to 239: 1.16 (1.01, 1.34) 239 to 308: 1.39 (1.22, 1.60) SO_2 as continuous variable: Odds ratio per 100 µg/m^3: 1.11 (1.06, 1.16)

Study	Methods	Pollutant Data	Findings
Xu et al. (1995) Four residential areas: Congwen, Dongchen, Xichen, Xuanwu Beijing, China Period of Study: 1988	Outcome(s): Preterm delivery Study design: Prospective cohort study N: 25,370 singleton first live births Statistical Analysis: Multiple linear and logistic regression Covariates: Temperature, humidity, day of wk, season, residential area, maternal age, and gender of child.	2 monitors for SO_2: Dongcheng and Xicheng Dongcheng annual mean: 108 μg/m^3 SD: 141 μg/m^3) Xicheng annual mean: 93 μg/m^3 (SD: 122 μg/m^3) Copollutants: TSP	Exposure response relationship between quartiles of SO_2 and crude incidence rates of preterm birth. Dose dependent relationship between SO_2 and gestational age. The estimated reduced length of gestation was 0.075 wks or 12.6 h per 100/m^3 increase in SO_2. When TSP and SO_2 included in a multipollutant model, the effect of SO_2 was reduced by 32%. Effect on gestational age (wk) per 100 μg/m^3 regression coef and SE for lagged moving avg of SO_2. lag 0: −0.016 (0.021). lag 1: −0.022 (0.021) lag 6: −0.067 (0.024), p < 0.01 lag 7: −0.075 (0.024) , p < 0.01 lag 8: −0.075 (0.025), p < 0.01 OR for each quartile of SO_2 1st: 1.00. 2nd: 1.70 (1.15, 2.52) 3rd: 1.74 (1.03, 2.92). 4th: 1.58 (0.87, 2.86) Adjusted OR for preterm delivery: 1.21 (1.01, 1.46) per ln μg/m^3 increase in SO_2
Yang et al. (2003a) Kaohsiung, Taiwan Period of Study: 1995-1997	Outcome(s): Term LBW Study design: Cohort N: 13,396 first parity singleton live births Statistical Analysis: Multiple linear regression Covariates: Maternal age, season, marital status, maternal education, gender Statistical package: SAS	Mean: trimester exposure (μg/m^3) 1st trimester 33rd: 26.02 67th: 36.07 2nd trimester 33rd: 25.76 67th: 35.63 3rd trimester 33rd: 25.39 67th: 36.96 Copollutants: PM_{10} (r = 0.45, 0.46)	A significant exposure-response relationship between maternal exposures to SO_2 and birth weight was found first trimester of pregnancy. Reduction in birth weight: 1st trimester: 33rd-67th: 3.68 g (−12.45, 19.21) >67th: 18.11 g (1.88, 34.34) Continuous: 0.52 g (0.09, 2.63) 2nd trimester: 33rd-67th: 1.78 g (−17.91, 14.35) >67th: 13.53 g (−2.62, 29.68) Continuous: 0.19 g (−0.78, 1.8) 3rd trimester: 33rd-67th: 0.43 g (−16.56, 15.70) >67th: 1.97 g (−18.24, 14.30) Continuous: 0.03 g (−1.21, 1.37)

Table F-9. Long-term exposure to SO_2 and mortality.

Study	Pollutant Data	Methods	Findings
UNITED STATES			
Abbey et al. (1999) Three California air basins: San Diego, San Francisco, South Coast (Los Angeles and eastward) Period of Study: 1977-1992	24-h avg SO_2: 5.6 ppb	Prospective cohort study of 6,338 nonsmoking non-Hispanic white adult members of the Adventist Health Study followed for all cause, cardiopulmonary, nonmalignant respiratory, and lung cancer mortality. Participants were aged 27-95 yrs at enrollment in 1977. 1,628 (989 females, 639 males) mortality events followed through 1992. All results were stratified by gender. Used Cox proportional hazards analysis, adjusting for age at enrollment, past smoking, environmental tobacco smoke exposure, alcohol use, education, occupation, and body mass index. Analyzed mortality from all natural causes, cardiopulmonary, nonmalignant respiratory, and lung cancer.	SO_2 was not associated with total RR = 1.07 (95% CI: 0.92, 1.24) for male and 1.00 (95% CI: 0.88, 1.14) for female per 5 ppb increase in multiyear avg SO_2 , cardiopulmonary, or respiratory mortality for either sex. Lung cancer mortality showed large risk estimates for most of the pollutants in either or both sexes, but the number of lung cancer deaths in this cohort was very small (12 for female and 18 for male) Generally wide confidence intervals (relative to other U.S. cohort studies).
