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Integrated Science Assessment for Carbon Monoxide

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

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Acronyms and Abbreviations

α	alpha, ambient exposure factor
a	air exchange rate of the microenvironment
AA	abdominal aorta(s)
AADT	annual average daily traffic
ABR	auditory brainstem response
ACS	American Cancer Society
ACS-CPS-II	ACS Cancer Prevention Study II
ADP	adenosine diphosphate
AEFV	area under the expiratory flow-volume curve
AGL	above ground level
Akt	Akt cell signaling pathway
AMI	acute myocardial infarction
AMP	adenosine monophosphate
ANOVA	analysis of variance
APO E	apolipoprotein E
ARI	acute respiratory infection
AP	action potential
APD	action potential duration
APEX	Air Pollution Exposure
APHEA	Air Pollution and Health: A European Approach
APTT	activated partial thromboplastin time
AQ	air quality
AQCD	Air Quality Criteria Document
AQS	Air Quality System
AR	gastronomy reared
ARCO	gastronomy reared + CO exposure
ARIC	Atherosclerosis Risk in Communities
ARID	gastronomy reared with iron deficient diet
ARIDCO	gastronomy reared with iron deficient diet + CO exposure
ATP	adenosine triphosphate
ATS	American Thoracic Society
AVP	aortic valve prosthesis

β	beta, beta coefficient, slope
B lymphocytes	bursa-dependent lymphocytes
BALF	bronchoalveolar lavage fluid
BC	black carbon
BEAS-2B	human bronchial epithelial cell line
BEIS	Biogenic Emissions Inventory System
BELD	Biogenic Emissions Landcover Database
BHR	bronchial hyper-responsiveness
BK_{Ca}	voltage and Ca^{2+}-activated K^+ channel(s)
BP	blood pressure
BQ-123	endothelin A (ET_A) receptor antagonist
BS	black smoke
BSP	black smoke particles
C_a	ambient concentration
CA	cardiac arrhythmia
Ca^{2+}	calcium ion
CAA	Clean Air Act
CAD	coronary artery disease
CALINE	California Line Source Dispersion Model
CAMP	Childhood Asthma Management Program
cAMP	cyclic AMP
CAP(s)	concentrated ambient particles, compound action potential(s)
CASAC	Clean Air Scientific Advisory Committee
CASN	Cooperative Air Sampling Network
CAth	cardiac atherosclerosis
CBSA	Core-Based Statistical Area
CCGG	Carbon Cycle Greenhouse Gases Group
CD	cardiac dysrhthmias
CD-1	mouse strain
CDC	Centers for Disease Control and Prevention
$CdCl_2$	cadmium chloride
CFK	Coburn-Forster-Kane
CFR	Code of Federal Regulations
cGMP	cyclic GMP
CH_2O	formaldehyde

CH_2O_2	formic acid
CH_3	methyl groups
CH_3CHO	acetaldehyde
CH_3CO	acetyl radical(s)
$CH_3CO_3NO_2$	PAN, peroxyacetyl nitrate
CH_3O_2	methyl peroxy radical
CH_3OOH	methyl hydroperoxide
CH_4	methane
ChAT	choline acetyl-transferase
CHD	coronary heart disease
CHF	congestive heart failure
CI	confidence interval(s)
CIS	cerebral ischemic stroke
C_j	airborne concentration at location *j*
CL/P	cleft lip with or without palate
CNS	central nervous system
CO	carbon monoxide
CO_2	carbon dioxide
COD	coefficient of divergence
CoH, COH	coefficient of haze
COHb	carboxyhemoglobin (% concentration measured in (mL CO/mL blood))
COMb	carboxymyoglobin
CONUS	contiguous U.S.
COPD	chronic obstructive pulmonary disease
CPS II	Cancer Prevention Study II
C-R	concentration-response
CRC	Coordinating Research Council
CrMP	collapsin response mediator protein
CRP	C-reactive protein
CSA	Combined Statistical Area
CVD	cardiovascular disease
d	straight-line distance between monitor pairs
df	degrees of freedom
D_L	lung diffusing capacity
D_LCO	lung diffusing capacity of CO

D_mCO	capacity for diffusion of CO into the muscle
DMT-1	divalent metal transporter-1
DMV	dorsal motor nucleus of the vagus nerve
DNA	deoxyribonucleic acid
DOCA	Deoxycorticosterone acetate
dP/dt_{LV}	left ventricular maximal and minimal first derived pressure ($+dP/dt_{LV}$, $-dP/dt_{LV}$)
dP/dt_{RV}	right ventricular maximal and minimal first derived pressure ($+dP/dt_{RV}$, $-dP/dt_{RV}$)
DSA	deletion/substitution/addition
E	exposure over some duration
E_a	exposure to pollutant of ambient origin
EC	elemental carbon
ED	emergency department
EKG, ECG	electrocardiogram
E_{na}	exposure to pollutant of non-ambient origin
eNOS	endothelial nitric oxide synthase
EPA	U.S. Environmental Protection Agency
EPO	erythropoietin
EPR	Electron Paramagnetic Resonance
EPRI	Electric Power Research Institute
ESRL	Earth System Research Laboratory
ET-1	endothelin-1
ET_A	endothelin A (ET_A) receptor
ETS	environmental tobacco smoke
EXPOLIS	six-city European air pollution study
FAS	apoptosis stimulating fragment
FC	interference filter
FEF	forced expiratory flow (L/s)
FEF_{25-75}	forced expiratory flow between the times at which 25% and 75% of the vital capacity is reached
FEM	Federal equivalent method
FEV_1	forced expiratory volume in 1 second
f_i	fraction of time spent indoors
F_ICO	fractional concentration of CO in ambient air
F_{inf}	infiltration factor

f_o	fraction of time spent outdoors
FR	Federal Register
FGR	fetal growth restriction(s)
FRM	Federal reference method
FSH	follicle stimulating hormone
FVC	forced vital capacity
FVII	Factor VII
FW	fresh weight
GAM	generalized additive model(s)
GD	gestational day
GEE	generalized estimating equations
GEM	gas extraction monitor
GFAP	glial fibrillary acidic protein
GFC	gas filter correlation
GLM	generalized linear models
GLMM	generalized linear mixed models
GMD	Global Monitoring Division
GMP	guanosine monophosphate
GSH	glutathione
GSSG	oxidized glutathione
GTP	guanosine triphosphate
GWP(s)	global warming potential(s)
H	atomic hydrogen, hydrogen radical, height
h	hour
H_2O_2	hydrogen peroxide
H9c2	rat embryonic cardiomyocytes
Hb	hemoglobin
HC(s)	hydrocarbon(s)
HCFC(s)	hydrochlorofluorocarbon(s)
HCO	formyl radical
HEAPSS	Health Effects of Air Pollution among Susceptible Subpopulations
HEK293	human embryonic kidney cells (experimentally transformed cell line)
Hep3B	Human hepatocarcinoma cell line
HF	heart failure, high frequency (HRV parameter)
HFLFR	high frequency to low frequency ratio (HRV parameter)

HH	hypobaric hypoxia
HIF-1α	hypoxia-inducible factor
HO	heme oxygenase
HO_2	hydroperoxy radical
HO-1	inducible isoform of heme oxygenase
HO-2	constitutively expressed isoform of heme-oxygenase
HO/CO	heme oxygenase/carbon monoxide system
HR	heart rate, hazard ratio
H/R	hypoxia followed by reoxygenation
HRV	heart rate variability
HS	hemorrhagic stroke
HUVEC(s)	human umbilical vein endothelial cell(s)
hν	photon
IARC	International Agency for Research on Cancer
IC	inferior colliculus
ICAM-1	intercellular adhesion molecule
ICD	implantable cardioverter defibrillator(s)
ICR	Institute for Cancer Research
IDW	inverse-distance-weighted
IHD	ischemic heart disease
IL-x	interleukin-6, 8, etc.
INDAIR	Indoor Air Model
IOM	Institute of Medicine
IQR	interquartile range
IR	immunoreactivity
IS	ischemic stroke
ISA	Integrated Science Assessment
ITA	internal thoracic artery of the heart
I_{to}	transient outward current
IUGR	intrauterine growth restriction
K^+	potassium ion
k	dissociation rate
k_{CO}	dissociation rate of carbon monoxide from hemoglobin
K_m	Michaelis Constant; Michaelis-Menten equation of enzyme kinetics
k_{O2}	Dissociation rate of oxygen from hemoglobin

LBW	low birth weight (<2,500 grams, (≈5lbs, 8 oz))
LCA+	leucocyte common antigen cells
LD	lactational day
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LF	low frequency (HRV parameter)
LH	luetenizing hormone
LOAEL	lowest observed adverse effect level
LOD	limit of detection
LOESS	locally weighted scatterplot smoothing
LPS	lipopolysaccharide
LTP	long-term potentiation
LUR	land use regression
LV	left ventricle
LV+S	left ventricular plus septum
LVDP	left ventricular developed pressure
LVESP	left ventricular end diastolic pressure
LVSF	left ventricular shortening fraction
LVW	left ventricular work
M	Haldane coefficient representing the CO chemical affinity for Hb [or Mb]), Reaction mediator.
MAPK	mitogen-activated protein kinase
MAO-A	monoamine oxidase A
Mb	myoglobin
MC	ultrafine particle mass concentration
METs	metabolic equivalent unit(s)
MHC	major histocompatibility complex
MI	myocardial infarction, “heart attack”
min	minute(s)
MIP-2	macrophage inflammatory protein-2
mitral E to A ratio	mitral ratio of peak early to late diastolic filling velocity
MMEF	maximal midexpiratory flow
MMP	matrix metalloproteinase
MOA(s)	mode(s) of Action
MOBILE6	Mobile source emission factor model
MODIS	Moderate Resolution Imaging Spectroradiometer

MONICA	Monitoring of Trends and Determinants in Cardiovascular Disease
MOPITT	Measurement of Pollution in the Troposphere
MPO	myeloperoxidase
MPT	mitochondrial permeability transition
MR	maternally reared
mRNA	messenger RNA
MSA	Metropolitan Statistical Area
MSNA	muscle sympathetic nerve activity
MT	million tons
MVO_2	myocardial oxygen consumption
NAAQS	National Ambient Air Quality Standards
NADPH	nicotinamide adenine dinucleotide phosphate
NADH-TR	nicotinamide adenine dinucleotide - tetrazolium reductase
NAPAP	National Acid Precipitation Assessment Program
NARSTO	North American Research Strategy for Tropospheric Ozone
NAS	National Academy of Sciences
NASA	National Aeronautics and Space Administration
Nb	neuroglobin
NC	ultrafine particle number concentration
NDIR	nondispersive infrared
NE	norepinephrine
NEI	National Emissions Inventory
NF-κB	nuclear factor kappa B
NIHL	noise-induced hearing loss
NMDA	N-methyl-D-aspartate
NMHC(s)	nonmethane hydrocarbon(s)
NMMAPS	National Morbidity, Mortality, and Air Pollution Study
NN	normal-to-normal (NN or RR) time interval between each QRS complex in the EKG
nNOS	neuronal nitric oxide synthase (NOS)
NO	nitric oxide
$NO^{\bullet}$	nitric oxide free radical
NO_2	nitrogen dioxide
NOAA	National Oceanic and Atmospheric Administration
NOAEL	no observed adverse effect level
$NO^{\bullet}$-Hb	nitrosyl bound Hb

$NO^{\bullet}$-Mb	nitrosyl bound Mb
NO_X	nitrogen oxides, oxides of nitrogen
NRC	National Research Council
NTS	nucleus of the solitary tract (in brainstem)
O_3	ozone
O_2Hb	oxyhemoglobin (% concentration in mL O_2 / mL blood)
O_2Mb	oxymyoglobin
OAE	otoacoustic emissions
OAQPS	Office of Air Quality Planning and Standards
OC	organic carbon
OH, $OH^{\bullet}$	hydroxyl group, hydroxyl radical
OR	odds ratio
OS	occlusive stroke
OSPM	Operational Street Pollution Model
P	penetration factor
P, p	probability
P90	90th percentile of the absolute difference in concentrations
P_A	alveolar pressure
PA	pulmonary artery (myocytes)
PACF	partial auto-correlation functions
P_ACO	alveolar pressure for carbon monoxide
PAF	platelet activating factor
PAH	polycyclic aromatic hydrocarbon
PAHT	pulmonary artery hypertension
PAN	peroxyacetyl nitrate ($CH_3CO_3NO_2$)
P_AO_2	alveolar pressure for oxygen
P_aO_2	arterial oxygen pressure
PARP	poly(ADP-ribose) polymerase
P_B	barometric pressure (in mmHg)
PBN	N-tert-butyl-alpha-phenylnitrone
P_C	average partial pressure in lung capillaries
pCO	partial pressure of CO
P_CO_2	average partial pressure of O_2 in lung capillaries
PDGF	platelet derived growth factor
PEE	prediction equation estimates

PEF	peak expiratory flow
PEFD(s)	Personal Exposures Frequency Distributions
PEM(s)	personal exposure monitor(s)
P_{H2O}	saturation pressure of water vapor
PHD	pulmonary heart disease
P_I	partial pressure of inhaled air
Pi	inorganic phosphate
PI3K	phosphoinositide 3-kinase
P_ICO	CO partial pressure in inhaled air
PIH	primary intracerebral hemorrhage
PKB	protein kinases B
PM	particulate matter
$PM_{2.5}$	particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5 μm (referred to as fine PM)
PM_{10}	particulate matter with a nominal mean aerodynamic diameter less than or equal to 10 μm
$PM_{10-2.5}$	particulate matter with a nominal mean aerodynamic diameter greater than 2.5 μm and less than or equal to 10 μm (referred to as thoracic coarse particulate matter or the course fraction of PM_{10}). Concentration may be measured or calculated as the difference between measured PM_{10} and measured $PM_{2.5}$ concentrations.
PMN	polymorphonuclear leukocytes
PNC	particle number concentration / count
PND	post natal day
pNEM/CO	probabilistic NAAQS Exposure Model for CO
PNN	proportion of interval differences of successive normal-beat intervals in EKG
PNN_{50}	proportion of interval differences of successive normal-beat intervals greater than 50 ms in EKG
PNS	peripheral nervous system
pO_2	partial pressure of oxygen in lung capillaries
pPRB	policy-relevant background
PT	prothrombin time
PTB	preterm birth
PVCD	peripheral vascular and cerebrovascular disease
PvO_2	venous oxygen tension
PVO_2	peak oxygen consumption
Q	cardiac output
QCP	Quantitative Circulatory Physiology

$\dot{Q}_{or}$	blood flow to other tissues
RA	radial artery of the heart
RAW 264.7	mouse macrophage cell line
RBC	red blood cell
RF	radiative forcing
rho(0)	rho(0) cells (cells lacking mitochondrial DNA)
Ri	Richardson number
rMSSD	mean squared differences of successive difference normal-beat to normal-beat (NN or RR) time intervals between each QRS complex in the EKG
RNA	ribonucleic acid
ROE	Report on the Environment
ROFA	residual oil fly ash (particles)
ROS	reactive oxygen species
RR	normal-to-normal (NN or RR) time interval between each QRS complex in the EKG
RR	risk ratio(s)
RUPERT	Reducing Urban Pollution Exposure from Road Transport
RV	right ventricle (of heart)
RVEDP	right ventricular end diastolic pressure
RVESP	right ventricular end-systolic pressure
RVSF	right ventricular shortening fraction
RVW	right ventricular work
SA	sphinganine
SAA	serum amyloid A
SAB	Science Advisory Board
SBP	systolic blood pressure, spontaneous bacterial peritonitis
SDNN	standard deviation normal-to-normal (NN or RR) time interval between each QRS complex in the EKG
sEng	soluble endoglin
SES	socioeconomic status
SF_6	sulfur hexafluoride (tracer gas)
sFlt	soluble Fms-like tyrosine kinase-1
SGA	small for gestational age
sGC	soluble guanylate cyclase
SHEDS	Stochastic Human Exposure and Dose Simulation
SHR	Spontaneously hypertensive rat strain

SIDS	sudden infant death syndrome
SIPs	State Implementation Plan(s)
siRNA	small inhibitory RNA
SLAMS	State and Local Air Monitoring Stations
SMC	smooth muscle cell(s)
SnMP	tin-(IV)-mesoporphyrin
SNP	single-nucleotide polymorphism
SnPP-IX	tin protoporphyrin IX
SO	sphingosine
SO_2	sulfur dioxide
SO_4^{2-}	sulfate
SOD	superoxide dismutase
SOPHIA	Study of Particles and Health in Atlanta
STEMS	Space-Time Exposure Modeling System
STN	Speciation Trends Network
STPD	standard temperature and pressure, dry
SV	stroke volume
SVEB	supraventricular (atrium or atrioventricular node) ectopic beats
τ	tau, photochemical lifetime
T lymphocytes	thymus-dependent lymphocytes
TBARS	thiobarbituric acid reactive substances
TC	total carbon
TFAM	mitochondrial transcription factor A
Tg	teragram(s)
TH	tyrosine hydroxylase
THP-1	human monocyte-derived cell line, (can differentiate into macrophages)
TIA	transient ischemic attack
TNF-α	tissue necrosis factor alpha
TPM	total particulate matter
TSP	total suspended particles
UFP	ultrafine particle(s)
ULTRA	Exposure and Risk Assessment for Fine and Ultrafine Particles in Ambient Air (Study)
URI	upper respiratory infection
URTI	upper respiratory tract infection

USC	U.S. Code
V_A	alveolar ventilation
Vb	blood volume
V_{CO}	endogenous CO production rate
V_D	Dead space volume
V_E	ventilation rate
VEGF	vascular endothelial growth factor
VLF	very low energy frequency (HRV parameter)
V_{max}	maximum velocity
VO_2 max	maximum volume per time, of oxygen (maximal oxygen consumption, maximal oxygen uptake or aerobic capacity)
VOC(s)	volatile organic compound(s)
VPB	ventricular premature beat
vWF	von Willebrand factor
W	width
WBC	white blood cell
WHI	Women's Health Initiative
WKY	Wistar-Kyoto rat strain
ZnPP IX	Zn protoporphyrin IX

Chapter 1. Introduction

The Integrated Science Assessment (ISA) is a concise evaluation and synthesis of the most policy-relevant science for reviewing the national ambient air quality standards (NAAQS). Because the ISA communicates critical science judgments relevant to the NAAQS review, it forms the scientific foundation for the review of the NAAQS for carbon monoxide (CO). The existing primary CO standards include a 1-hour (h) average (avg) standard set at 35 parts per million (ppm), and an 8-h avg standard set at 9 ppm, neither to be exceeded more than once per year. There is currently no secondary standard for CO.

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" (42 U.S.C. 7408). Key information and judgments formerly contained in the Air Quality Criteria Document (AQCD) for CO 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 evaluation of the scientific evidence available at the time of the previous review of the NAAQS for CO that was completed in 2000.

The integrated *Plan for Review of the National Ambient Air Quality Standards for Carbon Monoxide* (U.S. EPA, 2008, 193995) identifies key policy-relevant questions that provide a framework for this assessment of the scientific evidence. These questions frame the entire review of the NAAQS for CO and thus are informed by both science and policy considerations. The ISA organizes, presents, and integrates the scientific evidence which is considered along with findings from risk analyses and policy considerations to help the U.S. Environmental Protection Agency (EPA) address these questions during the NAAQS review. In evaluating the health evidence, the focus of this assessment is on scientific evidence that is most relevant to the following questions taken directly from the Integrated Review Plan:

- Has new information altered the scientific support for the occurrence of health effects following short- and/or long-term exposure to levels of CO found in the ambient air?

- To what extent is key evidence becoming available that could inform our understanding of human subpopulations that are particularly sensitive to CO exposures? Is there new or emerging evidence on health effects beyond cardiovascular and respiratory endpoints (e.g., systemic effects, developmental effects, birth outcomes) that suggest additional sensitive subpopulations should be given increased focus in this review (e.g., neonates)?

- What do recent studies focused on the near-roadway environment, including bus stops and intersections, tell us about high-exposure human subpopulations and the health effects of CO? What information is available on elevated exposures due to other transportation sources, such as shipping, port operations, and recreational vehicles? What is the effect of altitude on CO sources and health effects?

- At what levels of CO exposure do health effects of concern occur?

- To what extent is key scientific evidence becoming available to improve our understanding of the health effects associated with various time periods of CO exposures, including not only daily but also chronic (months to years) exposures? To what extent is critical research becoming available that could improve our understanding of the relationship between various health endpoints and different lag periods (e.g., single-day, multiday distributed lags)?

Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at http://epa.gov/hero. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISAs) and the Integrated Risk Information System (IRIS).

- To what extent does the evidence suggest that alternate dose indicators other than carboxyhemoglobin (COHb) levels (e.g., tissue oxygenation) should be evaluated to characterize the biological effect?

- Has new information altered conclusions from previous reviews regarding the plausibility of adverse health effects caused by CO exposure?

- To what extent have important uncertainties identified in the last review been reduced and/or have new uncertainties emerged?

- Have new information or scientific insights altered the scientific conclusions regarding the occurrence of direct (or indirect) welfare effects associated with levels of CO found in the ambient air?

1.1. Legislative Requirements

Two sections of the Clean Air Act (CAA, the Act) govern the establishment and revision of the NAAQS. Section 108 of the Act (42 U.S.C. 7408) directs the Administrator to identify and list "air pollutants" that "in [her] judgment, may reasonably be anticipated to endanger public health and welfare" and whose "presence … in the ambient air results from numerous or diverse mobile or stationary sources" and to issue air quality criteria for those that are listed (42 U.S.C. 7408). Air quality criteria are intended to "accurately reflect the latest scientific knowledge useful in indicating the kind and extent of identifiable effects on public health or welfare which may be expected from the presence of [a] pollutant in ambient air…" 42 U.S.C. 7408(b).

Section 109 of the Act (42 U.S.C. 7409) directs the 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 U.S. 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 susceptible population(s), and the kind and degree of the uncertainties that must be addressed. The selection of any particular approach to providing an

[1] The legislative history of section 109 of the Clean Air Act 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)].

[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."

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, 465-472, 475-76 (D.C. Cir. 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).

1.2. History of the NAAQS for CO

On April 30, 1971, EPA promulgated identical primary and secondary NAAQS for CO, under Section 109 of the Clean Air Act, set at 9 ppm, 8-h avg and 35 ppm, 1-h avg, neither to be exceeded more than once per year (36 FR 8186). In 1979, EPA published the *Air Quality Criteria Document for Carbon Monoxide* (1979, 017687), which updated the scientific criteria upon which the initial CO standards were based. A Staff Paper (U.S. EPA, 1979, 194665) was prepared and, along with the AQCD (1979, 017687), served as the basis for development of proposed rulemaking (45 FR 55066) published on August 18, 1980. Delays due to uncertainties regarding the scientific basis for the final decision resulted in EPA announcing a second public comment period (47 FR 26407). Following substantial reexamination of the scientific data, EPA prepared an Addendum to the 1979 AQCD (1984, 012690) and an updated Staff Paper (1984, 012691). Following review by CASAC, EPA announced its final decision (50 FR 37484) not to revise the existing primary standard and to revoke the secondary standard for CO on September 13, 1985, due to a lack of evidence of direct effects on public welfare at ambient concentrations.

In 1987, EPA initiated action to revise the criteria for CO and subsequently released a revised AQCD (U.S. EPA, 1991, 017643) for CASAC and public review. In a "closure letter" (McClellan, 1991, 194666) sent to the Administrator, the CASAC concluded that the AQCD (U.S. EPA, 1991, 017643) ". . . provides a scientifically balanced and defensible summary of current knowledge of the effects of this pollutant and provides an adequate basis for the EPA to make a decision as to the appropriate primary NAAQS for CO." A revised Staff Paper subsequently was reviewed by CASAC and the public, and in a "closure letter" (McClellan, 1992, 194667) sent to the Administrator, CASAC stated ". . . that a standard of the present form and with a numerical value similar to that of the present standard would be supported by the present scientific data on health effects of exposure to carbon monoxide." Based on the revised AQCD (U.S. EPA, 1991, 017643) and staff conclusions and recommendations contained in the revised Staff Paper (U.S. EPA, 1992, 084191), the Administrator announced the final decision (59 FR 38906) on August 1, 1994, that revision of the primary NAAQS for CO was not appropriate at that time.

In 1997, revisions to the 1991 AQCD (U.S. EPA, 1991, 017643) were initiated. A workshop was held in September 1998 to review and discuss material contained in the revised draft AQCD. On June 9, 1999, CASAC held a public meeting to review the draft AQCD and a draft exposure analysis methodology document. Comments from CASAC and the public were considered in a second draft AQCD, which was reviewed at a CASAC meeting, held on November 18, 1999. After revision of the second draft AQCD, the final AQCD (U.S. EPA, 2000, 000907) was released in August 2000. EPA put the review on hold when Congress called on the National Research Council (NRC) to conduct a review of the impact of meteorology and topography on ambient CO concentrations in high altitude and extreme cold regions of the U.S. In response, the NRC convened the committee on Carbon Monoxide Episodes in Meteorological and Topographical Problem Areas, which focused on

Fairbanks, Alaska as a case study in an interim report, which was completed in 2002. A final report, *Managing Carbon Monoxide Pollution in Meteorological and Topographical Problem Are*as, was published in 2003 (National Research Council, 2003, 042550) and offered a wide range of recommendations on management of CO air pollution, cold start emissions standards, oxygenated fuels, and CO monitoring. EPA did not complete the NAAQS review which started in 1997.

1.3. ISA Development

EPA initiated the current review of the NAAQS for CO on September 13, 2007 with a call for information from the public (72 FR 52369). In addition to the call for information, publications were identified through an ongoing literature search process that includes extensive computer database mining on specific topics. Literature searches were conducted routinely to identify studies published since the last review, focusing on publications from 1999 to May 2009. Search strategies were iteratively modified to optimize identification of pertinent publications. Additional papers were 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. Publications considered for inclusion in the ISA were added to the Health and Environmental Research Online (HERO) database recently developed by EPA (http://cfpub.epa.gov/ncea/hero/); note that all references in the ISA include a HERO ID that provides a link to the database. Typically, only information that had undergone scientific peer review and had been published or accepted for publication was considered, along with analyses conducted by EPA using publicly available data. This review has attempted to evaluate all relevant data published since the last review pertaining to the atmospheric science of CO, human exposure to ambient CO, and epidemiologic, controlled human exposure, and animal toxicological studies on CO, including those related to exposure-response relationships, mode(s) of action (MOA), or susceptible populations. Added to the body of research on CO effects 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 CO. An extensive literature search for data on the ecological effects of ambient CO did not identify any relevant information published since the review of the ecological effects evidence in the 1979 CO AQCD (U.S. EPA, 1979, 017687).

In general, in assessing the scientific quality and relevance of health and environmental effects studies, the following considerations have been taken into account when selecting studies for inclusion in the ISA or its annexes. The selection process for studies included in this ISA is shown in Figure 1-1.

- Are the study populations, subjects, or animal models adequately selected and are they sufficiently well defined to allow for meaningful comparisons between study or exposure groups?
- Are the statistical analyses appropriate, properly performed, and properly interpreted? Are likely covariates adequately controlled or taken into account in the study design and statistical analysis?
- Are the air quality data, exposure, or dose metrics of adequate quality and sufficiently representative of information regarding ambient CO?
- Are the health or welfare effect measurements meaningful and reliable?

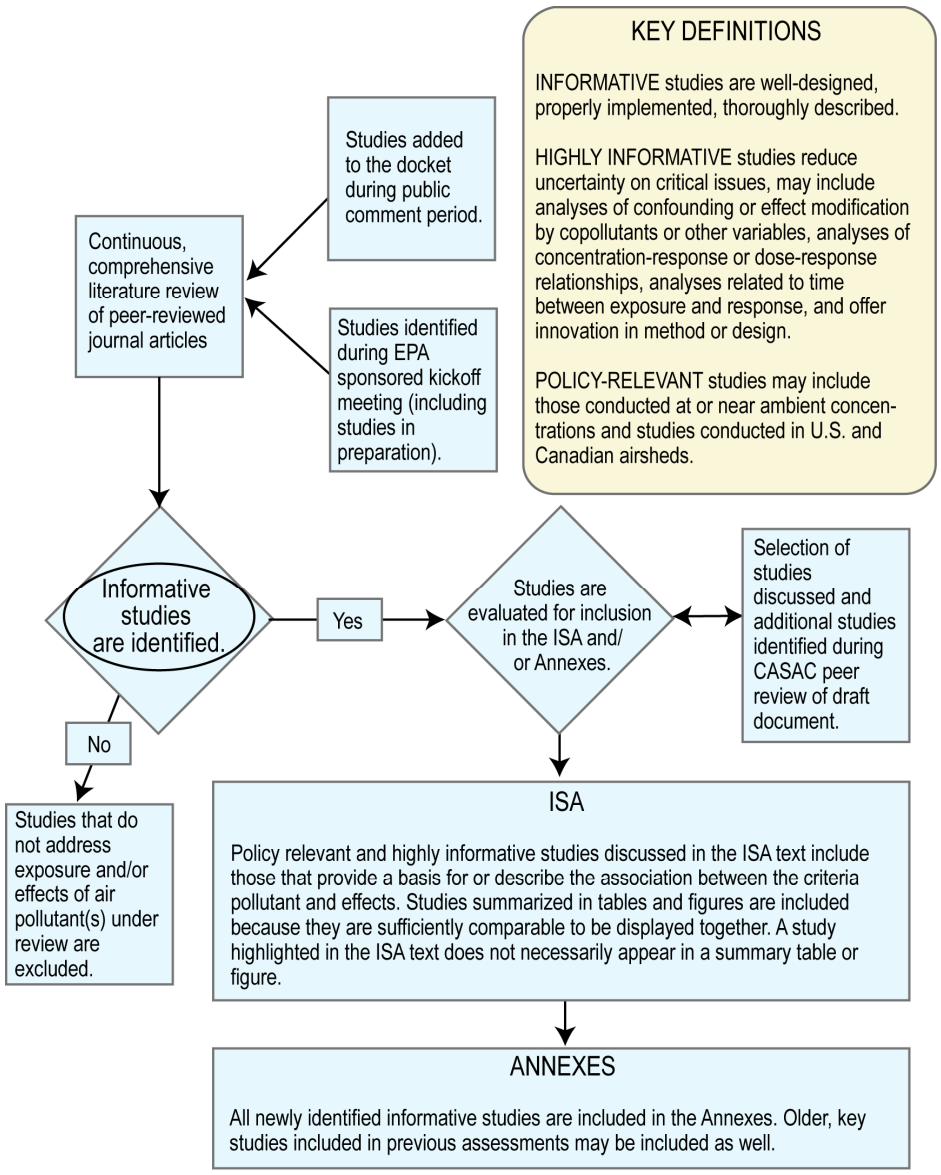

Figure 1-1. Identification of studies for inclusion in the ISA.

In selecting epidemiologic studies, EPA considered whether a given study presented information on associations with short- or long-term CO exposures at or near ambient levels of CO; considered approaches to evaluate issues related to potential confounding by other pollutants; assessed potential effect modifiers; addressed health endpoints and populations not previously extensively researched; and evaluated important methodologic issues (e.g., lag or time period between exposure and effects, model specifications, thresholds, mortality displacement) related to interpretation of the health evidence. Among the epidemiologic studies selected, particular emphasis was placed on those studies most relevant to the review of the NAAQS. Specifically, studies conducted in the United States (U.S.) or Canada were discussed in more detail than those from other geographical regions. Particular emphasis was placed on: (1) recent multicity studies that employ standardized analysis methods for evaluating effects of CO and that provide overall estimates for effects based on combined analyses of information pooled across multiple cities; (2) studies that help understand quantitative relationships between exposure concentrations and effects; (3) new studies that provide evidence on effects in susceptible populations; and (4) studies that consider and report CO as a component of a complex mixture of air pollutants.

Criteria for the selection of research evaluating controlled human exposure or animal toxicological studies included a focus on studies conducted using relevant pollutant exposures. For both types of studies, relevant pollutant exposures are considered to be those generally within one or two orders of magnitude of ambient CO concentrations. Studies in which higher doses were used may also be considered if they provide information relevant to understanding MOAs or mechanisms, as noted below.

Evaluation of controlled human exposure studies focused on those that approximated expected human exposure conditions in terms of concentration and duration. In the selection of controlled human exposure studies, emphasis is placed on studies that (1) investigate potentially susceptible populations such as people with cardiovascular diseases; (2) address issues such as concentration-response or time-course of responses; (3) include control exposures to filtered air; and (4) have sufficient statistical power to assess findings.

Review of the animal toxicological evidence focused on studies that approximate expected human dose conditions, which will vary depending on the toxicokinetics and biological sensitivity of the particular laboratory animal species or strains studied. Due to resource constraints on exposure duration and numbers of animals tested, animal studies typically utilize high-concentration exposures to acquire data relating to mechanisms and assure a measureable response. Such studies were considered to the extent that they provided useful information to inform our understanding of interspecies differences and potential sensitivity differences between healthy and susceptible human populations.

These criteria provide benchmarks for evaluating various studies and for focusing on the policy-relevant studies in assessing the body of health and welfare effects evidence. Detailed critical analysis of all CO health and welfare effects studies, especially in relation to the above considerations, is beyond the scope of this document. Of most relevance for evaluation of studies is whether they provide useful qualitative or quantitative information on exposure-effect or exposure-response relationships for effects associated with current ambient air concentrations of CO that can inform decisions on whether to retain or revise the standards.

In developing the CO ISA, EPA began by reviewing and summarizing the evidence on atmospheric sciences and exposure and the health effects evidence from in vivo and in vitro toxicological studies, controlled human exposure studies, and epidemiologic studies. In November 2008, EPA invited EPA staff and other researchers with expertise in CO to a teleconference to review the scientific content of preliminary draft materials for the draft ISA and the annexes. The purpose of the initial peer review teleconference was to ensure that the ISA is up to date and focused on the most policy-relevant findings, and to assist EPA with integration of evidence within and across disciplines. Subsequently, EPA addressed comments and completed the initial integration and synthesis of the evidence.

The integration of evidence on health or welfare effects involves collaboration between scientists from various disciplines. As described in the section below, the ISA organization is based on health effect categories. As an example, an evaluation of health effects evidence would include summaries of findings from epidemiologic, controlled human exposure, and toxicological studies, and integration of the results to draw conclusions based on the causal framework described below. Using the causal framework described in Section 1.6, EPA scientists consider aspects such as strength, consistency, coherence and biological plausibility of the evidence, and develop draft causality judgments on the nature of the relationships. The draft integrative synthesis sections and conclusions are reviewed by EPA internal experts and, as appropriate, by outside expert authors. In practice, causality determinations often entail an iterative process of review and evaluation of the evidence. The draft ISA is released for review by the CASAC and the public, and comments received on the characterization of the science as well as the implementation of the causal framework are carefully considered in revising and completing the ISA.

1.4. 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 is an integrated summary of key findings and conclusions regarding the source to dose paradigm, MOA, and important health effects of CO, including cardiovascular, nervous system,

perinatal/developmental, respiratory, and mortality outcomes. Chapter 3 highlights key concepts and evidence relevant to understanding the sources, ambient concentrations, atmospheric behavior, and exposure to ambient CO. Chapter 4 describes the dosimetry and pharmacokinetics of CO, including formation and fate of carboxyhemoglobin (COHb). Chapter 5 presents a discussion of the MOA of CO and evaluates and integrates epidemiologic, human clinical, and animal toxicological information on health effects related to short-term exposures (i.e., hours, days, or weeks) and long-term exposures (i.e., months or years) to CO, including cardiovascular and systemic effects, central nervous system (CNS) effects, birth outcomes and developmental effects, respiratory effects, and mortality.

A series of annexes supplement this ISA. The annexes provide tables summarizing 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 CO, sampling and analytic methods for measurement of CO concentrations, emissions, sources and human exposure to CO (Annex A);
- studies on the dosimetry and pharmacokinetics of CO (Annex B);
- epidemiologic studies of health effects from short- and long-term exposure to CO (Annex C);
- controlled human exposure studies of health effects related to exposure to CO (Annex D); and
- toxicological studies of health effects in laboratory animals (Annex E)

Within Annexes B through E, detailed information about methods and results of health studies is summarized in tabular format, and generally includes information about concentrations of CO and averaging times, study methods employed, results and comments, and quantitative results for relationships between effects and exposure to CO. As noted in the section above, the most pertinent results of this body of studies are brought into the ISA.

1.5. Document Scope

For the current review of the primary CO standards, relevant scientific information on human exposures and health effects associated with exposure to ambient CO has been assessed. Health effects resulting from accidental exposures to very high concentrations of non-ambient CO (i.e., CO poisoning) are not directly relevant to ambient exposures, and as such, a discussion of these effects has deliberately been excluded from this document. For a detailed review of the effects of high-level exposures to CO, the reader is referred to the extensive body of literature related to CO poisoning (Ernst and Zibrak, 1998, 049822; Penney, 2007, 194668; Raub et al., 2000, 002180). In addition, results of studies investigating the relationship between blood COHb concentrations and health effects (e.g., Hedblad et al., 2006, 199512) may be informative regarding the biological plausibility of health effects associated with changes in COHb concentrations. However, the lack of data on ambient concentrations and the likely contribution of non-ambient CO to COHb in these studies complicates the interpretation of the results with respect to ambient CO exposure, and therefore these studies will not be discussed in this review. The possible influence of other atmospheric pollutants on the interpretation of the role of CO in health effects studies is considered in this assessment. This includes other pollutants with the potential to co-occur in the environment (e.g., nitrogen dioxide [NO_2], sulfur dioxide [SO_2], ozone [O_3], and particulate matter [PM]).

The review also assesses relevant scientific information associated with known or anticipated public welfare effects that may be identified. The 1979 CO AQCD (U.S. EPA, 1979, 017687) reviewed research on the effects of CO on vegetation and soil microflora, which showed that visible symptoms and effects on growth, yield, and reproduction were observed in some studies at very high CO concentrations (1,000-10,000 ppm or greater), while biochemical and physiological responses, including reduced nitrogen fixation, were observed at lower concentrations (1,000 ppm and below). As discussed in Section 1.3, a critical review of the ecological effects literature identified no

information published since the 1979 CO AQCD (U.S. EPA, 1979, 017687) pertinent to ambient CO exposures; hence, no section on ecological effects appears in this assessment. The reader is referred to the 1979 CO AQCD (U.S. EPA, 1979, 017687) for a detailed discussion of the effects of high CO concentrations on plants and microorganisms. The definition of public welfare for the NAAQS includes considerations of climate. Thus, the climate forcing effects of CO are summarized in Chapter 2 and are discussed in detail in Chapter 3, where distinctions are drawn between global-scale conclusions related to climate and the strongly variable continental and regional climate forcing effects from CO.

1.6. EPA Framework for Causal Determination

The EPA has developed a consistent and transparent basis to evaluate the causal nature of air pollution-induced health or environmental effects. The framework described below establishes uniform language concerning causality and brings more specificity to the findings. This standardized language was drawn 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*, (2008, 156586) the most recent comprehensive work on evaluating causality.

This introductory section focuses on the evaluation of health effects evidence. While focusing on human health outcomes, the concepts are also generally relevant to causality determination for welfare 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 NAS (2008, 156586), International Agency for Research on Cancer (2006, 093206), *EPA Guidelines for Carcinogen Risk Assessment* (2005, 086237), Centers for Disease Control and Prevention (2004, 056384), and National Acid Precipitation Assessment Program (1991, 095894). 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 have supported decision-making under conditions of uncertainty.

1.6.1. 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 human volunteers 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 can help characterize effects of concern, exposure-response relationships, susceptible populations and MOAs. In the absence of controlled human exposure or epidemiologic data, animal data alone may be sufficient to support a likely causal determination, assuming that humans respond similarly to the experimental species.

1.6.2. Association and Causation

“Cause” is a significant, effectual relationship between an agent and an effect on health or public welfare. “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, 2008, 156586). 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 and environmental outcomes reported in these studies have complex etiologies. Diseases such as asthma, coronary heart disease (CHD) or cancer are typically initiated by 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, 093070; IOM, 2008, 156586). Effects on ecosystems are often also multifactorial with a complex web of causation. 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.

1.6.3. Evaluating Evidence for Inferring Causation

Moving from association to causation involves the elimination of alternative explanations for the association. In estimating the causal influence of an exposure on health or environmental effects, 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, e.g., the lack of knowledge about the correct value for a specific measure or estimate. 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. Uncertainty assessment is more quantitative. The process begins with simpler measures (e.g., 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 situations. The net result is that the assessment will be based on a number of assumptions with varying degrees of uncertainty. Uncertainties commonly encountered in evaluating health evidence for the criteria air pollutants are outlined below for epidemiologic and experimental studies. Various approaches to evaluating uncertainty include classical statistical methods, sensitivity analysis, or probabilistic uncertainty analysis, in order of increasing complexity and data requirements. The ISA generally evaluates uncertainties qualitatively in assessing the evidence from across studies; in some situations quantitative analysis approaches, such as metaregression, may be used.

Meta-analysis may be a valuable tool for evaluating evidence by combining results from a body of studies. Blair et al. (1995, 079190) observe that meta-analysis can enhance understanding of associations between exposures and effects that are not readily apparent in examination of individual study results and can be particularly useful for formally examining sources of heterogeneity.

However, these authors note that meta-analysis may not be useful when the relationship between the exposure and outcome is obvious, when only a few studies are available for a particular exposure-outcome relationship, where there is limited access to data of sufficient quality, or where there is substantial variation in study design or population. In addition, important differences in effect estimates, exposure metrics, or other factors may limit or even preclude quantitative statistical combination of multiple studies.

Controlled human exposure studies evaluate the effects of exposures to a variety of pollutants in a highly controlled laboratory setting. Also referred to as human clinical studies, these experiments allow investigators to expose subjects to known concentrations of air pollutants under carefully regulated environmental conditions and activity levels. In some instances, controlled human exposure studies can also be used to characterize concentration-response relationships at pollutant concentrations relevant to ambient conditions. Controlled human exposures are typically conducted using a randomized crossover design, with subjects exposed both to CO and a clean air control. In this way, subjects serve as their own controls, effectively controlling for many potential confounders. However, human clinical studies are limited by a number of factors, including a small sample size and short exposure times. The repetitive nature of ambient CO exposures at levels that can vary widely may lead to cumulative health effects, but this type of exposure is not practical to replicate in a laboratory setting. In addition, although subjects do serve as their own controls, personal exposure to pollutants in the hours and days preceding the controlled exposures may vary significantly between and within individuals. Endogenous production of CO creates a body burden of CO that, together with personal exposure from nonambient sources, contributes to baseline COHb levels. Endogenous production rates vary within and among individuals, particularly for individuals with diseases such as hemolytic anemia or chronic inflammation. This body burden of CO and COHb limits the lower range of exposures that can be practically covered in controlled human exposure studies. Finally, human clinical studies require investigators to adhere to stringent health criteria for a subject to be included in the study, and therefore the results cannot necessarily be generalized to an entire population. Although some human clinical studies have included health-compromised individuals such as those with coronary artery disease (CAD), these individuals must also be relatively healthy and do not represent the most sensitive individuals in the population. Thus, a lack of observation of effects from human clinical studies does not necessarily mean that a causal relationship does not exist. While human clinical studies provide important information on the biological plausibility of associations observed between air pollutant exposure and health outcomes in epidemiologic studies, observed effects in these studies may underestimate the response in certain populations.

Epidemiologic studies provide important information on the associations between health effects and exposure of human populations to ambient air pollution. In the evaluation of epidemiologic evidence, one important consideration is potential confounding. Confounding is ". . . a confusion of effects. Specifically, the apparent effect of the exposure of interest is distorted because the effect of an extraneous factor is mistaken for or mixed with the actual exposure effect (which may be null)" (Rothman and Greenland, 1998, 086599). One approach to remove spurious associations due to possible confounders is to control for characteristics that may differ between exposed and unexposed persons; this is frequently termed "adjustment." Scientific judgment is needed regarding likely sources and magnitude of confounding, together with consideration of 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 CO to health effects when it is a component of a complex air pollutant mixture. Reported CO effect estimates in epidemiologic studies may reflect independent CO effects on health outcomes. Ambient CO may also be serving as an indicator of complex ambient air pollution mixtures that share the same source as CO (e.g., motor vehicle emissions). Alternatively, copollutants may mediate the effects of CO or CO may influence the toxicity of copollutants.

Another important consideration in the evaluation of epidemiologic evidence is effect modification. "Effect-measure modification differs from confounding in several ways. The main difference is that, whereas confounding is a bias that the investigator hopes to prevent or remove from the effect estimate, effect-measure modification is a property of the effect under study . . . In epidemiologic analysis one tries to eliminate confounding but one tries to detect and estimate effect-measure modification" (Rothman and Greenland, 1998, 086599). Examples of effect modifiers in some of the studies evaluated in this ISA include environmental variables, such as temperature or humidity, individual risk factors, such as education, cigarette smoking status, age in a prospective

cohort study, and community factors, such as percent of population > 65 yr old. It is often possible to stratify the relationship between health outcome and exposure by one or more of these risk factor variables. For variables that modify the association, effect estimates in each stratum will be different from one another and different from the overall estimate, indicating a different exposure-response relationship may exist in populations represented by these variables. Effect modifiers may be encountered (a) within single-city time-series studies or (b) across cities in a two-stage hierarchical model or meta-analysis.

Several statistical methods are available to detect and control for potential confounders, with none of them being completely satisfactory. 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. In addition, more than one pollutant may exert similar health effects, resulting in independently observed associations for multiple pollutants. For example, $PM_{2.5}$ and NO_2 have each been linked to cardiovascular effects in epidemiologic studies. Correlation between CO concentrations and various copollutants, such as $PM_{2.5}$ and NO_2, makes it difficult to quantitatively interpret associations between different pollutant exposures and health effects. Thus, results of models that attempt to distinguish CO effects from those of copollutants must be interpreted with caution. The number and degree of diversity of covariates, as well as their relevance to the potential confounders, remain matters of scientific judgment. Despite these limitations, the use of multipollutant models is still the prevailing approach employed in most air pollution epidemiologic studies and provides 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. 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 or health outcome 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.

Adjustment for potential confounders can be influenced by differential exposure measurement error. There are several components that contribute to exposure measurement error in epidemiologic studies, including the difference between true and measured ambient concentrations, the difference between average personal exposure to ambient pollutants and ambient concentrations at central monitoring sites, and the use of average population exposure rather than individual exposure estimates. Consideration of issues important for evaluation of exposure to ambient CO include: (1) spatial variability of CO concentrations across urban areas, particularly with respect to highly traveled roadways; (2) location of CO monitors at varying distances from roads; and (3) the detection limit of instruments in the CO monitoring network. Previous AQCDs have examined the role of measurement error for non-reactive pollutants in time-series epidemiologic studies using simulated data and mathematical analyses and suggested that transfer of effects from the “causal” variable to the confounder would only occur under unusual circumstances (i.e., “true” predictors having high positive or negative correlation; substantial measurement error; or extremely negatively correlated measurement errors) (U.S. EPA, 2004, 056905).

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, multicity 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. Intervention studies, because of their quasi-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. These studies evaluate the effects of exposures to a variety of pollutants in a highly controlled laboratory setting and allow exploration of MOAs or mechanisms by which a pollutant may cause effects. 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. Consideration of evidence on the non-hypoxic effects of CO via cell signaling and alteration of heme protein function along with evidence on COHb-mediated hypoxic stress, provides a more complete understanding of the biological response to CO. There are, however, uncertainties associated with quantitative extrapolations between laboratory animals and humans on the pathophysiological effects of any pollutant. Animal species can differ from each other in fundamental aspects of physiology and anatomy (e.g., metabolism, airway branching, hormonal regulation) that may limit extrapolation.

Interpretations of experimental studies of air pollution effects in laboratory animals, as in the case of environmental comparative toxicology studies, are affected by limitations associated with extrapolation models. The differences between humans and rodents with regard to pollutant absorption and distribution profiles based on metabolism, hormonal regulation, breathing pattern, exposure dose, and differences in lung structure and anatomy, all have to be taken into consideration. Also, in spite of a high degree of homology and the existence of a high percentage of orthologous genes across humans and rodents (particularly mice), extrapolation of molecular alterations at the gene level is complicated by species-specific differences in transcriptional regulation. Given these molecular differences, at this time there are uncertainties associated with quantitative extrapolations between laboratory animals and humans of observed pollutant-induced pathophysiological alterations under the control of widely varying biochemical, endocrine, and neuronal factors.

1.6.4. Application of Framework for Causal Determination

EPA uses a two-step approach to evaluate the scientific evidence on health or environmental 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 loads or 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 (1965, 071664) and have been widely used (CDC, 2004, 056384; IARC, 2006, 093206; IOM, 2008, 156586; U.S. EPA, 2005, 086237).These aspects (Hill, 1965, 071664) have been modified (Table 1-2) for use in causal determinations specific to health and welfare effects or pollutant exposures (U.S. EPA, 2009, 179916).[2] Some aspects are more likely than others to be relevant for evaluating evidence on the health or environmental effects of criteria air pollutants. For example, the analogy aspect does not always apply, especially for the gaseous criteria pollutants, and specificity would not be expected for multi-etiologic health outcomes, such as asthma or cardiovascular disease, or ecological effects related to acidification. Aspects that usually play a larger role in determination of causality are consistency of results across studies, coherence of effects observed in different study types or disciplines, biological plausibility, exposure-response relationship, and evidence from "natural" experiments.

[1] The "aspects" described by Hill (1965, 071664) 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 aspects were developed for interpretation of epidemiologic results. 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.

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

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 results among investigations, possible reasons such as differences in exposure, confounding factors, and the power of the study are considered.
Coherence	An inference of causality from epidemiologic associations may be strengthened by other lines of evidence (e.g., clinical and animal studies) that support a cause-and-effect interpretation of the association. Evidence on ecological or welfare effects may be drawn from a variety of experimental approaches (e.g., greenhouse, laboratory, and field) and subdisciplines of ecology (e.g., community ecology, biogeochemistry and paleological/historical reconstructions). The coherence of evidence from various fields greatly adds to the strength of an inference of causality. The absence of other lines of evidence, however, is not a reason to reject causality.
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 proposed mechanistic linking between an effect and exposure to the agent is an important source of support for causality, especially when data establishing the existence and functioning of those mechanistic links are available. A lack of biologic understanding, however, is not a reason to reject causality.
Biological gradient (exposure-response relationship)	A well characterized 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.
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. However, given a truly causal agent, a small magnitude in the effect could follow from a lower level of exposure, a lower potency, or the prevalence of other agents causing similar effects. While large effects support causality, modest effects therefore do not preclude it.
Experimental evidence.	The strongest evidence for causality can be provided when a change in exposure brings about a change in occurrence or frequency of health or welfare effects.
Temporal relationship of the observed association	Evidence of a temporal sequence between the introduction of an agent, and appearance of the effect, constitutes another argument in favor of causality.
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, 071664). Based on our 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. At the scale of ecosystems, as in epidemiology, complexity is such that single agents causing single effects, and single effects following single causes, are extremely unlikely. 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.
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.

Although 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, 071664). For example, one cannot simply count the number of studies reporting statistically significant results or statistically nonsignificant results 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. In addition, it is important to note that the aspects 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 preclude a determination of causality (See discussion in CDC, 2004, 056384).

1.6.5. Determination of Causality

In the ISA, EPA assesses the results of recent relevant publications, building upon evidence available during the previous NAAQS review, to draw conclusions on the causal relationships between relevant pollutant exposures and health or environmental effects. 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* (2008, 156586), EPA's Guidelines for Carcinogen Risk Assessment (2005, 086237), and the

[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.

U.S. Surgeon General's smoking reports (CDC, 2004, 056384). 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 across the health and environmental effects disciplines. 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.

	Health Effects	Ecological and Welfare Effects
Causal relationship	Evidence is sufficient to conclude that there is a causal relationship with relevant pollutant exposures. That is, the pollutant has been shown to result in health effects in studies in which chance, bias, and confounding could be ruled out with reasonable confidence. For example: a) controlled human exposure studies that demonstrate consistent effects; or b) observational studies that cannot be explained by plausible alternatives or are supported by other lines of evidence (e.g., animal studies or mode of action information). Evidence includes replicated and consistent high-quality studies by multiple investigators.	Evidence is sufficient to conclude that there is a causal relationship with relevant pollutant exposures. That is, the pollutant has been shown to result in effects in studies in which chance, bias, and confounding could be ruled out with reasonable confidence. Controlled exposure studies (laboratory or small- to medium-scale field studies) provide the strongest evidence for causality, but the scope of inference may be limited. Generally, determination is based on multiple studies conducted by multiple research groups, and evidence that is considered sufficient to infer a causal relationship is usually obtained from the joint consideration of many lines of evidence that reinforce each other.
Likely to be a causal relationship	Evidence is sufficient to conclude that a causal relationship is likely to exist with relevant pollutant exposures, but important uncertainties remain. That is, the pollutant has been shown to result in health effects in studies in which chance and bias can be ruled out with reasonable confidence but potential issues remain. For example: a) observational studies show an association, but copollutant exposures are difficult to address and/or other lines of evidence (controlled human exposure, animal, or mode of action information) are limited or inconsistent; or b) animal toxicological evidence from multiple studies from different laboratories that demonstrate effects, but limited or no human data are available. Evidence generally includes replicated and high-quality studies by multiple investigators.	Evidence is sufficient to conclude that there is a likely causal association with relevant pollutant exposures. That is, an association has been observed between the pollutant and the outcome in studies in which chance, bias and confounding are minimized, but uncertainties remain. For example, field studies show a relationship, but suspected interacting factors cannot be controlled, and other lines of evidence are limited or inconsistent. Generally, determination is based on multiple studies in multiple research groups.
Suggestive of a causal relationship	Evidence is suggestive of a causal relationship with relevant pollutant exposures, but is limited because chance, bias and confounding cannot be ruled out. For example, at least one high-quality epidemiologic study shows an association with a given health outcome but the results of other studies are inconsistent.	Evidence is suggestive of a causal relationship with relevant pollutant exposures, but chance, bias and confounding cannot be ruled out. For example, at least one high-quality study shows an effect, but the results of other studies are inconsistent.
Inadequate to infer a causal relationship	Evidence is inadequate to determine that a causal relationship exists with relevant pollutant exposures. The available studies are of insufficient quantity, quality, consistency or statistical power to permit a conclusion regarding the presence or absence of an effect.	The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of an effect.
Not likely to be a causal relationship	Evidence is suggestive of no causal relationship with relevant pollutant exposures. Several adequate studies, covering the full range of levels of exposure that human beings are known to encounter and considering susceptible populations, are mutually consistent in not showing an effect at any level of exposure.	Several adequate studies, examining relationships with relevant exposures, are consistent in failing to show an effect at any level of exposure.

For the CO ISA, determination of causality involved the evaluation of evidence for different types of health effects associated with short- and long-term exposure periods. In making determinations of causality for CO, evidence was evaluated for health outcome categories, such as cardiovascular effects, and then conclusions were drawn based upon the integration of evidence from across disciplines (e.g., epidemiology, clinical studies and toxicology) and also across the suite of related individual health outcomes. To accomplish this integration, evidence from multiple and various types of studies was considered. Response was evaluated over a range of observations which was determined by the type of study and methods of exposure or dose and response measurements. Results from different protocols were compared and contrasted.

In drawing judgments regarding causality for the criteria air pollutants, EPA focuses on evidence of effects at relevant pollutant exposures. To best inform reviews of the NAAQS, these evaluations go beyond a determination of causality at any dose or concentration to emphasize the relationship apparent at relevant pollutant exposures. Concentrations generally within an order of magnitude or two of ambient pollutant measurements are considered to be relevant for this determination. Building upon the determination of causality are questions relevant to quantifying health or environmental risks based on our understanding of the quantitative relationships between pollutant exposures and health or welfare effects. While the causality determination is based primarily on evaluation of health or environmental effects evidence, EPA also evaluates evidence related to the doses or levels at which effects are observed. Considerations relevant to evaluation of quantitative relationships for health and environmental effects are summarized below.

1.6.5.1. Effects on Human Populations

Once a determination is made regarding the causal relationship between the pollutant and outcome category, important questions regarding quantitative relationships include:

- What is the concentration-response, exposure-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 populations appear to be differentially affected (i.e., more susceptible to effects)?

To address these questions, the entirety of policy-relevant quantitative evidence is evaluated to best quantify those concentration-response relationships that exist. This requires evaluation of pollutant concentrations and exposure durations at which effects were observed for exposed populations, including potentially susceptible populations. This integration of evidence resulted in identification of a study or set of studies that best approximated the concentration-response relationships between health outcomes and CO, given the current state of knowledge and the uncertainties that surrounded these estimates. To accomplish this, evidence is considered from multiple and diverse types of studies. To the extent available, the ISA evaluates results from across epidemiologic studies that use various methods to evaluate the form of relationships between CO and health outcomes and draws conclusions on the most well-supported shape of these relationships. Animal data may also inform evaluation of concentration-response relationships, particularly relative to MOAs and characteristics of susceptible populations. Chapter 2 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, such as the low data density in the lower concentration range, possible influence of exposure measurement error, and individual differences in susceptibility to air pollution health effects, tend to smooth and "linearize" the concentration-response function. In addition, 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, 156359; Crump et al., 1976, 003192; Hoel, 1980, 156555). These attributes of population dose-response may explain why the available human data at ambient concentrations for some environmental pollutants (e.g., PM, O_3, lead [Pb], environmental tobacco smoke [ETS], radiation) do not exhibit evident thresholds for cancer or noncancer health effects, even though likely mechanisms include nonlinear processes for some key events. These attributes of human population dose-response relationships have been extensively discussed in the broader epidemiologic literature (Rothman and Greenland, 1998, 086599).

Publication bias is a source of uncertainty regarding the magnitude of health risk estimates. It is well understood that studies reporting non-null findings are more likely to be published than reports of null findings, and publication bias can also result in overestimation of effect estimate sizes (Ioannidis, 2008, 188317). For example, effect estimates from single-city epidemiologic studies have been found to be generally larger than those from multicity studies (Anderson et al., 2005, 087916) Although publication bias commonly exists for many research areas, it may be present to a lesser degree for epidemiologic studies on CO. In general, epidemiologic studies have focused on the effects of PM, and CO was largely considered as a potentially confounding copollutant of PM. Thus, CO effect estimates may have been presented in these studies regardless of the statistical significance of the results.

Finally, identification of the susceptible population groups contributes to an understanding of the public health impact of pollutant exposures. In this ISA, the term "susceptible population" will be used as an overarching concept to encompass populations variously described as susceptible,

vulnerable, or sensitive. “Susceptible populations” is defined here as those populations that have a greater likelihood of experiencing health effects related to exposure to an air pollutant (e.g., CO) due to a variety of factors including but not limited to: genetic or developmental factors, race, gender, lifestage, lifestyle (e.g., smoking status and nutrition) or preexisting disease; as well as population-level factors that can increase an individual's exposure to an air pollutant (e.g., CO) such as socioeconomic status [SES], which encompasses reduced access to health care, low educational attainment, residential location, and other factors. Epidemiologic studies can help identify susceptible populations by evaluating health responses in the study population. Examples include stratified analyses for subsets of the population under study or testing for interactions or effect modification by factors such as gender, age group, or health status. Experimental studies using animal models of susceptibility or disease can also inform the extent to which health risks are likely greater in specific population groups. Further discussion of these groups is presented in Section 5.7.

1.6.5.2. Effects on Ecosystems or Public Welfare

Key questions for understanding the quantitative relationships between exposure (or concentration or deposition) to a pollutant and risk to ecosystems or the public welfare include:

- What elements of the ecosystem (e.g., types, regions, taxonomic groups, populations, functions, etc.) appear to be affected, or are more sensitive to effects?
- Under what exposure conditions (amount deposited or concentration, duration and pattern) are effects seen?
- What is the shape of the concentration-response or exposure-response relationship?

Evaluations of causality generally consider the probability of quantitative changes in ecological and welfare effects in response to exposure. A challenge to the quantification of exposure-response relationships for ecological effects is the great regional and local variability in ecosystems. Thus, exposure-response relationships are often determined for a specific ecological system and scale, rather than at the national or even regional scale. Quantitative relationships therefore are available site by site. For example, an ecological response to deposition of a given pollutant can differ greatly between ecosystems. Where results from greenhouse or animal ecotoxicological studies are available, they may be used to aid in characterizing exposure-response relations, particularly relative to mechanisms of action, and characteristics of sensitive biota.

1.6.6. 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 or in cardiovascular health measures. Some health outcome events, such as hospitalization for respiratory or cardiovascular diseases, are clearly considered adverse; what is more difficult is determining the extent of change in the more subtle health measures that is adverse. 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.

For example, the extent to which changes in lung function are adverse has been discussed by the American Thoracic Society (ATS) in an official statement titled *What Constitutes an Adverse Health Effect of Air Pollution?* (2000, 011738). This statement updated the guidance for defining adverse respiratory health effects that had been published 15 years earlier (ATS, 1985, 006522), 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 individual has a level associated with significant impairment. Exposure to air pollution could shift the distribution such that no

identifiable individual experiences clinically relevant effects. This shift toward decreased lung function, however, would be considered adverse because individuals within the population would have diminished reserve function and therefore would be at increased risk to further environmental insult.