Dockery et al. (1993) and reanalysis by Krewski et al. (2000) Harriman, TN; Portage, WI; St. Louis, MO; Steubenville, OH; Topeka, KS; Watertown, MA; Period of Study: 1974-1991.	24-h avg SO_2 ranged from 1.6 (Topeka) to 24.0 (Steubenville) ppb.	A prospective cohort study to study the effects of air pollution with main focus on PM components in six U.S. cities, which were chosen based on the levels of air pollution (Portage, WI, the least polluted to Steubenville, OH, the most polluted). Cox proportional hazards regression was conducted with data from a 14-to-16-yr follow-up of 8,111 adults in the six cities, adjusting for smoking, sex, BMI, occupational exposures, etc. $PM_{2.5}$ and sulfate were associated with these causes of deaths.	SO_2 result presented only graphically. Fine particles and sulfate showed better fit than SO_2. In the reanalysis by Krewski et al (2000), SO_2 showed positive associations with total RR = 1.05 (95% CI: 1.02, 1.09) per 5 ppb increase in the avg SO_2 over the study period, cardiopulmonary (1.05 (95% CI: 1.00, 1.10)), and lung cancer deaths (1.03 (95% CI: 0.91, 1.16)), but in this dataset, SO_2 was highly correlated with $PM_{2.5}$ (r = 0.85), sulfate (r = 0.85), and NO_2 (r = 0.84)

Study	Pollutant Data	Methods	Findings
Krewski et al. (2000); Jerrett et al. (2003); Krewski et al. (2003); Re-analysis/sensitivity analysis of Pope et al. (1995) study.	Multiyear avg of 24-h avg 9.3 ppb.	Re-analysis of Pope et al. (1995) study. Extensive sensitivity analysis with ecological covariates and spatial models to account of spatial pattern in the ACS data.	In the Jerret et al. reanalysis the relative risk estimates for total mortality was 1.06 (95% CI: 1.05, 1.07) per 5 ppb increase in the annual avg SO_2. In the spatial filtering model (this was the model that resulted in the largest reduction of SO_2 risk estimate when sulfate was included), the SO_2 total mortality risk estimate was 1.07 (95% CI: 1.03, 1.11) in the single-pollutant model and 1.04 (95% CI: 1.02, 1.06) with sulfate in the model. The risk estimates for $PM_{2.5}$ and sulfate were diminished when SO_2 was included in the models. In the sensitivity analysis conducted by Krewski et al. SO_2 was significantly associated with all-cause mortality in a single-pollutant model: 1.30 (1.23, 1.38). In the spatial analysis, SO_2 was found to be the only gaseous pollutant strongly associated with all-cause and cardiopulmonary disease mortality: Relative Risk (95% CI) (per 19.9 μg/m^3 Sulfates) Spatial Analysis, All-Cause: Independent Observations: Sulfates + SO_2: 1.05 (0.98, 1.12) Fine particles + SO_2: 1.03 (0.95, 1.13) Independent Cities: Sulfates + SO_2: 1.13 (1.02, 1.25) Fine particles + SO_2: 1.14 (0.98, 1.32) Regional Adjustment: Sulfates + SO_2: 1.10 (0.97, 1.24) Fine particles + SO_2: 1.11 (0.93, 1.33) Spatial Filtering: Sulfates + SO_2: 1.05 (0.97, 1.14) Cardiopulmonary Disease: Independent Observations: Sulfates + SO_2: 1.13 (1.03, 1.24) Fine particles + SO_2: 1.17 (1.03, 1.33) Independent Cities: Sulfates + SO_2: 1.18 (1.04, 1.34) Fine particles + SO_2: 1.25 (1.05, 1.49) Regional Adjustment: Sulfates + SO_2: 1.12 (0.96, 1.32) Fine particles + SO_2: 1.23 (0.97, 1.55) Spatial Filtering: Sulfates + SO_2: 1.10 (0.99, 1.22) Lung Cancer: Independent Observations: Sulfates + SO_2: 1.37 (1.08, 1.73) Independent Cities: Sulfates + SO_2: 1.39 (1.08, 1.81)
Lipfert et al. (2006) 32 Veterans Administration hospitals nationwide in the U.S. Period of Study: 1976-1996	SO_2 mean levels NR.	Cohort study of approximately 50,000 U.S. veterans (all males) diagnosed with hypertension. Mean age at recruitment was 51 yrs. Exposure to O_3 during four periods (1960-1974, 1975-1981, 1982-1988, 1989-1996) associated with mortality over three periods (1976-1981, 1982-1988, 1989-1996). Long-term exposures to TSP, PM_{15}, PM_{10}, $PM_{2.5}$, $PM_{15-2.5}$, SO_4^{2-}, NO_2, and CO also analyzed. Used Cox proportional hazards regression, adjusting for race, smoking, age, systolic and diastolic blood pressure, body mass index, and socioeconomic factors.	SO_2 andd Pb were considered less thoroughly. The authors presented only qualitative results for SO_2 from the "screening regressions" which indicated negatively significant risk estimate in the univariate model and non-significant positive estimate in the multivariate model.

Study	Pollutant Data	Methods	Findings
Lipfert et al. (2000b) 32 Veterans Administration hospitals nationwide in the U.S. Period of Study: 1976-2001	Mean of the 95th percentile of the 24-h avg SO_2 for 1997-2001 period: 15.8 ppb.	Update of the Lipfert et al. (2000a) study, with follow-up period extended to 2001. Study focused on the traffic density data. The county-level traffic density was derived by dividing vehicle-km traveled by the county land area. Because of the wide range of the traffic density variable, log-transformed traffic density was used in their analysis. They reported that traffic density was a better predictor of mortality than ambient air pollution variables, with the possible exception of O_3. The log-transformed traffic density variable was weakly correlated with SO_2 (r = 0.32) in this data set.	RR using the 1997-2001 air quality data period: 0.99 (95% CI: 0.97, 1.01) per 5 ppb increase; in a single-pollutant model. The 2-pollutant model with the traffic density variable: 0.99 (95% CI: 0.96, 1.01) per 5 ppb.
Lipfert et al. (2006b) 32 Veterans Administration hospitals nationwide in the U.S. Period of Study: 1997-2001	Mean of the 95th percentile of the 24-h avg SO_2 for 1999-2001 period: 16.3 ppb.	Update of the Lipfert et al. (2000a) study, examined $PM_{2.5}$ chemical constituents data. The analysis used county-level air pollution data for the period 1999-2001 and cohort mortality data for 1997-2001.	Traffic density was the most important predictor of mortality, but associations were also seen for EC, V, nitrate, and Ni. NO_2, O_3, and PM_{10} also showed positive but weaker associations. The risk estimate for SO_2 was essentially the same as that reported in the 2006a Lipfert et al. analysis (0.99 (95% CI: 0.96, 1.01) per 5 ppb) in a single-pollutant model. Multipollutant model results were not presented for SO_2.
Pope et al. (1995) U.S. nationwide Period of Study: 1982-1989	Not analyzed/ reported.	Investigated associations between long-term exposure to PM and the mortality outcomes in the American Cancer Society cohort. Ambient air pollution data from 151 U.S. metropolitan areas in 1981 were linked with individual risk factors in 552,138 adults who resided in these areas when enrolled in the prospective study in 1982. Death outcomes were ascertained through 1989. Cox proportional hazards model adjusted for smoking, education, BMI, and occupational exposures. $PM_{2.5}$ and sulfate were associated with total, cardiopulmonary, and lung cancer mortality, but not with mortality for all other causes.	Gaseous pollutants not analyzed.
Pope et al. (2002) U.S. nationwide Period of Study: 1982-1998	24-h avg mean of 118 MSA's in1980: 9.7 ppb; mean of 126 MSA's during 1982-1998: 6.7 ppb.	Prospective cohort study of approximately 500,000 members of American Cancer Society cohort enrolled in 1982 and followed through 1998 for all cause, cardiopulmonary, lung cancer, and all other cause mortality. Age at enrollment was 30+ yrs. Air pollution concentrations in urban area of residence at time of enrollment assessed from 1982 through 1998. Other pollutants considered include TSP, PM_{15}, PM_{10}, $PM_{2.5}$, $PM_{15-2.5}$, SO_4^{2-}, SO_2, NO_2, and CO.	$PM_{2.5}$ was associated with total, cardiopulmonary, lung cancer mortality, but not with deaths for all other causes. SO_2 was associated with all the mortality outcomes, including all other causes of deaths. SO_2's risk estimate for total mortality was 1.03 (95% CI: 1.02, 1.05) per 5 ppb increase (1982-1998 average).Residential location was known only at enrollment to study in 1982. Thus, exposure misclassification possible.