It is important to recognize that the more subtle health outcomes may be linked to health events that are clearly adverse. For example, air pollution has been shown to affect markers of transient myocardial ischemia such as ST-segment abnormalities and onset of exertional angina. In some cases, these effects are silent yet may still increase the risk of a number of cardiac events, including MI and sudden death.

1.7. Summary

This ISA is a concise evaluation and synthesis of the most policy-relevant science for reviewing the NAAQS for CO, and it is the chief means for communicating the critical science judgments relevant to that NAAQS review. It reviews the most policy-relevant evidence from atmospheric science, exposure, and health and environmental effects studies and includes mechanistic evidence from basic biological science. This final ISA incorporates clarification and revisions based on public comments and advice and comments provided by EPA's CASAC on the first and second draft ISAs (Brain and Samet, 2009, 194669; Brain and Samet, 2010, 202840). Annexes to the ISA provide additional details of the literature published since the last review. A framework for making critical judgments concerning causality was 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 current and future assessments. This ISA should assist EPA and others, now and in the future, to accurately represent what is presently known and what remains unknown concerning the effects of CO on human health and public welfare.

References

Anderson HR; Atkinson RW; Peacock JL; Sweeting MJ; Marston L (2005). Ambient particulate matter and health effects: Publication bias in studies of short-term associations. Epidemiology, 16: 155-163. 087916

ATS (1985). American Thoracic Society: Guidelines as to what constitutes an adverse respiratory health effect, with special reference to epidemiologic studies of air pollution. Am Rev Respir Dis, 131: 666-668. 006522

ATS (2000). What constitutes an adverse health effect of air pollution? Official statement of the American Thoracic Society. Am J Respir Crit Care Med, 161: 665-673. 011738

Blair A; Burg J; Foran J; Gibb H; Greenland S; Morris R; Raabe G; Savitz D; Teta J; Wartenberg D; Wong O; Zimmerman R (1995). Guidelines for application of meta-analysis in environmental epidemiology. Regul Toxicol Pharmacol, 22: 189-197. 079190

Brain JD; Samet JM (2009). Review of EPA's Integrated Science Assessment for carbon monoxide (first external review draft). Clean Air Scientific Advisory Committee, Science Advisory Board. Washington, DC. EPA-CASAC-09-011. 194669

Brain JD; Samet JM.. (2010). Review of Integrated Science Assessment for Carbon Monoxide (Second External Review Draft). Clean Air Scientific Advisory Committee, Science Advisory Board. Washington, DC. EPA-CASAC-10-005. 202840

CDC (2004). The health consequences of smoking: A report of the Surgeon General. Centers for Disease Control and Prevention, U.S. Department of Health and Human Services. Washington, DC. 056384

Clewell HJ; Crump KS (2005). Quantitative estimates of risk for noncancer endpoints. Risk Anal, 25: 285-289. 156359

Crump KS; Hoel DG; Langley CH; Peto R (1976). Fundamental carcinogenic processes and their implications for low dose risk assessment. Cancer Res, 36: 2973-2979. 003192

Ernst A; Zibrak JD (1998). Carbon monoxide poisoning. N Engl J Med, 339: 1603-1608. 049822

Gee GC; Payne-Sturges DC (2004). Environmental health disparities: A framework integrating psychosocial and environmental concepts. Environ Health Perspect, 112: 1645-1653. 093070

Hedblad B; Engström G; Janzon E; Berglund G; Janzon L (2006). COHb% as a marker of cardiovascular risk in never smokers: results from a population-based cohort study. Scand J Public Health, 34: 609-615. 199512

Hill AB (1965). The environment and disease: Association or causation. J R Soc Med, 58: 295-300. 071664

Hoel DG (1980). Incorporation of background in dose-response models. Fed Proc, 39: 73-75. 156555

IARC (2006). IARC monographs on the evaluation of carcinogenic risks to humans: Preamble. International Agency for Research on Cancer, World Health Organization. Lyon,France . http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf . 093206

Ioannidis JPA (2008). Why most discovered true associations are inflated. Epidemiology, 19: 640-648. 188317

IOM (2008). Improving the Presumptive Disability Decision-Making Process for Veterans; Committee on Evaluation of the Presumptive Disability Decision-Making Process for Veterans, Board on Military and Veterans Health. Washington, DC: Institue of Medicine of the National Academies, National Academies Press. 156586

McClellan RO (1991). CASAC Closure on the 1991 AQCD for Carbon Monoxide. Clean Air Scientific Advisory Committee, Science Advisory Board, U.S. Environmental Protection Agency. Washington, DC. US EPA-SAB-CASAC-LTR-92-015. 194666

McClellan RO (1992). CASAC Closure on the OAQPS Staff Paper for Carbon Monoxide. Clean Air Scientific Advisory Committee, Science Advisory Board, U.S. Environmenal Protection Agency. Washington, DC. US EPA-SAB-CASACLTR-2-016. 194667

Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at http://epa.gov/hero. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISAs) and the Integrated Risk Information System (IRIS).

NAPAP (1991). The experience and legacy of NAPAP report of the Oversight Review Board. National Acid Precipitation Assessment Program. Washington, DC. 095894

National Research Council (2003). Managing carbon monoxide pollution in meteorological and topographical problem areas. Washington, DC: National Research Council of the National Academies Press. 042550

Penney DG (2007). Carbon Monoxide Poisoning. Boca Raton, FL: CRC Press. 194668

Raub JA; Mathieu-Nolf M; Hampson NB; Thom SR (2000). Carbon monoxide poisoning--a public health perspective. Toxicology, 145: 1-14. 002180

Rothman KJ; Greenland S (1998). Modern epidemiology. Philadelphia, PA: Lippincott-Raven Publishers. 086599

U.S. EPA (1979). Air quality criteria for carbon monoxide. U.S. Environmental Protection Agency. Washington, DC. EPA-600/8-79-022. 017687

U.S. EPA (1979). Assessment of adverse health effects from carbon monoxide and implications for possible modifications of the standard. U.S. EPA. Research Triangle Park, NC. 194665

U.S. EPA (1984). Review of the NAAQS for carbon monoxide: Reassessment of scientific and technical information. Office of Air Quality Planning and Standards, U.S. Environmental Protection Agency. Research Triangle Park, NC. EPA-450/5-84-004. 012691

U.S. EPA (1984). Revised evaluation of health effects associated with carbon monoxide exposure: An addendum to the 1979 EPA air quality criteria document for carbon monoxide. U.S. Environmental Protection Agency. Washington, DC. EPA-600/8-83-033F. 012690

U.S. EPA (1991). Air quality criteria for carbon monoxide. U.S. Environmental Protection Agency. Research Triangle Park, NC. EPA/600/8-90/045F. http://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=3000554R.txt. 017643

U.S. EPA (1992). Review of the national ambient air quality standards for carbon monoxide: 1992 reassessment of scientific and technical information OAQPS staff paper. U.S. Environmental Protection Agency. Washington, DC. EPA-452/R-92-004. 084191

U.S. EPA (2000). Air quality criteria for carbon monoxide. National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency. Research Triangle Park, NC. EPA 600/P-99/001F. 000907

U.S. EPA (2004). Air quality criteria for particulate matter. U.S. Environmental Protection Agency. Research Triangle Park, NC. EPA/600/P-99/002aF-bF. 056905

U.S. EPA (2005). Guidelines for carcinogen risk assessment, Risk Assessment Forum Report. U.S. Environmental Protection Agency. Washington, DC. EPA/630/P-03/001B. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=116283. 086237

U.S. EPA (2008). Plan for review of the National Ambient Air Quality Standards for carbon monoxide. U.S. Environmental Protection Agency. Research Triangle Park, NC. EPA-HQ-OAR-2008-0015; FRL-8792-1. 193995

U.S. EPA (2009). Integrated Science Assessment for Particulate Matter. U.S. Environmental Protection Agency. Washington, DC. EPA/600/R-08/139. 179916

Chapter 2. Integrative Overview

The subsequent chapters of this ISA present the most policy-relevant information related to this review of the NAAQS for CO, including a synthesis of the evidence presented in the 2000 CO AQCD (U.S. EPA, 2000, 000907), along with the assessment of more recent studies. This chapter integrates important findings from the disciplines evaluated in this current assessment of the CO scientific literature, which includes the atmospheric sciences, ambient air data analyses, climate forcing effects, exposure assessment, dosimetry, and health effects research (animal toxicological studies, controlled human exposure studies, and epidemiologic studies). The EPA framework for causal determinations described in Chapter 1 has been applied to the body of evidence evaluated in this assessment in order to characterize the relationship between exposure to CO at relevant concentrations and health effects. The EPA framework applied here employs a five-level hierarchy that classifies the weight of evidence for causation:

- Causal relationship
- Likely to be a causal relationship
- Suggestive of a causal relationship
- Inadequate to infer a causal relationship
- Not likely to be a causal relationship

This evaluation led to causal determinations for several health outcome categories and characterization of the magnitude of the response, including responses in susceptible populations, over a range of relevant concentrations. This integration of evidence also provides a basis for characterizing the concentration-response relationships of CO and adverse health outcomes for the U.S. population, given the current state of knowledge.

This chapter summarizes and integrates the newly available scientific evidence that best informs consideration of the policy-relevant questions that frame this assessment, which are presented in Chapter 1. Section 2.1 discusses the trends in ambient concentrations and sources of CO. Section 2.2 provides an overview of climate forcing related directly and indirectly to CO. Section 2.3 provides a brief summary of factors influencing personal exposure to ambient CO. Section 2.4 summarizes CO dosimetry and pharmacokinetics and describes what is known regarding the modes of action of CO. Section 2.5 integrates the evidence from studies that examined health effects related to short- and long-term exposure to CO and discusses important uncertainties identified in the interpretation of the scientific evidence. Section 2.6 summarizes policy-relevant considerations associated with exposure to CO including evidence of effects in potentially susceptible populations and information on the shape of the concentration-response function. Finally, Section 2.7 presents an integrated summary of the health effects of CO, reports the levels at which effects are observed and discusses important uncertainties to consider in the interpretation of the scientific evidence.

2.1. Ambient CO Sources and Concentrations

CO is formed by incomplete combustion of carbon-containing fuels and by photochemical reactions in the atmosphere. Nationally, on-road mobile sources constituted more than half of total CO emissions in 2002, or ~61 of ~117 million tons (MT) of total CO emissions, based on the most recent publicly available data meeting data quality objectives from EPA's National Emissions

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Inventory (NEI). In metropolitan areas in the U.S., as much as 75% of all CO emissions result from on-road vehicle exhaust. The majority of these on-road CO emissions are derived from gasoline-powered vehicles. When emissions from incomplete combustion of fuels powering nonroad mobile sources, such as farm and construction equipment, lawnmowers, boats, ships, snowmobiles, and aircraft, are included, all mobile sources accounted for ~80% of total CO emissions in the U.S. in 2002. Other primary sources of CO include wildfires, controlled vegetation burning, residential biomass combustion, and industrial processes. While CO emissions from nonroad mobile sources, wild fires, and industry have remained fairly constant, on-road mobile source CO emissions have decreased by roughly 5% per year since the early 1990s. Secondary sources of CO include the oxidation of both anthropogenic and biogenic hydrocarbons, such as methane and isoprene and other carbon containing species including aldehydes and alcohols. During summer when biogenic emissions are at their peak, secondary sources of CO are estimated to be a significant fraction of total U.S. sources; however, secondary sources are dispersed over the entire country, while direct emissions are concentrated near primary sources, such as on-road mobile sources, which are mainly in urban areas. Although these estimates are generated using well-established approaches, uncertainties are inherent in the emission factors and models used to represent sources for which emissions have not been directly measured, and these uncertainties vary by source category, season, and region.

Significant reductions in ambient CO concentrations and in the number of NAAQS exceedances have been observed over the past 25 yr, a continuation of trends documented in the 2000 CO AQCD (U.S. EPA, 2000, 000907). Nationwide ambient CO data from the EPA Air Quality System (AQS) for the years 2005-2007 show that the median 1-h daily maximum (max) concentration across the U.S. was 0.7 ppm; the mean was 0.9 ppm; the 95th percentile was 2.4 ppm; and the 99th percentile was 3.8 ppm. Roughly one-third of the 1-h daily max data fell below the limit of detection (LOD) for the majority of CO monitors reporting to AQS. The median 8-h daily max ambient CO concentration for the years 2005-2007 was 0.5 ppm; the mean was 0.7 ppm; the 95th percentile was 1.7 ppm; and the 99th percentile was 2.6 ppm. Half of the 8-h daily max concentrations fell below the LOD for the majority of CO monitors in the field. The current CO NAAQS are 35 ppm (1-h avg) and 9 ppm (8-h avg), not to be exceeded more than once per year. During the years 2005-2007, 1-h and 8-h CO concentrations did not exceed the NAAQS level more than once per year at any monitoring site. Moreover, in these 3 yr, a 1-h avg concentration in excess of 35 ppm was reported only once (39 ppm), and there were only 7 reported 8-h avg values nationwide in excess of 9 ppm in all 3 yr. Seasonally divided box plots of data from 2005-2007 compiled for spatially diverse urban metropolitan areas illustrate the tendency for higher median CO concentrations and wider variations in concentrations in the winter and fall compared with the spring and summer (Section 3.5).

Policy-relevant background (PRB) concentrations include contributions from natural sources everywhere in the world and from anthropogenic sources outside the U.S., Canada, and Mexico. PRB concentrations of CO were estimated for this assessment using data for the years 2005-2007 collected at 12 remote sites in the U.S. which are part of the National Oceanic and Atmospheric Administration's (NOAA) Global Monitoring Division (GMD) and are not part of the EPA national regulatory network. The 3-yr avg CO PRB averaged ~0.13 ppm in Alaska, ~0.10 ppm in Hawaii, and ~0.13 ppm over the contiguous U.S. (CONUS). The analysis for North American PRB in this assessment was made by segregating the three Alaska sites based on their high latitude and the two Hawaii sites based on their distance from the continent, and then treating the remaining seven sites as being more representative of the CONUS PRB. Note that these seven sites are affected by anthropogenic emissions in North America to varying degrees.

2.2. Climate Forcing Effects

Recent data do not alter the current well-established understanding of the role of urban and regional CO in continental- and global-scale chemistry outlined in the 2000 CO AQCD (U.S. EPA, 2000, 000907) and subsequently confirmed in the recent global assessments of climate change by the Intergovernmental Panel on Climate Change (IPCC, 2001, 156587; IPCC, 2007, 092765). CO is a weak direct contributor to radiative forcing (RF) and greenhouse warming. Sinha and Toumi (1996, 193747) estimated the direct RF of CO computed for all-sky conditions at the tropopause to be

0.024 W/m^2 based on an assumed change in CO mean global concentrations from 25 to 100 ppb since preindustrial times. The direct RF attributed to CO over this time frame is ~1.5% of the direct RF for CO_2 estimated by the IPCC (Forster et al., 2007, 092936).

More importantly, CO can indirectly cause increased RF because it reacts with tropospheric OH and thus can increase the lifetime of trace gases in the atmosphere including the GHGs CH_4 and O_3. Additionally, the major pathway for removal of CO from the atmosphere is reaction with OH to produce CO_2. CH_4, O_3, and CO_2 absorb infrared radiation from the Earth's surface and contribute to the greenhouse effect. Indirect RF attributed to 1750-2005 emissions of CO through changes in concentration of the GHGs O_3, CH_4, and CO_2 was estimated by Forster et al. (2007, 092936) to be ~0.2 W/m^2, or ~12% of the direct RF of CO_2 (Figure 3-7). The future direct and indirect integrated RF for year 2000 emissions of CO was estimated to be ~0.2 W/m^2·yr with ~50% uncertainty over both 20-yr and 100-yr time horizons (Figure 3-8). The RF related to short-lived CO is ~25% of that for CO_2 for a 20-yr time horizon but only ~7% of that for longer-lived CO_2 over a 100-yr horizon. Overall, the evidence reviewed in this assessment is sufficient to conclude that **a causal relationship exists between current atmospheric concentrations of CO and effects on climate**.

2.3. Exposure to Ambient CO

Very few recent exposure assessment studies involve ambient CO concentration data. The studies of personal exposure to ambient CO presented here generally found that the largest percentage of time in which an individual is exposed to ambient CO occurs indoors but that the highest ambient CO exposure levels occur in transit. In-vehicle CO concentrations are typically reported to be between 2 and 5 times higher than ambient concentrations, although peak in-vehicle concentrations more than an order of magnitude higher than corresponding ambient monitor concentrations have also been reported. Among commuters, exposures were higher for those traveling in automobiles in comparison with those traveling on buses and motorbikes and with those cycling or walking. Ambient CO exposure in automobiles has been demonstrated to vary with vehicle ventilation settings, and a very small portion of that exposure is thought to come from the vehicle in which the exposed person travels. High near-road CO concentrations can be important for those living in the near-road environment because virtually all of ambient CO infiltrates indoors. Hence, indoor exposure to ambient CO is determined by the CO concentration outside the building. CO concentration in the near-road environment has been shown to decrease sharply with downwind distance from a highway, wind direction, and emission source strength (e.g., number of vehicles on a highway); natural and urban topography also influence localized ambient CO concentrations.

Recent exposure assessment studies support one of the main conclusions of the 2000 CO AQCD (U.S. EPA, 2000, 000907), that central site ambient CO monitors may overestimate or underestimate individuals' personal exposure to ambient CO because ambient CO concentration is spatially variable, particularly when analyzing exposures in the near-road environment. Exposure error may occur when the ambient CO concentration measured at the central site monitor is used as an ambient exposure surrogate and differs from the actual ambient CO concentration outside a subject's residence and/or worksite. For example, measurement at a "hot spot" could skew community exposure estimates upwards, and likewise measurement at a location with few CO sources could skew exposure estimates downwards. Correlations across CO monitors can vary widely within and between cities across the U.S. as a function of natural and urban topography, meteorology, source strength and proximity to sources. Typically, intersampler correlation ranges from 0.35 to 0.65 for monitors sited at different scales within a metropolitan area, although it can be greater than 0.8 in some areas.

Health effects estimates from time-series epidemiologic studies are not biased by spatial variability in CO concentrations if concentrations at different locations are correlated in time. Exposure assessment in epidemiologic studies is also complicated by the existence of CO in multipollutant mixtures emitted by combustion processes, making it difficult to quantify the health effects related specifically to CO exposure compared with those related to another combustion-related pollutant or mix of pollutants. In most circumstances, exposure error tends to bias a health effect estimate downward (Sheppard et al., 2005, 079176; Zeger et al., 2000, 001949). Spatial and temporal variability not fully captured by ambient monitors and correlation of CO with copollutants

are examples of sources of uncertainty that could widen confidence intervals of health effects estimates.

2.4. Dosimetry, Pharmacokinetics, and Mode of Action

2.4.1. Dosimetry and Pharmacokinetics

Upon inhalation, CO elicits various health effects by binding to and altering the function of a number of heme-containing molecules, mainly hemoglobin (Hb). The formation of COHb reduces the oxygen (O_2)-carrying capacity of blood and impairs the release of O_2 from oxyhemoglobin (O_2Hb) to the tissues. The 2000 CO AQCD (U.S. EPA, 2000, 000907) has a detailed description of the well-established Coburn-Forster-Kane (CFK) equation, which has been used for many years to model COHb formation. Since then, models have been developed that include myoglobin (Mb) and extravascular storage compartments, as well as other dynamics of physiology relevant to CO uptake and elimination. These models have indicated that CO has a biphasic elimination curve, due to initial washout from the blood followed by a slower flux from the tissues. The flow of CO between the blood and alveolar air or tissues is controlled by diffusion down the pCO gradient. The uptake of CO is governed not only by this CO pressure differential but also by physiological parameters, such as minute ventilation and lung diffusing capacity that can, in turn, be affected by factors such as exercise, age, and medical conditions (e.g., obstructive lung disease). Susceptible populations, such as health-compromised individuals, are at a greater risk from COHb-induced health effects due to altered CO kinetics, compromised cardiopulmonary processes, and increased baseline hypoxia levels. Altitude also may have a substantial effect on the kinetics of COHb formation, especially for visitors to high-altitude areas. Compensatory mechanisms, such as increased cardiac output, combat the decrease in barometric pressure. Altitude also increases the endogenous production of CO through upregulation of heme oxygenase (HO). CO is considered a second messenger and is endogenously produced from the catabolism of heme proteins by enzymes such as HO-1 (the inducible form of heme oxygenase) and through endogenous lipid peroxidation. Finally, CO is removed from the body by expiration and oxidation to CO_2.

2.4.2. Mode of Action

The diverse effects of CO are dependent upon concentration, duration of exposure, and the cell types and tissues involved. Responses to CO are not necessarily due to a single process and may instead be mediated by a combination of effects including COHb-mediated hypoxic stress and other mechanisms such as free radical production and the initiation of cell signaling. However, binding of CO to reduced iron in heme proteins with subsequent alteration of heme protein function is the common mechanism underlying the biological responses to CO (see Section 5.1).

As discussed in the 2000 CO AQCD (U.S. EPA, 2000, 000907), the most well-known pathophysiological effect of CO is tissue hypoxia caused by binding of CO to Hb. Not only does the formation of COHb reduce the O_2-carrying capacity of blood, but it also impairs the release of O_2 from O_2Hb. Compensatory alterations in hemodynamics, such as vasodilation and increased cardiac output, protect against tissue hypoxia. Depending on the extent of CO exposure, these compensatory changes may be effective in people with a healthy cardiovascular system. However, hemodynamic responses following CO exposure may be insufficient in people with decrements in cardiovascular function, resulting in health effects, as described in Section 5.2. Binding of CO to Mb, as discussed in the 2000 CO AQCD (U.S. EPA, 2000, 000907) and in Section 4.3.2.3, can also impair the delivery of O_2 to tissues. Mb has a high affinity for CO, about 25 times that of O_2; however, pathophysiologic effects are seen only after high-dose exposures to CO, resulting in COMb concentrations far above baseline levels.

Nonhypoxic mechanisms underlying the biological effects of CO have been the subject of recent research since the 2000 CO AQCD (U.S. EPA, 2000, 000907). Most of these mechanisms are related to CO's ability to bind heme-containing proteins other than Hb and Mb. These mechanisms, which may be interrelated, include alteration in nitric oxide (NO) signaling, inhibition of

cytochrome *c* oxidase, heme loss from proteins, disruption of iron homeostasis, alteration in cellular redox status, alteration in ion channel activity and modulation of protein kinase pathways. CO is a ubiquitous cell signaling molecule with numerous physiological functions. The endogenous generation and release of CO from heme by HO-1 and HO-2 is tightly controlled, as is any homeostatic process. However, exogenously-applied CO has the capacity to disrupt multiple heme-based signaling pathways due to its nonspecific nature. Only a limited amount of information is available regarding the impact of exogenous CO on tissue and cellular levels of CO and on signaling pathways. However, recent animal studies demonstrated increased tissue CO levels and biological responses following exposure to 50 ppm CO. Whether or not environmentally-relevant exposures to CO lead to adverse health effects through altered cell signaling is an open question for which there are no definitive answers at this time. However, experiments demonstrating oxidative/nitrosative stress, inflammation, mitochondrial alterations and endothelial dysfunction at concentrations of CO within one or two orders of magnitude higher than ambient concentrations suggest a potential role for such mechanisms in pathophysiologic responses. Furthermore, prolonged increases in endogenous CO resulting from chronic diseases may provide a basis for the enhanced sensitivity of susceptible populations to CO-mediated health effects such as is seen in individuals with coronary artery disease.

2.5. Health Effects

This assessment reviewed health effects evidence regarding the effect of CO on several categories of health outcomes. Table 2-1 presents the overall conclusions of the ISA regarding the presence of a causal relationship between short-term (i.e., hours, days, or weeks) or long-term (i.e., months or years) exposure to relevant CO concentrations (defined in Chapter 1 as generally within one or two orders of magnitude of ambient CO concentrations) and health outcome categories. Summaries of the evidence supporting each causal determination and considerations relevant to application of the causal framework are provided in the following subsections.

Table 2-1. Causal determinations for health effects categories.

Outcome Category	Exposure Period	Causality Determination
Cardiovascular morbidity	Short-term	Likely to be a causal relationship
	Long-term	Inadequate to infer a causal relationship
Central nervous system effects	Short- and long-term	Suggestive of a causal relationship
Birth outcomes and Developmental effects	Long-term	Suggestive of a causal relationship
Respiratory morbidity	Short-term	Suggestive of a causal relationship
	Long-term	Inadequate to infer a causal relationship
Mortality	Short-term	Suggestive of a causal relationship
	Long-term	Not likely to be a causal relationship

2.5.1. Cardiovascular Morbidity

The most compelling evidence of a CO-induced effect on the cardiovascular system at COHb levels relevant to the current NAAQS comes from a series of controlled human exposure studies among individuals with coronary artery disease (CAD) (Section 5.2). These studies, described in the 1991 (U.S. EPA, 1991, 017643) and 2000 (U.S. EPA, 2000, 000907) CO AQCDs, demonstrate consistent decreases in the time to onset of exercise-induced angina and ST-segment changes following CO exposures resulting in COHb levels of 2-6% (Section 5.2.4). No human clinical studies have been designed to evaluate the effect of controlled exposures to CO resulting in COHb concentrations lower than 2%. Human clinical studies published since the 2000 CO AQCD

(U.S. EPA, 2000, 000907) have reported no association between CO and ST-segment changes or arrhythmia; however, none of these studies included individuals with diagnosed heart disease.

While the exact physiological significance of the observed ST-segment changes among individuals with CAD is unclear, ST-segment depression is a known indicator of myocardial ischemia. It is also important to note that the individuals with CAD who participated in these controlled exposure studies may not be representative of the most sensitive individuals in the population. It is conceivable that the most sensitive individuals respond to levels of COHb lower than those evaluated in controlled human exposure studies. Variability in activity patterns and severity of disease among individuals with CAD is likely to influence the critical level of COHb which leads to adverse cardiovascular effects.

The degree of ambient CO exposure which leads to attainment of critical levels of COHb will also vary between individuals. Although endogenous COHb is generally <1% in healthy individuals, higher endogenous COHb levels are observed in individuals with certain medical conditions. Nonambient exposures to CO, such as exposure to environmental tobacco smoke (ETS), may increase COHb above endogenous levels, depending on the gradient of pCO. Ambient exposures may cause a further increase in COHb. Modeling results described in Chapter 4 indicate that increases of ~1% COHb are possible with exposures of several ppm CO depending on exposure duration and exercise level.

Findings of epidemiologic studies conducted since the 2000 CO AQCD (U.S. EPA, 2000, 000907) are coherent with results of the controlled human exposure studies. These recent studies observed associations between ambient CO concentration and emergency department (ED) visits and hospital admissions (HAs) for ischemic heart disease (IHD), congestive heart failure (CHF) and cardiovascular diseases (CVD) as a whole and were conducted in locations where the mean 24-h avg CO concentrations ranged from 0.5 ppm to 9.4 ppm (Table 5-7). All but one of these studies that evaluated CAD outcomes (IHD, MI, angina) reported positive associations (Figure 5-2). Although CO is often considered a marker for the effects of another traffic-related pollutant or mix of pollutants, evidence indicates that CO associations generally remain robust in copollutant models and supports a direct effect of short-term ambient CO exposure on CVD morbidity. These studies add to findings reported in the 2000 CO AQCD (U.S. EPA, 2000, 000907) that demonstrated associations between short-term variations in ambient CO concentrations and exacerbation of heart disease.

The known role of CO in limiting O_2 availability lends biological plausibility to ischemia-related health outcomes following CO exposure. However, it is not clear whether the small changes in COHb associated with ambient CO exposures result in substantially reduced O_2 delivery to tissues. Recent toxicological studies suggest that CO may also act through other mechanisms by initiating or disrupting cellular signaling. Studies in healthy animals demonstrated oxidative injury and inflammation in response to 50-100 ppm CO, while studies in animal models of disease demonstrated exacerbation of cardiomyopathy and increased vascular remodeling in response to 50 ppm CO. Further investigations will be useful in determining whether altered cell signaling contributes to adverse health effects following ambient CO exposure.

Given the consistent and coherent evidence from epidemiologic and human clinical studies, along with biological plausibility provided by CO's role in limiting O_2 availability, it is concluded that **a causal relationship is likely to exist between relevant short-term exposures to CO and cardiovascular morbidity.**

Only two epidemiologic studies were identified that investigated the relationship between long-term exposure to CO and cardiovascular effects, and the results of these studies provide very limited evidence of an association (Section 5.2.2). Considering the lack of evidence from controlled human exposure studies and the very limited evidence from toxicological studies on cardiovascular effects following long-term exposure to CO, the available evidence is **inadequate to conclude that a causal relationship exists between relevant long-term exposures to CO and cardiovascular morbidity.**

2.5.2. Central Nervous System Effects

Exposure to high levels of CO has long been known to adversely affect central nervous system (CNS) function, with symptoms following acute CO poisoning including headache, dizziness,

cognitive difficulties, disorientation, and coma. However, the relationship between ambient levels of CO and neurological function is less clear and has not been evaluated in epidemiologic studies. Studies of controlled human exposures to CO discussed in the 2000 CO AQCD (U.S. EPA, 2000, 000907) reported inconsistent neural and behavioral effects following exposures resulting in COHb concentrations of 5-20%. No new human clinical studies have evaluated central nervous system or behavioral effects of exposure to CO. At ambient-level exposures, healthy adults may be protected against CO-induced neurological impairment owing to compensatory responses including increased cardiac output and cerebral blood flow. However, these compensatory mechanisms are likely impaired among certain potentially susceptible groups including individuals with reduced cardiovascular function.

Toxicological studies that were not discussed in the 2000 CO AQCD (U.S. EPA, 2000, 000907) employed rodent models to show that CO exposure during the in utero or perinatal period can adversely affect adult outcomes, including behavior, neuronal myelination, neurotransmitter levels or function, and the auditory system (discussed in Section 5.3). In utero CO exposure, including both intermittent and continuous exposure, has been shown to impair multiple behavioral outcomes in offspring (75-150 ppm). In utero CO exposure (75 and 150 ppm) was associated with significant myelination decrements and neurotransmitter effects (up to 200 ppm). Finally, perinatal CO exposure has been shown to affect the developing auditory system of rodents, inducing permanent changes into adulthood (12.5-100 ppm), some of which appear to be reactive oxygen species mediated. Considering the combined evidence from controlled human exposure and toxicological studies, the evidence is **suggestive of a causal relationship between relevant short- and long-term exposures to CO and central nervous system effects.**

2.5.3. Birth Outcomes and Developmental Effects

The most compelling evidence for a CO-induced effect on birth and developmental outcomes is for preterm birth (PTB) and cardiac birth defects. These outcomes were not addressed in the 2000 CO AQCD (U.S. EPA, 2000, 000907), which included only two studies that examined the effect of ambient CO on low birth weight (LBW). Since then, a number of studies have been conducted looking at varied outcomes, including PTB, birth defects, fetal growth (including LBW), and infant mortality.

There is limited epidemiologic evidence that CO during early pregnancy (e.g., first month and first trimester) is associated with an increased risk of PTB. The only U.S. studies to investigate the PTB outcome were conducted in California, and these reported consistent positive associations with CO exposure during early pregnancy when exposures were assigned from monitors within close proximity of the mother's residential address. Additional studies conducted outside of the U.S. provide supportive, though less consistent, evidence of an association between CO concentration and PTB.

Very few epidemiologic studies have examined the effects of CO on birth defects. Two of these studies found maternal exposure to CO to be associated with an increased risk of cardiac birth defects. Human clinical studies also demonstrated the heart as a target for CO effects (Section 5.2). Animal toxicological studies provide additional evidence for cardiac effects with reported transient cardiomegaly at birth after continuous in utero CO exposure (60, 125, 250 and 500 ppm CO) and delayed myocardial electrophysiological maturation (150 ppm CO). Toxicological studies have also shown that continuous in utero CO exposure (250 ppm) induced teratogenicity in rodent offspring in a dose-dependent manner that was further affected by dietary protein (65 ppm CO) or zinc manipulation (500 ppm CO). Toxicological studies of CO exposure over the duration of gestation have shown skeletal alterations (7 h/day, CO 250 ppm) or limb deformities (24 h/day, CO 180 ppm) in prenatally exposed offspring.

There is evidence of ambient CO exposure during pregnancy having a negative effect on fetal growth in epidemiologic studies. In general, the reviewed studies, summarized in Figures 5-7 through 5-9, reported small reductions in birth weight (ranging ~5-20 g). Several studies examined various combinations of birth weight, LBW, and small for gestational age (SGA)/intrauterine growth restriction (IUGR) and inconsistent results are reported across these metrics. It should be noted that having a measurable, even if small, change in a population is different than having an effect on a subset of susceptible births and increasing the risk of IUGR/LBW/SGA. It is difficult to conclude if CO is related to a small change in birth weight in all births across the population, or a marked effect

in some subset of births. Toxicology studies have found associations between CO exposure in laboratory animals and decrements in birth weight (90-600 ppm), as well as reduced prenatal growth (65-500 ppm CO).

In general, there is limited epidemiologic evidence that CO is associated with an increased risk of infant mortality during the neonatal or post-neonatal periods. In support of this limited evidence, animal toxicological studies provide some evidence that exogenous CO exposure to pups in utero significantly increased postnatal mortality (7 h/day and 24 h/day, 250 ppm CO; 24 h/day, 90 or 180 ppm CO) and prenatal mortality (7 h/day, 250 ppm CO).

Evidence exists for additional developmental outcomes which have been examined in toxicological studies but not epidemiologic or human clinical studies, including behavioral abnormalities, learning and memory deficits, locomotor effects, neurotransmitter changes, and changes in the auditory system. Structural aberrations of the cochlea involving neuronal activation (12.5, 25 and 50 ppm CO) and auditory related nerves (25 ppm CO) were seen in pups after neonatal CO exposure. Auditory functional testing using otoacoustic emissions testing (OAE at 50 ppm CO) and 8th cranial nerve action potential (AP) amplitude measurements (12, 25, 50, 100 ppm CO) in rodents exposed perinatally to CO showed auditory decrements at postnatal day (PND) 22 (OAE and AP) and permanent changes in AP into adulthood (50 ppm CO). Furthermore, exogenous CO may interact with or disrupt the normal physiological roles that endogenous CO plays in the body. There is evidence that CO plays a role in maintaining pregnancy, controlling vascular tone, regulating hormone balance, and sustaining normal ovarian follicular maturation.

Overall, there is limited, though positive, epidemiologic evidence for a CO-induced effect on PTB and birth defects, and weak evidence for a decrease in birth weight, other measures of fetal growth, and infant mortality. Animal toxicological studies provide support and coherence for these effects. Both hypoxic and nonhypoxic mechanisms have been proposed in the toxicological literature (Section 5.1), though a clear understanding of the mechanisms underlying reproductive and developmental effects is still lacking. Taking into consideration the positive evidence for some birth and developmental outcomes from epidemiologic studies and the resulting coherence for these associations in animal toxicological studies, the evidence is **suggestive of a causal relationship between relevant long-term exposures to CO and developmental effects and birth outcomes**.

2.5.4. Respiratory Morbidity

New epidemiologic studies, supported by the body of literature summarized in the 2000 CO AQCD (U.S. EPA, 2000, 000907), provide evidence of positive associations between short-term exposure to CO and respiratory-related outcomes including pulmonary function, respiratory symptoms, medication use, hospital admissions, and ED visits. The majority of the studies evaluated have not conducted extensive analyses to examine the potential influence of model selection or effect modifiers on the association between CO and respiratory morbidity. A limited number of studies have examined the potential confounding effects of copollutants on CO risk estimates, and found that CO risk estimates were generally robust to the inclusion of O_3, SO_2, and PM in two-pollutant models, but were slightly attenuated in models with NO_2. However, the limited amount of evidence from studies that have examined the effect of gaseous pollutants on CO-respiratory morbidity risk estimates in two-pollutant models, specifically NO_2, has contributed to the inability to disentangle the effects attributed to CO from the larger complex air pollution mix (particularly motor vehicle emissions), and this limits interpretation of the results observed in the epidemiologic studies evaluated. A key uncertainty in interpreting the epidemiologic studies evaluated is the biological mechanism(s) that could explain the effect of CO on respiratory health. Animal toxicological studies, however, provide some evidence that short-term exposure to CO (50-100 ppm) can cause oxidative injury and inflammation and alter pulmonary vascular remodeling. Controlled human exposure studies have not extensively examined the effect of short-term exposure to CO on respiratory morbidity, with a very limited number of studies reporting inconsistent effects of CO on pulmonary function. Although these controlled human exposure studies do not provide evidence to support CO-related respiratory health effects, epidemiologic studies show positive associations for CO-induced lung-related outcomes and animal toxicological studies demonstrate the potential for an underlying biological mechanism, which together provide evidence that is **suggestive of a causal relationship between relevant short-term exposures to CO and respiratory morbidity.**

Currently, only a few studies have been conducted that examine the association between long-term exposure to CO and respiratory morbidity, including allergy. Although some studies did observe associations between long-term exposure to CO and respiratory health outcomes, key uncertainties still exist. These uncertainties include: the lack of replication and validation studies to evaluate new methodologies (i.e., Deletion/Substitution/Addition (DSA) algorithm) that have been used to examine the association between long-term exposure to CO and respiratory health effects; whether the respiratory health effects observed in response to long-term exposure to CO can be explained by the proposed biological mechanisms; and the lack of copollutant analyses to disentangle the respiratory effects associated with CO due to its high correlation with NO_2 and other combustion-related pollutants. Overall, the evidence available is **inadequate to conclude that a causal relationship exists between relevant long-term exposures to CO and respiratory morbidity.**

2.5.5. Mortality

The recently available multicity studies, which consist of larger sample sizes, along with the single-city studies, evaluated reported associations that are generally consistent with the results of the studies evaluated in the 2000 CO AQCD (U.S. EPA, 2000, 000907). However, to date the majority of the literature has not conducted extensive analyses to examine the potential influence of model selection, effect modifiers, or confounders on the association between CO and mortality.

The multicity studies reported comparable CO mortality risk estimates for total (nonaccidental) mortality, with the APHEA2 European multicity study showing slightly higher estimates for cardiovascular mortality in single-pollutant models. However, when examining potential confounding by copollutants, these studies consistently showed that although CO mortality risk estimates remained positive, they were reduced when NO_2 was included in the model. But this observation may not be "confounding" in the usual sense in that NO_2 may also be an indicator of other pollutants or pollution sources (e.g., traffic).

Of the studies evaluated, only the APHEA2 study focused specifically on the CO-mortality association and in the process examined: (1) model sensitivity; (2) the CO-mortality C-R relationship; and (3) potential effect modifiers of CO mortality risk estimates. The sensitivity analysis indicated an approximate 50-80% difference in CO risk estimates from a reasonable range of alternative models, which suggests that some model uncertainty likely influences the range of CO mortality risk estimates obtained in the studies evaluated. The examination of the CO-mortality concentration-response relationship found very weak evidence for a CO threshold at 0.5 mg/m^3 (0.43 ppm). Finally, when examining a variety of city-specific variables to identify potential effect modifiers of the CO-mortality relationship, the APHEA2 study found that geographic region explained most of the heterogeneity in CO mortality risk estimates.

The results from the single-city studies are generally consistent with the multicity studies in that some evidence of a positive association was found for mortality upon short-term exposure to CO. However, the CO-mortality associations were often but not always attenuated when copollutants were included in the regression models. In addition, limited evidence was available to identify cause-specific mortality outcomes (e.g., cardiovascular causes of death) associated with short-term exposure to CO.

The evidence from the recent multi- and single-city studies suggests that an association between short-term exposure to CO and mortality exists, but limited evidence is available to evaluate cause-specific mortality outcomes associated with CO exposure. In addition, the attenuation of CO risk estimates which was often observed in copollutant models contributes to the uncertainty as to whether CO is acting alone or as an indicator for other combustion-related pollutants. Overall, the epidemiologic evidence is **suggestive of a causal relationship between relevant short-term exposures to CO and mortality.**

The evaluation of new epidemiologic studies conducted since the 2000 CO AQCD (U.S. EPA, 2000, 000907) that investigated the association between long-term exposure to CO and mortality consistently found null or negative mortality risk estimates. No such studies were discussed in the 2000 CO AQCD (U.S. EPA, 2000, 000907). The reanalysis of the American Cancer Society (ACS) data by Jerrett et al. (2003, 087380) found no association between long-term exposure to CO and mortality. Similar results were obtained in an updated analysis of the ACS data when using earlier (1980) CO data, but negative associations were found when using more recent (1982-1998) data.