Willis et al. (2003) Re-analysis/ sensitivity analysis of Pope et al. (1995) study.	Multiyear average of 24-h avg using MSA scales: 9.3 ppb; using county scales: 10.7 ppb.	Investigation of the effects of geographic scale over which the air pollution exposures are averaged. Exposure estimates were averaged over the county scale, and compared the original ACS results in which MSA scale avg exposures were used. Less than half of the cohort used in the MSA-based study were used in the county scale based analysis because of the limited availability of sulfate monitors and because of the loss of subjects from the use of five-digit zip codes	In the analysis comparing the 2-pollutant model with sulfate and SO_2, they found that, in the MSA-scale model, the inclusion of SO_2 reduced sulfate risk estimates substantially (>25%), but not substantially (< 25%) in the county-scale model. In the MSA-level anlaysis (with 113 MSA's), SO_2 relative risk estimate was 1.04 (95% CI: 1.02, 1.06) per 5 ppb increase, with sulfate in the model. In the county-level anaysis (91 counties) with sulfate in the model, the corresponding estimate was smaller (RR = 1.02 [95% CI: 1.00, 1.05]). The correlations between covariates are different between the MSA-level data and county-level data.

Study	Pollutant Data	Methods	Findings
CANADA			
Finkelstein et al. (2003) Ontario, Canada Period of Study: 1992-1999	24-h avg (ppb): 4.9 (1.0)	Cohort consisting of 5,228 people >40 yrs old that were referred for pulmonary function testing between 1985 and 1999. Within the cohort identified nonaccidental deaths that occurred from 1992 through 1999. Used air quality data for TSP from 1992-1994 and SO_2 for 1993-1995. Analyzed the association between TSP or SO_2 and socioeconomic status and mortality using a Cox proportional hazards model stratified by sex and 5-yr age groups.	Using the high income-low pollutant level as the reference the following results were reported for each of the mortality endpoints: Relative Risk (95% CI) All causes High income-high pollutant level: 1.35 (1.05, 1.73) Low income-low pollutant level: 1.64 (1.21, 2.24) Low income-high pollutant level: 2.40 (1.61, 3.58) Interaction with age group: 0.97 (0.95, 0.99) Cardiopulmonary causes High income-high pollutant level: 1.54 (1.13, 2.10) Low income-low pollutant level: 2.05 (1.45, 2.91) Low income-high pollutant level: 3.36 (2.12, 5.32) Interaction with age group: 0.95 (0.92, 0.97)
EUROPE			
Beelen et al. (2008) The Netherlands Period of Study: 1987-1996.	Cohort study on diet and cancer with 120,852 subjects followed from 1987 to 1996. BS, NO_2, SO_2, and $PM_{2.5}$ and traffic-exposure estimates were analyzed. Cox regression model adjusted for age, sex, smoking, and area-level socioeconomic status.	Mean SO_2 Levels: Mean: 4.8 ppb, with a range of 1.5 to 11.8 ppb. Copollutants: $PM_{2.5}$ BS NO_2	Traffic intensity on the nearest road was not associated with exposure SO_2. Background SO_2 levels were not associated with mortality. Adjusted RR (per 20 μg/m^3 SO_2) All cause: 0.97 (0.90,1.05) Cardiovascular: 0.94 (0.82, 1.06) Respiratory: 0.88 (0.64, 1.22)
Elliott et al. (2007) Great Britain; 1966-1994 air pollution; 1982-1998 mortality in four periods.	24-h avg SO_2 levels declined from 41.4 ppb in 1966-1970 to 12.2 ppb in 1990-1994	A small area analysis of mortality rates in electoral ward, with the mean area of 7.4 km^2 and the mean population of 5,301 per electoral ward. Deaths rates were computed for four successive 4-yr periods from 1982 to 1994. The number of wards in these four periods ranged from 118 in the 1994-1998 period to 393 in the 1982-1986 period. Poisson model was fit to model observed deaths for each ward with a linear function for pollutant and random intercept, with and without adjustment for social deprivation.	They observed associations for both BS and SO_2 and mortality outcomes. The estimated effects were stronger for respiratory illness than other causes of mortality for the most recent exposure periods and most recent mortality period (pollution levels were lower). The adjustment for social deprivation reduced the risk estimates for both pollutants. The adjusted risk estimates for SO_2 for the pooled mortality periods using the most recent exposure windows were: 1.021 (95% CI: 1.018, 1.024) for all-cause; 1.015 (95% CI: 1.011, 1.019) for cardiovascular; and 1.064% (95% CI: 1.056, 1.072) for respiratory causes per 5 ppb increase in SO_2. The risk estimates for the most recent mortality period using the most recent exposure windows were larger.