These results were further confirmed in an extended analysis of the ACS data. The Women's Health Initiative (WHI) Study also found no association between CO and CVD events (including mortality) using the mortality data from recent years (1994-1998), while the series of Veterans Cohort studies found no association or a negative association between mean annual 95th percentile of hourly CO values and mortality. An additional study was identified that used a cross-sectional study design, which reported results for a study of U.S. counties that are generally consistent with the cohort studies: positive associations between long-term exposure to $PM_{2.5}$ and SO_4^{2-} and mortality, and generally negative associations with CO. Overall, the consistent null and negative associations observed across epidemiologic studies which included cohort populations encompassing potentially susceptible populations (i.e., post-menopausal women and hypertensive men) combined with the lack of evidence for respiratory and cardiovascular morbidity outcomes following long-term exposure to CO; and the absence of a proposed mechanism to explain the progression to mortality following long-term exposure to CO provide supportive evidence that there is **not likely to be a causal relationship between relevant long-term exposures to CO and mortality.**

2.6. Policy-Relevant Considerations

2.6.1. Susceptible Populations

The examination of populations potentially at greater risk for health effects due to CO exposure is an important consideration in setting NAAQS to provide an adequate margin of safety for both the general population and sensitive populations (see Section 5.7 for a more detailed discussion). During the evaluation of the CO literature, numerous studies were identified that examined whether underlying factors increased the susceptibility of an individual to CO-related health effects. These types of studies were those that included stratified analyses, examined individuals with an underlying health condition, or used animal models of disease.

The most important susceptibility characteristic for increased risk due to CO exposure is CAD, also known as coronary heart disease (CHD). As discussed in Section 5.7, there were approximately 13.7 million individuals with CHD in the U.S. in 2007. Persons with a normal cardiovascular system can tolerate substantial concentrations of CO, if they vasodilate or increase cardiac output in response to the hypoxia produced by CO. In contrast, individuals unable to vasodilate in response to CO exposure may show evidence of ischemia at low concentrations of COHb. Many of the controlled human exposure studies have focused on individuals with CAD, and several studies have found that controlled exposures to CO resulting in COHb concentrations of 2-6% result in significant decreases in time to onset of exercise-induced angina or ST-segment changes in patients with stable angina. Epidemiologic studies found limited evidence for increased hospital admissions for ischemic heart disease (IHD) in individuals with secondary diagnoses of dysrhythmias or congestive heart failure (CHF). This combined evidence from controlled human exposure and epidemiologic studies indicates that individuals with underlying cardiovascular disease, particularly CAD, are a large population that is susceptible to increased health effects in response to exposure to ambient CO. Additional evidence for increased CO-induced cardiovascular effects is provided by toxicological studies that observed altered cardiac outcomes in animal models of cardiovascular disease.

Other medical conditions that have been linked to increased susceptibility to CO-induced health effects include COPD, diabetes, and anemia. Individuals with hypoxia resulting from COPD may be particularly sensitive to CO during submaximal exercise typical of normal daily activity. The results available from epidemiologic and controlled human exposure studies provide preliminary evidence that individuals with obstructive lung disease (e.g., COPD patients with underlying hypoxia, asthmatics) may be susceptible to cardiovascular or respiratory effects due to CO exposure. Diabetics are known to have elevated exhaled CO concentrations indicative of increased endogenous CO production rates. In addition, some recent epidemiologic studies provide preliminary evidence for increased associations between short-term CO exposure and ED visits and hospital admissions for cardiovascular disease (CVD) among diabetics compared to non-diabetics, as well as associations between short-term CO exposure and changes in HRV parameters among subjects with metabolic syndrome, but not among healthy subjects. Increased endogenous CO production and the potential

for higher baseline COHb concentrations in individuals with diabetes, combined with the limited epidemiologic evidence showing cardiovascular effects, suggests that diabetics are potentially susceptible to short-term exposure to CO. Individuals with various forms of anemia experience lowered hematocrit or produce altered forms of hemoglobin, resulting in decreased arterial O_2 content; in addition, individuals with hemolytic anemia exhibit increased endogenous CO production rates and COHb levels. This suggests that individuals with anemia who have diminished O_2-carrying capacity and/or high baseline COHb levels may be more susceptible to health effects due to ambient CO exposure, although no studies were identified that evaluated specific CO-related health effects in anemic individuals.

Aging alters physiological parameters that influence the uptake, distribution, and elimination of CO. The general impact of these changes over an individual's lifetime increases the time required for both loading and elimination of CO from the blood. As noted in the 2000 CO AQCD (U.S. EPA, 2000, 000907), changes in metabolism that occur with age, particularly declining maximal oxygen uptake, may make the aging population susceptible to the effects of CO via impaired oxygen delivery to the tissues. Some epidemiologic studies reported increases in IHD or myocardial infarction (MI) HAs among older adults as compared to all-age groups or younger adults in response to short-term exposure to CO. Older adults represent a large and growing fraction of the U.S. population and have a higher prevalence of CAD and other cardiovascular conditions than the general population; combined with the limited evidence available from epidemiologic studies, this indicates that older adults are a potentially susceptible population for increased health effects due to CO.

During gestational exposure, fetal CO pharmacokinetics differ from maternal kinetics, in part because human fetal Hb has a higher CO affinity than adult Hb. At steady-state conditions, fetal COHb concentrations are up to 10-15% higher on a relative basis than maternal COHb levels, and these levels are maintained over a longer period since the half-life for fetal CO Hb is approximately twice that of maternal COHb (7.5 h versus 4 h). Some epidemiologic studies reported higher associations between short-term CO exposure and IHD or MI HAs among older adults as compared to all-age groups or younger adults. Epidemiologic studies provide some evidence that CO exposure during pregnancy is associated with changes in birth outcomes, including PTB, cardiac birth defects, reductions in birth weight, and infant mortality in the postneonatal period. Toxicological studies report effects in laboratory animals that lend biological plausibility to outcomes observed in epidemiologic studies, including decrements in birth weight, reduced prenatal growth, and effects on the heart. Toxicological evidence also exists for additional developmental outcomes which have not been examined in epidemiologic or human clinical studies, including behavioral abnormalities, learning and memory deficits, locomotor effects, neurotransmitter changes, and changes in the auditory system. This evidence suggests that critical developmental phases may be characterized by enhanced sensitivity to CO exposure.

COHb concentrations are generally higher in males than in females, and the COHb half-life is longer in healthy men than in women of the same age. However, women experience fluctuating COHb levels through the menstrual cycle due to variations in the endogenous CO-production rate. Only a limited number of epidemiologic studies have examined gender differences, and found some evidence for larger effects in males compared to females when examining the association between short-term CO exposure and IHD HAs. The limited epidemiologic evidence combined with known gender-related differences in endogenous CO production do not provide sufficient basis for determining whether CO disproportionately affects males or females.

Increased altitude induces a number of physiological changes as compensatory mechanisms to counteract the effects of decreased barometric pressure and the resulting altitude-induced hypobaric hypoxia (HH). These changes generally increase both CO uptake and elimination, with increased COHb levels observed in subjects at rest and decreased COHb observed in individuals exposed to CO during exercise. In addition, baseline COHb levels increase due to increased endogenous CO production. A controlled human exposure study observed an additive effect of CO exposure and simulated high altitude on the reduction in time to onset of angina among a group of individuals with CAD. Acclimatization occurs as the length of stay at high altitude increases, indicating that visitors to high-altitude locations may have an increased risk of health effects due to CO exposure and represent a potentially susceptible population.

Physiological changes associated with exercise tend to increase both uptake and elimination of CO. In a controlled human exposure study, healthy subjects exposed to CO and achieving COHb levels of ~5% observed a significant decrement in exercise duration and maximal effort capability

during heavy exercise. Due to the counterbalancing effects of increased COHb formation and elimination rates, it is unclear whether individuals engaging in light to moderate exercise represent a population potentially susceptible to ambient CO exposure.

CO concentrations on and adjacent to heavily traveled roadways are several times higher than concentrations measured at fixed-site monitors not located adjacent to roadways. In addition, studies of commuters have shown that commuting time is an important determinant of CO exposure for those traveling by car, bicycle, public transportation, and walking. Census data indicate that 17.9 million occupied homes nationwide (16.1%) are located within approximately 90 m of a freeway, railroad, or airport, and that 5.5 million U.S. workers (5%) commute 60 min or more to work in automobiles. This evidence for elevated on-road and near-road CO concentrations combined with residential and commuting data indicates that the large numbers of individuals who spend a substantial amount of time on or near heavily traveled roadways are an important population that is potentially susceptible to increased health risks due to ambient CO exposure.

Endogenous CO production can be altered by medications or other substances, including nicotinic acid, allyl-containing compounds (acetamids and barbiturates), diphenylhydantoin, progesterone, contraceptives, and statins. One epidemiologic study observed an association between short-term CO exposure and an increase in SDNN for CAD patients not taking beta blockers; however, this association did not persist in CAD patients taking beta blockers. Other compounds such as carbon disulfide and sulfur-containing chemicals (parathion and phenylthiourea) increase CO following metabolism by cytochrome p450s. The p450 system may also cause large increases in CO produced from the metabolic degradation of dihalomethanes such as methylene chloride. Minor sources of endogenous CO include the auto-oxidation of phenols, photo-oxidation of organic compounds, and lipid peroxidation of cell membrane lipids. Taken together, this evidence indicates that individuals ingesting medications and other substances that enhance endogenous or metabolic CO production represent a population that is potentially susceptible to increased health effects due to additional exposure to ambient CO.

Overall, the controlled human exposure, epidemiologic, and toxicological studies evaluated in this assessment provide evidence for increased susceptibility among multiple populations. Medical conditions that increase endogenous CO production rates may also contribute to increased susceptibility to health effects from ambient CO exposure. Although the weight of evidence varies depending on the factor being evaluated, the clearest evidence indicates that individuals with CAD are most susceptible to an increase in CO-induced health effects.

2.6.2. Concentration- and Dose-Response Relationships

Currently, very limited information is available in the human clinical and epidemiologic literature regarding the CO concentration- or dose-response (C-R, D-R) relationships and the potential existence of a CO threshold. Two human clinical studies described in the 1991 (U.S. EPA, 1991, 017643) and 2000 (U.S. EPA, 2000, 000907) CO AQCDs have evaluated the D-R relationship between percent COHb (a measure of internal dose of CO) and onset of exercise-induced angina among individuals with CAD. Anderson et al. (1973, 023134) exposed 10 adult men with stable angina (5 smokers and 5 nonsmokers) for 4 h to CO concentrations of 50 and 100 ppm, which resulted in average COHb concentrations of 2.9% and 4.5%, respectively. Both exposures significantly decreased the time to onset of exercise-induced angina relative to room air control (1.6% COHb). However, there was no difference in response between the two exposure concentrations of CO. In a much larger study, 63 adults with stable angina were exposed for 1 h to 2 concentrations of CO (average exposure concentrations of 117 and 253 ppm) resulting in average COHb concentrations in the range of 2.0-2.4% and 3.9-4.7% (Allred et al., 1989, 013018; Allred et al., 1989, 012697; Allred et al., 1991, 011871). Relative to control (average COHb 0.6-0.7%), COHb concentrations of 2.0-2.4% and 3.9-4.7% were observed to decrease the time required to induce ST-segment changes indicative of myocardial ischemia by 5.1% ($p = 0.01$) and 12.1% ($p < 0.001$), respectively. Increasing COHb concentration was similarly shown to decrease the time to onset of exercise-induced angina. As described in Allred et al. (1989, 013018; 1989, 012697; 1991, 011871), the observed dose-response relationship was further evaluated by regressing the percent change in time to ST-segment change or time to angina on actual COHb concentration (0.2% - 5.1%) using the three exposures (air control and two CO exposures) for each subject. Regression analyses were conducted separately for each individual and the averages of the intercepts and slopes across subjects were reported. This analysis demonstrated statistically significant decreases in time to angina and

ST-segment change of approximately 1.9% and 3.9%, respectively, per 1% increase in COHb concentration, with no evidence of a measurable threshold. The findings of Allred et al. (1989, 013018; 1989, 012697; 1991, 011871) provide evidence of a significant D-R relationship over a range of COHb concentrations relevant to the NAAQS. While several other laboratory studies have evaluated cardiovascular effects of CO exposure among adults with CAD, differences in study protocols and analytical methods do not allow for an informative pooled or quantitative meta-analysis of the D-R relationship across studies (Section 5.2.4).

Two studies in the epidemiologic literature attempted to examine the C-R relationship at the low end of CO concentrations through a threshold analysis. Samoli et al. (2007, 098420) in their examination of the association between short-term exposure to CO and mortality conducted an ancillary analysis to examine the potential presence of a CO threshold. In this analysis the authors compared city-specific models to the threshold model, which consisted of thresholds at 0.5 mg/m^3 (0.43 ppm) increments. Samoli et al. (2007, 098420) then computed the deviance between the two models and summed the deviances for a given threshold over all cities. While the minimum deviance suggested a potential threshold of 0.43 ppm (the lowest threshold examined), the comparison with the linear no-threshold model indicated weak evidence (p-value > 0.9) for a threshold. However, determining the presence of a threshold at the very low range of CO concentrations (i.e., at 0.43 ppm) in this data set is challenging, because, in 7 of the 19 European cities examined, the lowest 10% of the CO distribution was at or above 2 mg/m^3 (1.74 ppm). By only using the 12 cities in the analysis that had minimum CO concentrations approaching 0.5 mg/m^3 (0.43 ppm), a limited number of observations were examined around the threshold of interest, which subsequently contributed to the inability to draw conclusions regarding the potential presence of a threshold with any certainty. In addition to the time-series analyses investigating the association of CO concentrations with hospital admissions due to CVD among Medicare enrollees, Bell et al. (2009, 193780) performed subset analyses using datasets that included only days with CO levels below certain specified values, ranging from 1 to 10 ppm (in 1 ppm increments). When these various CO-limit values were evaluated, there were positive associations between cardiovascular health effects and CO concentrations at each level investigated in this study, thus providing no evidence for the existence of a threshold. The investigators also estimated an exposure-response curve allowing a nonlinear relationship between CO concentration and risk of CVD hospital admissions, and reported no evidence of departure from a linear exposure-response curve.

2.7. Integration of CO Health Effects

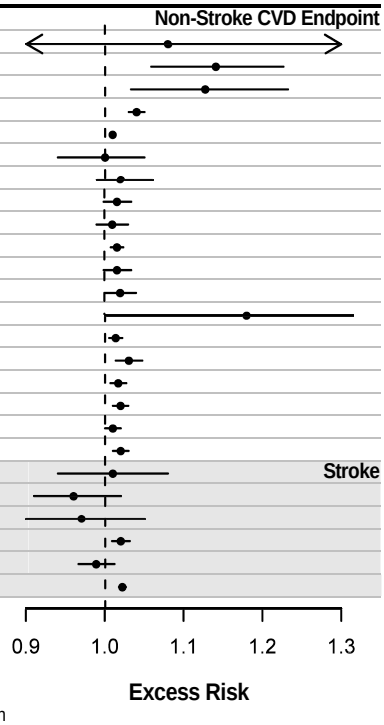
This section summarizes the main conclusions of this assessment regarding the health effects of CO and the concentrations at which those effects are observed. It also discusses important uncertainties that were considered in interpreting the health effects evidence. The clearest evidence for health effects associated with short-term exposure to CO is provided by studies of cardiovascular morbidity. The combined health effects evidence supports a likely causal relationship for this outcome. Controlled human exposure studies provide strong evidence of independent effects of CO on cardiac function, with effects being observed in patients with CAD following short-term CO exposures resulting in 2.0-2.4% COHb. Epidemiologic studies of ED visits and hospital admissions for ischemic heart disease report consistent positive associations with additional preliminary evidence for an increase in cardiovascular-related mortality provided by a multicity study. This epidemiologic evidence is coherent with ischemia-related effects observed in controlled human exposure studies. Recent toxicological evidence suggests that other mechanisms involving altered cellular signaling may play a role in cardiovascular disease outcomes following CO exposure.

Consistent decreases in time to onset of exercise-induced angina, along with ST-segment changes indicative of myocardial ischemia, were observed in individuals with CAD following controlled CO exposures resulting in COHb concentrations of 2-6%, with no evidence of a threshold at the lowest levels tested. Modeling results described in Chapter 4 indicated that increases of ~1% COHb are possible with exposures of several ppm CO, depending on exposure duration and exercise level. Baseline COHb levels are <1% in healthy individuals, with higher endogenous CO production observed in individuals with certain medical conditions. The volunteers who participated in these studies were diagnosed with moderate to severe CAD, although they may not be representative of the most sensitive individuals in the population. Variability in activity patterns and severity of

disease combined with daily fluctuations in baseline COHb levels may influence the critical level of increased COHb which leads to adverse cardiovascular effects in a particular individual. In addition, arterial COHb is transiently higher than venous COHb for several minutes following a rapid increase in inhaled CO concentration. Transient increases in ambient CO have the potential to elevate COHb to higher levels in the coronary arteries than in other vascular beds, possibly increasing heart CO levels and cardiovascular symptoms in diseased individuals. Quantification of the magnitude of effects at ambient concentrations from the results of controlled human exposure studies is difficult due to the gap between ambient concentrations and the higher concentrations used in these studies (i.e., experimental studies have not been conducted at levels within the range of current maximum ambient concentrations).

Epidemiologic studies consistently show associations between ambient CO concentrations and cardiovascular endpoints other than stroke, particularly hospitalizations and ED visits for ischemic heart disease, MI, and angina. These effects are robust to adjustment for copollutants. Since the heterogeneity of endpoints in these studies does not lend itself to a quantitative meta-analysis, a forest plot was used to summarize the results. Figure 2-1 presents unadjusted health effect estimates from U.S. and Canadian studies of short-term CO exposure and CVD hospitalizations, along with mean and 99th percentile concentrations during the study periods. Table 2-2 summarizes the range of mean and 99th percentile concentrations observed in the studies presented in Figure 2-1. This evidence for ischemia-related outcomes is coherent with effects observed in controlled human exposure studies, although uncertainty regarding the extent of reduced O_2 delivery to tissues following exposure to ambient CO concentrations contributes to the uncertainty in quantitative interpretation of effect estimates.

Study	Location	Mean*[a,b]	Avg Time	Lag	Outcome/ Group
					Non-Stroke CVD Endpoint
Symons et al. (2006, 091258)	Baltimore, MD	0.4 (2.3)	8-h max	0-3	CHF
Szyszkowicz (2007, 193793)	Montreal, Can	0.5	24-h avg	0	IHD
				0	IHD, 65+
Wellenius et al. (2005, 087483)	Pittsburgh, PA	1.03 (1.6-3.9)	24-h avg	0	CHF
Bell et al. (2009, 193780)	126 U.S. Counties	1.3 (1.2-22.1)[c]	1-h max	0	CVD, 65+
Fung et al. (2005, 074322)	Windsor, Can	1.3	1-h max	0-2	CVD, <65
				0-2	CVD, 65+
Metzger et al. (2004, 044222)	Atlanta, GA	1.8 (5.5-5.9)	1-h max	0-2	IHD
				0-2	CHF
Tolbert et al. (2007, 090316)	Atlanta, GA	1.6 (5.3-5.4)	1-h max	0-2	CVD
Peel et al. (2007, 090442)	Atlanta, GA	1.8 (5.5-5.9)	1-h max	0-2	IHD
				0-2	CHF
Koken et al. (2003, 049466)	Denver, CO	0.9 (1.3-2.0)	24-h avg	3	CHF
Mann et al. (2002, 036723)	California, US	2.07 (1.3-15.9)	8-h max	0-3	IHD
				0-3	IHD, sCHF
				0-3	IHD, sARR
Linn et al. (2000, 002839)	Los Angeles, CA	1.5 (1.1-8.3)	24-h avg	0	MI
				0	CHF
				0	CVD
Villeneuve et al. (2006, 090191)	Edmonton, Can	0.8	24-h avg	0-2	IS, 65+
				0-2	CIS, 65+
				0-2	HS, 65+
Wellenius et al. (2005, 088685)	Multicity, US	1.02** (1.2-7.1)	24-h avg	0-2	IS, 65+
				0-2	HS, 65+
Linn et al. (2000, 002839)	Los Angeles, CA	1.5 (1.1-8.3)	24-h avg	0	IS



*CO Mean and (99th percentile) concentrations in ppm. ** Median

[a] Mean concentrations (ppm) are presented as reported in the references. Studies are arranged in approximate order of increasing mean concentration, with adjustment for different averaging times using a 4:3:2 ratio of 1-h max, 8-h max, and 24-h avg values based on relationships derived from the national AQS CO distribution.

[b] 99th percentile concentrations (ppm) were obtained from the AQS database for durations and locations chosen to match those of the U.S. studies. When multiple monitors were available at the study location, the range of monitor specific 99th percentile concentrations during the study period is presented. No 99th percentile data are presented for Canadian studies.

[c] For the Bell et al. (2009, 193780) study, the concentration statistics represent the 1999-2005 average of daily county-specific values. The central estimate is the median county-average across the U.S. The 99th percentile values represent the counties with the lowest and highest 99th percentile concentrations. Additional cause-specific effect estimates adjusted for NO_2 are presented in Section 5.2.1.

Figure 2-1. Excess risk estimates from epidemiologic studies of short-term CO exposure and CVD hospitalizations along with author-reported mean and AQS-derived 99th percentile CO concentrations. See the footnotes related to concentration data.

Table 2-2. Range of mean and 99th percentile concentrations (ppm) in US and Canadian studies of short-term CO exposure and CVD hospitalizations. See the notes in Figure 2-1 for sources of concentration data.

Metric	1-h daily max	8-h daily max	24-h avg
Mean	1.3-1.8	0.4-2.07	0.5-1.5
99th percentile	1.2-22.1	1.3-15.9	1.1-8.3

Additional studies provide evidence for associations between CO exposure and other health outcomes, including CNS effects, birth outcomes and developmental effects, respiratory effects, and mortality. Although inconsistent results were reported in controlled human exposure studies on neural and behavioral effects, toxicological studies in rodents found that perinatal exposure to CO can have a range of effects on the adult nervous system. This combined evidence is suggestive of a causal relationship between both short- and long-term CO exposure and CNS effects. Differences in fetal pharmacokinetics from those of the mother result in fetal COHb levels that are up to 10-15% higher than maternal COHb levels. Epidemiologic studies provide some evidence that CO exposure during pregnancy is associated with changes in birth outcomes, including increased risk of PTB, cardiac birth defects, small reductions in birth weight, and infant mortality in the postneonatal period. This evidence, in conjunction with developmental effects observed in toxicological studies, is suggestive of a causal relationship between long-term exposure to CO and birth and developmental effects.

Evidence regarding the effect of short-term exposure to CO on respiratory morbidity is suggestive of a causal relationship, based on associations observed in epidemiologic studies and animal toxicological studies which indicate the potential for an underlying biological mechanism, while the evidence on long-term exposure and respiratory morbidity is inadequate to infer the presence of a causal relationship.

An evaluation of epidemiologic studies that examined the effect of short-term exposure to CO on mortality provides evidence that is suggestive of a causal relationship. Epidemiologic studies that examined mortality and long-term exposure to CO reported consistent null associations, which, combined with the lack of respiratory and cardiovascular morbidity or a proposed biological mechanism for mortality following long-term exposure, indicate that there is not likely to be a causal relationship between long-term exposure to CO and mortality.

Issues such as exposure error and isolation of the independent effect of CO as a component of a complex air-pollutant mixture contribute to uncertainty in interpreting the results of epidemiologic studies. Studies published since the 2000 CO AQCD (U.S. EPA, 2000, 000907) have provided insight regarding the nature and magnitude of these uncertainties. Exposures in near-road and on-road microenvironments are likely to be higher than concentrations measured at community-oriented regulatory monitors, which may result in over- or underestimation of the magnitude of ambient exposure for some individuals. Individuals who are susceptible to CO-induced health effects, such as those with CAD, may be at additional risk when experiencing elevated on-road CO concentrations. However, as discussed in Section 2.3 and in more detail in Section 3.6, spatial variability in absolute concentration will not introduce error into time-series epidemiologic studies if the concentrations are correlated in time. A recent study by Sarnat et al. (2009, 180084) found that associations between CO and cardiovascular ED visits were similar when based on different monitors within an urban center, regardless of monitor location or distance to population, while an association was not observed when using a rural monitor outside the urban area. This may have been related to the similarity of driving patterns and peak rush-hour times in the urban center as compared to the area around the rural monitor, where the temporal driving patterns were different. Simulations of ambient and nonambient exposures to a nonreactive pollutant indicated that nonambient exposure has no effect on the association between ambient exposure and health outcomes for the case where ambient and nonambient concentrations are independent, although variability is introduced. Nonambient exposure to CO is not expected to be temporally correlated with ambient CO concentrations, and therefore nonambient CO will not act as a confounder in epidemiologic associations with ambient CO. Exposure error is not likely to affect the magnitude of the population-averaged effect estimates observed in epidemiologic studies, although it would tend to widen the confidence intervals.

Epidemiologic studies consider the effects of CO as a component of a complex mixture of air pollutants that varies across space and time, with moderate to high correlations observed between CO concentrations and those of other combustion-related pollutants. On-road vehicle exhaust emissions are a nearly ubiquitous source of combustion pollutant mixtures that include CO, NO_2, and $PM_{2.5}$, and these emissions are the most important contributor to ambient CO in near-road locations. Correlations between CO and NO_2 reported in epidemiologic studies of short-term exposure to CO generally ranged from 0.3 to 0.86, with correlations reported in US studies ranging from 0.55 to 0.86. Correlations between CO and $PM_{2.5}$ reported in all studies ranged from 0.17 to 0.74, with correlations in US studies ranging from 0.43 to 0.62. This complicates the quantitative interpretation of effect estimates in these studies to apportion the relative extent to which CO at ambient concentrations is independently associated with cardiovascular or other effects, and the extent to which CO acts as a marker for the effects of another combustion-related pollutant or mix of pollutants.

As summarized in Tolbert et al. (2007, 090316), when toxicological or controlled human exposure studies of two correlated pollutants provide evidence that each exerts an independent health effect, two-pollutant models may be appropriate to adjust the effect estimate for each pollutant for confounding by the other pollutant. $PM_{2.5}$ and NO_2 have each been linked to cardiovascular health effects in epidemiologic studies. In two-pollutant models in which one of the pollutants is linked to the measured outcome and the other is a surrogate for the first pollutant, the copollutant model can help identify which is the better predictor of the effect, particularly if the etiologically linked pollutant is measured with more error than the second pollutant. Uncertainty is introduced in the size of the effect estimate and the portion of the effect size represented by each of the coefficients in the model by correlation between the two pollutants and by differential exposure measurement error. Since the spatial variability of CO is a larger contributor to measurement error than for other more homogenously distributed pollutants such as $PM_{2.5}$, robustness of CO effect estimates indicates that CO is the better predictor of effects in copollutant models. Although this complicates quantitative interpretation of the effect estimates reported in epidemiologic studies, the epidemiologic evidence for cardiovascular morbidity summarized in this assessment indicates that CO associations generally remain robust in copollutant models (Figure 5-6 and Figure 5-7), which, combined with the consistency of effects observed across studies, the coherence of epidemiologic health outcomes with effects observed in controlled human exposure studies, and the emerging evidence on the potential role for cell signaling effects at low tissue CO concentrations, supports an independent effect of short-term CO exposure on cardiovascular morbidity. This combined evidence supports a determination that the relationship between CO and cardiovascular morbidity is likely causal, while still recognizing that CO is a component of a mixture of combustion-related pollutants.

Evidence from controlled human exposure and epidemiologic studies indicates that individuals with underlying CVD, specifically CAD, are an important susceptible population at increased risk of health effects due to ambient CO. Potentially susceptible populations include those with other underlying diseases, including anemia, obstructive lung disease, or diabetes; older adults and fetuses during critical phases of development; commuters and those living near heavily traveled roadways; visitors to high-altitude locations; and individuals ingesting medications and other substances that enhance endogenous or metabolic CO production. Limited evidence is available from controlled human exposure studies of CAD patients indicating a statistically significant inverse relationship between COHb concentration and time to ST segment change or time to exercise-induced angina. Epidemiologic analyses investigating the exposure-response relationship for mortality and cardiovascular morbidity did not find evidence for a departure from linearity or a threshold for CO effects.

The new evidence reviewed in this ISA builds upon the health-effects evidence summarized in the 2000 CO AQCD (U.S. EPA, 2000, 000907), with many new epidemiologic studies adding to the body of evidence showing associations between acute cardiovascular effects and CO measured at ambient monitors. Controlled human exposure studies reviewed both in this ISA and the 2000 CO AQCD (U.S. EPA, 2000, 000907) show definitive evidence of cardiovascular effects among individuals with CAD following short-term CO exposure, resulting in COHb concentrations as low as 2.0-2.4%. Emerging toxicological evidence points to the potential role for CO in modes of action not directly related to COHb's role in O_2 delivery. In evaluating the several epidemiologic studies available at the time that reported associations between ambient CO and cardiovascular effects, the 2000 CO AQCD (U.S. EPA, 2000, 000907) considered those findings to be inconclusive for multiple reasons, including: questions regarding the consistency of the results among studies; the ability of

community fixed-site monitors to represent spatially variable ambient CO concentrations and personal exposures; the small expected increase in COHb due to ambient CO concentrations; the lack of biological plausibility for health effects to occur at such COHb levels, even in diseased individuals; the potentially greater impact of non-ambient exposure on COHb; and the possibility that ambient CO is serving as a surrogate for a mixture of combustion-related pollutants. Some of these uncertainties remain and complicate the quantitative interpretation of the epidemiologic findings, particularly regarding the biological plausibility of health effects occurring at COHb levels resulting from exposures to ambient CO concentrations measured at AQS monitors. New research summarized in this assessment reduces several of the other uncertainties noted in the 2000 CO AQCD (U.S. EPA, 2000, 000907) and demonstrates the lack of influence of nonambient exposure on effect estimates in epidemiologic studies, the consistency of epidemiologic study results, their robustness in copollutant models, and the coherence of ischemia-related outcomes with evidence from controlled human exposure studies. This consistent and coherent evidence from epidemiologic and human clinical studies, along with biological plausibility provided by the role of CO in limiting O_2 availability, is sufficient to conclude that a causal relationship is likely to exist between relevant short-term CO exposures and cardiovascular morbidity.

References

Allred EN; Bleecker ER; Chaitman BR; Dahms TE; Gottlieb SO; Hackney JD; Hayes D; Pagano M; Selvester RH; Walden SM; Warren J (1989). Acute effects of carbon monoxide exposure on individuals with coronary artery disease. Health Effects Institute. Boston, MA. 012697

Allred EN; Bleecker ER; Chaitman BR; Dahms TE; Gottlieb SO; Hackney JD; Pagano M; Selvester RH; Walden SM; Warren J (1989). Short-term effects of carbon monoxide exposure on the exercise performance of subjects with coronary artery disease. N Engl J Med, 321: 1426-1432. 013018

Allred EN; Bleecker ER; Chaitman BR; Dahms TE; Gottlieb SO; Hackney JD; Pagano M; Selvester RH; Walden SM; Warren J (1991). Effects of carbon monoxide on myocardial ischemia. Environ Health Perspect, 91: 89-132. 011871

Anderson EW; Andelman RJ; Strauch JM; Fortuin NJ; Knelson JH (1973). Effect of low-level carbon monoxide exposure on onset and duration of angina pectoris: a study in ten patients with ischemic heart disease. Ann Intern Med, 79: 46-50. 023134

Bell ML; Peng RD; Dominici F; Samet JM (2009). Emergency admissions for cardiovascular disease and ambient levels of carbon monoxide: Results for 126 U.S. urban counties, 1999-2005. Circulation, 120: 949-955. 193780

Forster P; Ramaswamy V; Artaxo P; Berntsen T; Betts R; Fahey DW; Haywood J; Lean J; Lowe DC; Myhre G; Nganga J; Prinn R; Raga G; Schultz M; Van Dorland R (2007). Changes in atmospheric constituents and in radiative forcing, Chapter 2. In Solomon S, Qin D; Manning M; Chen Z; Marquis M; Averyt KB; Tignor M; Miller HL (Ed.),IPCC Fourth Assessment Report (AR4): Climate Change 2007: Working Group I Report: The Physical Science Basis. (pp. 129-234). Cambridge, U.K. and New York, NY: Intergovernmental Panel on Climate Change; Cambridge University Press. 092936

Fung KY; Luginaah I; Gorey KM; Webster G (2005). Air pollution and daily hospital admissions for cardiovascular diseases in Windsor, Ontario. Can J Public Health, 96: 29-33. 074322

IPCC (2001). Climate Change 2001: The Scientific Basis. Contribution of Working Group I to the Third Assessment Report (TAR) of the Intergovernmental Panel on Climate Change [Houghton, J.T.,Y. Ding, D.J. Griggs, M. Noguer, P.J. van der Linden, X. Dai, K. Maskell, and C.A. Johnson (eds.)]. Cambridge, UK and New York, NY, USA: Intergovernmental Panel on Climate Change, Cambridge University Press. 156587

IPCC (2007). Climate Change 2007: The Physical Science Basis. Contribution of Working Group I to the Fourth Assessment Report (AR4) of the Intergovernmental Panel on Climate Change . Cambridge, UK and New York, NY: Intergovernmental Panel on Climate Change, Cambridge University Press. 092765

Jerrett M; Burnett RT; Willis A; Krewski D; Goldberg MS; DeLuca P; Finkelstein N (2003). Spatial analysis of the air pollution-mortality relationship in the context of ecologic confounders. J Toxicol Environ Health A Curr Iss, 66: 1735-1777. 087380

Koken PJM; Piver WT; Ye F; Elixhauser A; Olsen LM; Portier CJ (2003). Temperature, air pollution, and hospitalization for cardiovascular diseases among elderly people in Denver. Environ Health Perspect, 111: 1312-1317. 049466

Linn WS; Szlachcic Y; Gong H Jr; Kinney PL; Berhane KT (2000). Air pollution and daily hospital admissions in metropolitan Los Angeles. Environ Health Perspect, 108: 427-434. 002839

Mann JK; Tager IB; Lurmann F; Segal M; Quesenberry CP Jr; Lugg MM; Shan J; Van den Eeden SK (2002). Air pollution and hospital admissions for ischemic heart disease in persons with congestive heart failure or arrhythmia. Environ Health Perspect, 110: 1247-1252. 036723

Metzger KB; Tolbert PE; Klein M; Peel JL; Flanders WD; Todd KH; Mulholland JA; Ryan PB; Frumkin H (2004). Ambient air pollution and cardiovascular emergency department visits. Epidemiology, 15: 46-56. 044222

Peel JL; Metzger KB; Klein M; Flanders WD; Mulholland JA; Tolbert PE (2007). Ambient air pollution and cardiovascular emergency department visits in potentially sensitive groups. Am J Epidemiol, 165: 625-633. 090442

Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at http://epa.gov/hero. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISAs) and the Integrated Risk Information System (IRIS).

Samoli E; Touloumi G; Schwartz J; Anderson HR; Schindler C; Forsberg B; Vigotti MA; Vonk J; Kosnik M; Skorkovsky J; Katsouyanni K (2007). Short-term effects of carbon monoxide on mortality: An analysis within the APHEA project. Environ Health Perspect, 115: 1578-1583. 098420

Sarnat SE; Klein M; Sarnat JA; Flanders WD; Waller LA; Mulholland JA; Russell AG; Tolbert PE (2009). An examination of exposure measurement error from air pollutant spatial variability in time-series studies. J Expo Sci Environ Epidemiol, In Press: 1-12. 180084

Sheppard L; Slaughter JC; Schildcrout J; Liu L-JS; Lumley T (2005). Exposure and measurement contributions to estimates of acute air pollution effects. J Expo Sci Environ Epidemiol, 15: 366-376. 079176

Sinha A; Toumi R (1996). A comparison of climate forcings due to chloroflurocarbons and carbon monoxide. Geophys Res Lett, 23: 65-68. 193747

Symons JM; Wang L; Guallar E; Howell E; Dominici F; Schwab M; Ange BA; Samet J; Ondov J; Harrison D; Geyh A (2006). A case-crossover study of fine particulate matter air pollution and onset of congestive heart failure symptom exacerbation leading to hospitalization. Am J Epidemiol, 164: 421-433. 091258

Szyszkowicz M (2007). Air pollution and emergency department visits for ischemic heart disease in Montreal, Canada. Int J Occup Med Environ Health, 20: 167-173. 193793

Tolbert PE; Klein M; Peel JL; Sarnat SE; Sarnat JA (2007). Multipollutant modeling issues in a study of ambient air quality and emergency department visits in Atlanta. J Expo Sci Environ Epidemiol, 17: S29-S35. 090316

U.S. EPA (1991). Air quality criteria for carbon monoxide. U.S. Environmental Protection Agency. Research Triangle Park, NC. EPA/600/8-90/045F. http://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=3000554R.txt. 017643

U.S. EPA (2000). Air quality criteria for carbon monoxide. National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency. Research Triangle Park, NC. EPA 600/P-99/001F. 000907

Villeneuve PJ; Chen L; Stieb D; Rowe BH (2006). Associations between outdoor air pollution and emergency department visits for stroke in Edmonton, Canada. Eur J Epidemiol, 21: 689-700. 090191

Wellenius GA; Bateson TF; Mittleman MA; Schwartz J (2005). Particulate air pollution and the rate of hospitalization for congestive heart failure among medicare beneficiaries in Pittsburgh, Pennsylvania. Am J Epidemiol, 161: 1030-1036. 087483

Wellenius GA; Schwartz J; Mittleman MA (2005). Air pollution and hospital admissions for ischemic and hemorrhagic stroke among medicare beneficiaries. Stroke, 36: 2549-2553. 088685

Zeger SL; Thomas D; Dominici F; Samet JM; Schwartz J; Dockery D; Cohen A (2000). Exposure measurement error in time-series studies of air pollution: concepts and consequences. Environ Health Perspect, 108: 419-426. 001949

Chapter 3. Source to Exposure

3.1. Introduction

This chapter reviews concepts and findings in atmospheric sciences and exposure assessment that provide a foundation for the detailed presentation of evidence of CO-related health effects in subsequent chapters and for a causality finding regarding climate forcing effects of CO. Section 3.2 provides an overview of the primary and secondary sources of CO as well as the atmospheric chemistry involved in the production and removal of CO by oxidation processes. Section 3.3 provides a description of climate forcing caused directly and indirectly by CO. Descriptions of CO measurement methods, monitor siting requirements, and monitor locations are presented in Section 3.4. Ambient CO concentrations and their spatial and temporal variability are characterized in Section 3.5. The background concentrations of CO useful for risk and policy assessments informing decisions about the NAAQS, referred to as policy-relevant background (PRB) concentrations, are also presented in Section 3.5. Factors related to human exposure to ambient CO, and their implications for epidemiologic studies, are discussed in Section 3.6. Finally, a summary and conclusions of the chapter are presented in Section 3.7.

3.2. CO Sources, Emissions, and Chemistry

3.2.1. Direct CO Emissions

CO is formed primarily by incomplete combustion of carbon-containing fuels and photochemical reactions in the atmosphere. In general, any increase in fuel O_2 content, burn temperature, or mixing time in the combustion zone will tend to decrease production of CO relative to CO_2. CO emissions from large fossil-fueled power plants are typically very low since the boilers at these plants are tuned for highly efficient combustion with the lowest possible fuel consumption. Additionally, by allowing time for the furnace flue gases to mix with air and be oxidized by OH to CO_2 in the hot gas stream before the OH concentrations drop as the flue gases cool, the CO-to-CO_2 ratio in these emissions is shifted toward CO_2.