Filleul et al. (2005) Seven French cities Period of Study: 1975-2001	24-h avg SO_2 ranged from 5.9 ppb ("Area 3" in Lille) to 29.7 ppb ("Area 3" in Marseille) in the 24 areas in seven cities during 1974-1976. Median levels during 1990-1997 ranged from 3.0 ppb (Bordeaux) to 8.2 ppb (Rouen) in the five cities where data were available.	Cohort study of 14,284 adults who resided in 24 areas from seven French cities when enrolled in the PAARC survey (air pollution and chronic respiratory diseases) in 1974. Daily measurements of SO_2, TSP, BS, NO_2, and NO were made in 24 areas for three yrs (1974-76). Cox proportional hazards models adjusted for smoking, educational level, BMI, and occupational exposure. Models were run before and after exclusion of six area monitors influenced by local traffic as determined by the NO/NO_2 ratio >3.	Before exclusion of the six areas, none of the air pollutants were associated with mortality outcomes. After exclusion of these areas, analyses showed associations between total mortality and TSP, BS, NO_2, and NO, but not SO_2 (1.01 (95% CI: 0.97, 1.06) per 5 ppb multi-yr average). From these results, the authors noted that inclusion of air monitoring data from stations directly influenced by local traffic could overestimate the mean population exposure and bias the results. It should be noted that the table describing air pollution levels in Filleul et al.'s report indicates that the SO_2 levels in these French cities declined markedly between 1974-76 and 1990-1997 period, by a factor of 2 to 3, depending on the city, whereas NO_2 levels between the two periods were variable, increased in some cities, and decreased in others. This change in air pollution levels over the study period complicates interpretation of reported risk estimates.

Study	Pollutant Data	Methods	Findings
Lepeule et al. (2006) Bordeaux, France Period of Study : 1988–1997	24-h avg (µg/m^3): 10.3 (6.6)	Identified 439 non-accidental deaths and 158 cardiorespiratory deaths from the Personnes Agées QUID (PAQUID) cohort. Used a Cox proportional hazards model with time dependent covariates to examine the association between BS and sulfur dioxide-strong acidity (SO_2-AF) and non-accidental and cardiorespiratory mortality.	Relative Risk (per 10 µg/m^3 SO_2-AF) Non-accidental Mortality: 1.03 (0.86, 1.24) lag 0. 0.96 (0.88, 1.06) lag 1 0.96 (0.85, 1.09) lag 2. 1.03 (0.94, 1.12) lag 3 1.17 (0.99, 1.39) lag 4. 1.16 (0.86, 1.55) cumulative Cardiorespiratory mortality: 0.84 (0.65, 1.10) lag 0. 1.06 (0.94, 1.19) lag 1 1.19 (1.03, 1.37) lag 2. 1.19 (1.03, 1.37) lag 3 1.07 (0.95, 1.19) lag 4. 0.85 (0.66, 1.10) lag 5 1.15 (0.75, 1.77) cumulative
Nafstad et al. (2004) Oslo, Norway Period of Study: 1972-1998.	The yearly averages of 24-h avg SO_2 were reduced with a factor of 7 during the study period from 5.6 ppb in 1974 to 0.8 ppb in 1995.	Cohort study of 16,209 Norwegian men 40-49 yrs of age living in Oslo, Norway, in 1972-1973. Data from the Norwegian Death Register were linked with estimates of avg yearly air pollution levels at the participants' home addresses from 1974 to 1998. NO_X, rather than NO_2 was used. Exposure estimates for NO_X and SO_2 were constructed using models based on the subject's address, emission data for industry, heating, and traffic, and measured concentrations. Addresses linked to 50 of the busiest streets were given an additional exposure based on estimates of annual avg daily traffic. Cox proportional-hazards regression was used to estimate associations between exposure and total and cause-specific mortality, adjusting for age strata, education, occupation, smoking, physical activity level, and risk groups for cardiovascular diseases.	NO_X was associated with total, respiratory, lung cancer, and ischemic heart disease deaths. SO_2 did not show any associations with mortality (e.g., 0.97 (95% CI: 0.94, 1.01) per 5 ppb multi-yr average). The risk estimates presented for categorical levels of these pollutants showed mostly monotonic exposure-response relationships for NO_X, but not for SO_2. Note the very low levels of SO_2.

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