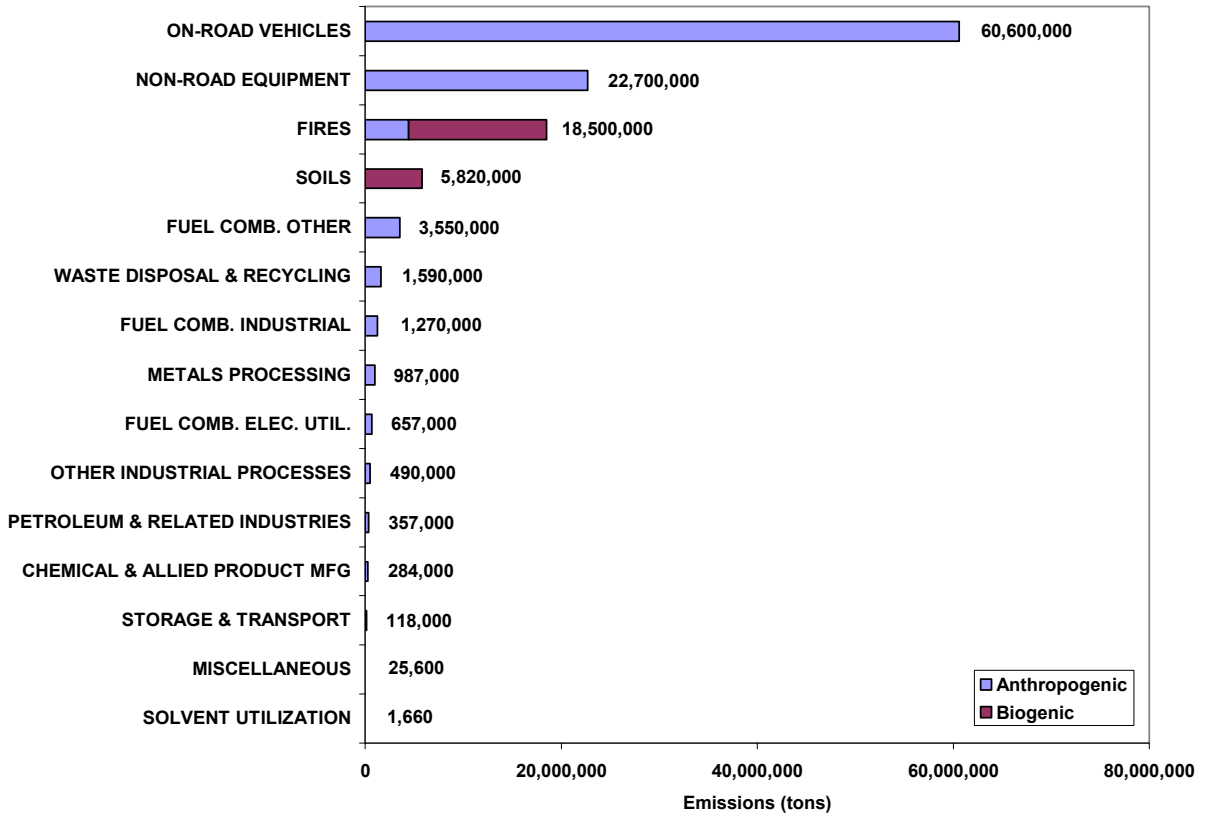
Figure 3-1 lists CO emissions totals in tons segregated by individual source sectors in the U.S. for 2002, which is the most recent publicly available CO emissions data meeting EPA's data quality assurance objectives. In the U.S., direct CO emissions data are tracked in the National Emissions Inventory (U.S. EPA, 2006, 157070), a composite of data from various sources including industries and state, tribal, and local air agencies, and from the Biogenic Emissions Inventory System (BEIS). NEI data are collected for all states, the District of Columbia, the U.S. territories of Puerto Rico and Virgin Islands, and some of the territories of federally recognized American Indian nations. Different data sources use different data collection methods, most of which are based on empirical estimates and engineering calculations rather than measurements. Most fuel combustion and industrial sources, for example, estimate their CO emissions using EPA-approved emission factors, as do on-road and non-road mobile source emitters where models (MOBILE6, MOVES, NONROAD) are available to calculate inventories (U.S. EPA, 2006, 157070). The NEI includes fires of anthropogenic and natural origin. Anthropogenic fires include structural fires, agricultural fires, prescribed burning, and slash burning; forest wildfires are considered to be of natural origin. Estimates of direct CO emission from

Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at http://epa.gov/hero. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISAs) and the Integrated Risk Information System (IRIS).

soil are calculated by the EPA using the BEIS model. Although these estimates are generated using well-established approaches, uncertainties are inherent in the emission factors and models used to represent sources for which emissions have not been directly measured. These uncertainties vary by source category, season, and region. Discussion of uncertainties is provided in subsequent paragraphs related to mobile sources, the largest source category.

Nationally, on-road mobile sources in the NEI constituted more than half of total CO emissions in 2002, or ~60.6 MT of ~116.8 MT total, which includes anthropogenic and biogenic emissions reported in the NEI and the BEIS (http://www.epa.gov/ttnchie1/emch/biogenic). High concentrations of CO can often occur in areas of heavy traffic. In metropolitan areas in the U.S., for example, as much as 75% of all CO emissions came from on-road vehicle exhaust in the 2002 NEI (U.S. EPA, 2006, 157070). When the emissions from incomplete combustion of fuels powering non-road mobile sources were included, all mobile sources accounted for ~80% of total CO emissions in the U.S. in 2002 (Figure 3-1).

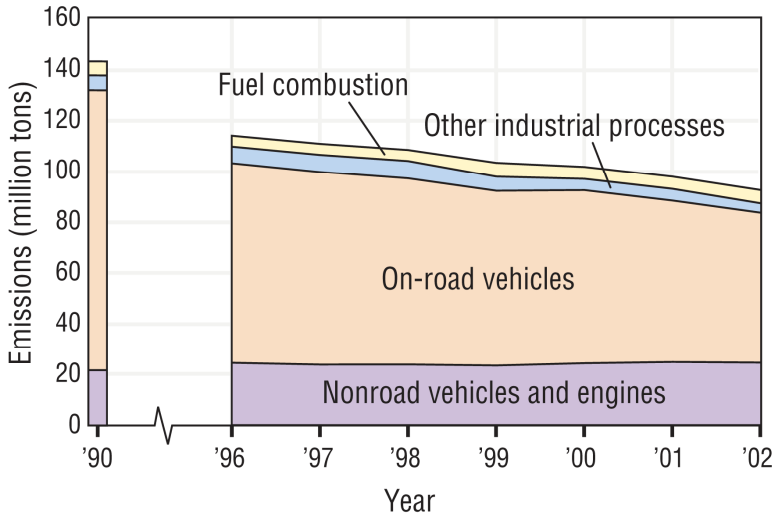
CO emissions from internal combustion engines vary substantially with ambient temperature and operating conditions. Substantial light-duty gasoline vehicle CO emissions occur during the cold start before the catalyst is warmed up. Most emission tests such as the Federal Test Procedure (FTP) which includes a cold start portion and is used to certify that vehicles meet EPA emission standards, are conducted at about 75ºF. Lower ambient temperatures result in increased CO emissions because spark ignition engines are required to run richer air:fuel ratios for longer periods of time, and also because the time before the catalyst is warmed up increases compared to the time for catalyst warm-up occurring at 75ºF (U.S. EPA, 2006, 199897). Thus, in addition to the vehicle CO emissions standards EPA implemented starting with the 1968 model year, EPA has also implemented a cold temperature CO emission standard for light-duty gasoline vehicles and trucks at 20ºF that phased in for 40% of the new fleet in the 1994 model year, 80% for the 1995 model year, and 100% with the 1996 and succeeding model years. The emission standard of 10 g/mile results in a reduction of about 20-30% in CO emissions at 20º F (57 FR 3188-31923 July 17, 1992). Increased vehicle CO emissions can also occur under conditions such as high rates of acceleration, rapid speed fluctuations, heavy-vehicle load demands (such as occur while pulling a trailer or going up a steep hill), and use of air-conditioning. Such driving conditions were not originally fully reflected in the FTP. EPA has issued a Supplemental Federal Test Procedure (SFTP) to control excess CO emissions under these conditions. These regulations were phased in for the 1998-2000 model years (61 FR 54852-54906 October 22, 1996). Moreover, the gasoline-powered spark ignition engines that predominate in light-duty on-road vehicles have higher uncontrolled CO emission rates than other combustion sources because they typically operate closer to the stoichiometric air-to-fuel ratio, have relatively short residence times at peak combustion temperatures, and have very rapid cooling of cylinder exhaust gases. By contrast, the diesel-powered engines that predominate in heavy-duty on-road vehicles and in off-road and non-road fixed combustion sources have much lower engine-out CO emissions than do the spark-ignition engines because the diesels typically operate at very high air-to-fuel ratios, which promote mixing oxygen and fuel, thus improving carbon burn.



Source: U.S. EPA (2006, 157070)

Figure 3-1. CO emissions (tons) in the U.S. by source sector in 2002 from the NEI and the BEIS. The "fires" category has been extracted from Tier 3 miscellaneous categories of the NEI, and biogenic fires are those attributed to forest wildfires. The "soils" category comprises the BEIS data. The "roadway vehicles" and "non-road vehicles" categories have been renamed here for clarity.

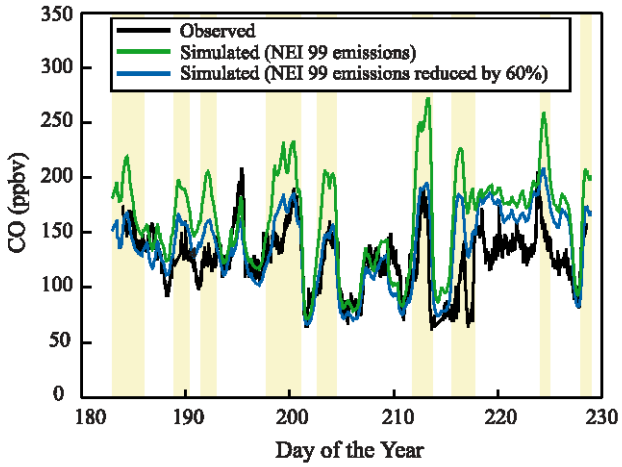
Figure 3-2 shows present and historical CO emissions from the traditionally inventoried anthropogenic source categories: (1) fuel combustion, which includes emissions from coal-, gas-, and oil-fired power plants and industrial, commercial, and institutional sources, as well as residential heaters (e.g., wood-burning stoves) and boilers; (2) industrial processes, which include chemical production, petroleum refining, metals production, and industrial processes other than fuel combustion; (3) on-road vehicles, which include cars, trucks, buses, and motorcycles; and (4) non-road vehicles and engines, such as farm and construction equipment, boats, ships, snowmobiles, aircraft, locomotive, and the two-stroke engines found in lawnmowers, chainsaws, and other small gasoline-powered equipment. Using these NEI data, trends in the national CO emissions can be computed and compared over time. So, for example, the national-scale estimated anthropogenic CO emissions decreased 35% between 1990 and 2002. The trend in Figure 3-2 demonstrates that controls in the on-road vehicle sector have produced nearly all the national-level CO reductions since 1990. (Data are presented here for 1990 and from 1996-2002 because only 1990 data have been updated to be comparable to the more recent inventories made since 1996.)



Source: U.S. EPA (2008, 157076)

Figure 3-2. Trends in anthropogenic CO emissions (MT) in the U.S. by source category for 1990 and 1996-2002.

With the exception of this downward trend resulting from emissions controls, anthropogenic CO emissions demonstrate less interannual variability than biogenic emissions (Bergamaschi et al., 2000, 192377). Several recent reports using both ambient concentrations and fuel-based emissions estimates have explored this annual-to-decadal emissions decrease in anthropogenic CO in finer detail; they include Harley et al. (2001, 193922; 2005, 088154), Parrish et al. (2002, 052472), Parrish (2006, 090352), Pollack et al. (2004, 184461), and Mobley et al. (2005, 194008). The consistent conclusion from those investigations has been that annual average U.S. on-road vehicle CO emissions have decreased at a rate of ~5% per year since the early 1990s. This can be seen from Figure 3-2 as well. Additional analyses by Harley et al. (2005, 088154) and Parrish (2006, 090352) were also consistent with the suggestion in Pollack et al. (2004, 184461) that the EPA MOBILE6 vehicle emissions model (http://www.epa.gov/otaq/m6.htm) now overestimates vehicle CO emissions by a factor of ~2. Field measurements by Bishop and Stedman (2008, 194670) were in accord with Parrish's (2006, 090352) findings that the measured trends of CO and NO_X concentrations from mobile sources in the U.S. indicated that modeled CO emission estimates were substantially too high. Hudman et al. (2008, 191253) found that the NEI overestimated anthropogenic CO emissions by 60% for the eastern U.S. during the period July 1-August 15, 2004 using aircraft observations of CO from the International Consortium for Atmospheric Research on Transport and Transformation (ICARTT) campaign (Fehsenfeld et al., 2006, 190531) and results from a tropospheric chemistry model (GEOS-Chem)(Figure 3-3).



Source: Reprinted with Permission of the Amercian Geophysical Union from Hudman et al. (2008, 191253)

Figure 3-3. Surface air CO concentrations at Chebogue Point during the ICARTT campaign. Observations (black) are compared to model results using the 1999 NEI anthropogenic emissions (green) and with these CO emissions reduced by 60% (blue). Yellow bands are periods of U.S. outflow diagnosed by Millet et al. (2006, 195106). Overestimation near day 200 is due to model misplacement of a large Alaskan/Canadian biomass burning plume.

Improvements in emissions technologies not correctly represented in MOBILE emissions models have been suggested as one cause for this discrepancy. For example, Pokharel et al. (2002, 052473; 2003, 053740) demonstrated substantial decrements in the CO fraction of tailpipe exhaust in several U.S. cities, and Burgard et al. (2006, 193222) documented improvements in emissions from heavy-duty on-road diesel engines. The Motor Vehicle Emission Simulator (MOVES) model has been designed to address some of the largest errors in the MOBILE model. It was released in final form in December 2009 (http://www.epa.gov/otaq/models/moves/index.htm).

Estimates of non-anthropogenic CO emissions are made using the BEIS model with data from the Biogenic Emissions Landcover Database (BELD) and annual meteorological data. National biogenic emissions, excluding fires, were estimated to contribute 5%, or ~5.8 MT, of total CO emissions from all sources in 2002. Biogenic wildfires in 2002 added another 12%, or ~14.1 MT, to the national CO emissions total and were responsible for 76.1% of all CO emissions estimates from fires. This is shown in Figure 3-1 using the NEI and BEIS data. Geogenic emissions of CO, also included in this inventory, include volcanic gases released from molten rock in the Earth's mantle. Mixing ratios of dissolved CO in this rock vary in a range from 0.01 to 2% as a function of the rock stratum surrounding the volcano and other geologic conditions. This high variability and infrequent though often violent release mean geogenic CO measurements are very difficult to make with precision, though on non-local scales the magnitude of their contribution is small relative to anthropogenic sources. Photodecomposition of organic matter in oceans, rivers, lakes, and other surface waters, and from soil surfaces also releases CO (Goldstein and Galbally, 2007, 193247). However, soils can act as a CO source or a sink depending on soil moisture, UV flux reaching the soil surface, and soil temperature (Conrad and Seiler, 1985, 029520). Soil uptake of CO is driven by anaerobic bacteria (Inman et al., 1971, 010972). Emissions of CO from soils appear to occur by abiotic processes, such as thermodecomposition or photodecomposition of organic matter. In general, warm and moist conditions found in most soils favor CO uptake, whereas hot and dry conditions found in deserts and some savannas favor the release of CO (King, 1999, 002828).

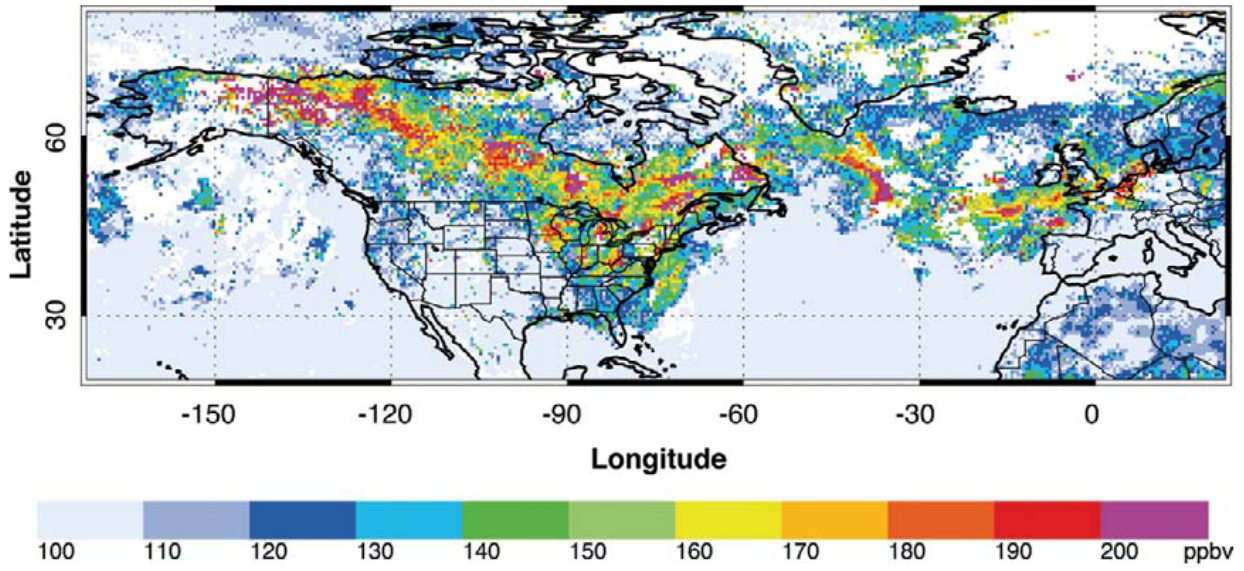
Biomass burning consists of wildfires and the intentional burning of vegetation to clear new land for agriculture and population resettlement; to control the growth of unwanted plants on pasture land; to manage forest resources with prescribed burning; to dispose of agricultural and domestic waste; and as fuel for cooking, heating, and water sterilization. Globally, most wildfires may be ignited directly as the result of human activities, leaving only 10-30% initiated by lightning

(Andreae, 1991, 078147). However, because fire management practices suppress natural wildfires, the buildup of fire fuels increases the susceptibility of forests to more severe but less frequent fires in the future. Thus there is considerable uncertainty in attributing the fraction of wildfire emissions to human activities because the emissions from naturally occurring fires that would have been present in the absence of fire suppression practices are not known.

Biomass burning also exhibits strong seasonality and interannual variability (van der Werf et al., 2006, 157084), with most biomass burned during the local dry season. This is true for both prescribed burns and wildfire. The unusually warm and dry weather in central Alaska and western Yukon in the summer of 2004, for example, contributed to the burning of 11 million acres there. These fires, the largest on record for this region, produced CO emissions easily tracked by the Measurement of Pollution in the Troposphere (MOPITT) instrument on NASA's Terra satellite (Figure 3-4). The high CO concentration measured by MOPITT coincided with the surface location of fires tracked using aerosol plumes identified by the Moderate Resolution Imaging Spectroradiometer (MODIS) also on Terra. Subsequent modeling by Pfister et al. (2005, 093009) showed that the CO contribution from these fires in July 2004 was 33.1 (± 5.5) MT that summer, or in the range of the total U.S. anthropogenic CO emissions during the same time. The smoldering phase of combustion yields higher CO emissions than the flaming phase. Using controlled combustion chamber experiments, Lobert et al. (1991, 029473) found that with a wide variety of vegetation types, on average, 84% of the CO from biomass fires was produced during the smoldering phase and 16% during the flaming phase of combustion.

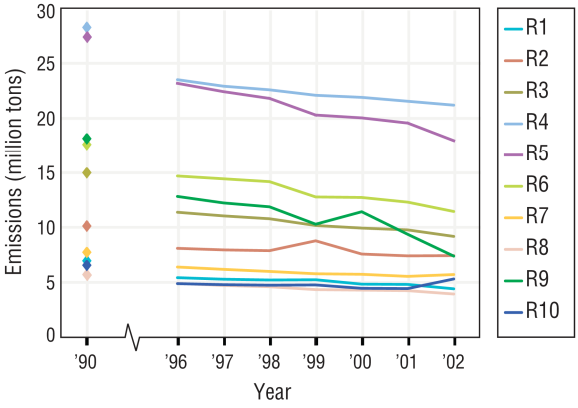
CO emissions data for EPA's 10 administrative Regions in the U.S., depicted in Figure 3-5, show a more nuanced view of the national concentrations and trends described above. Net anthropogenic CO emissions were estimated to have declined in all EPA Regions between 1990 and 2002, with the largest decrease (10.8 MT) occurring in Region 9 and the smallest (1.3 MT) in Region 10.

At state and local levels, CO emissions from on-road mobile sources or from fires can dominate in different locations across the U.S. Figure 3-6 illustrates this variability with CO state-level emissions totals and selected county totals in 2002 for Colorado (Annex A includes analogous data for Alaska, Utah, Massachusetts, Georgia, California, and Alabama). In Colorado, emissions from fires and on-road vehicles were nearly equal: ~0.9 MT from fires and ~1.1 MT from on-road vehicles. Emissions sources varied strongly across counties, however, with urban Denver County dominated by on-road vehicle emissions at 71% and rural Garfield County dominated by fire emissions at 67%.



Source: Reprinted with Permission of the American Meteorological Society from Fishman et al. (2008, 193927)

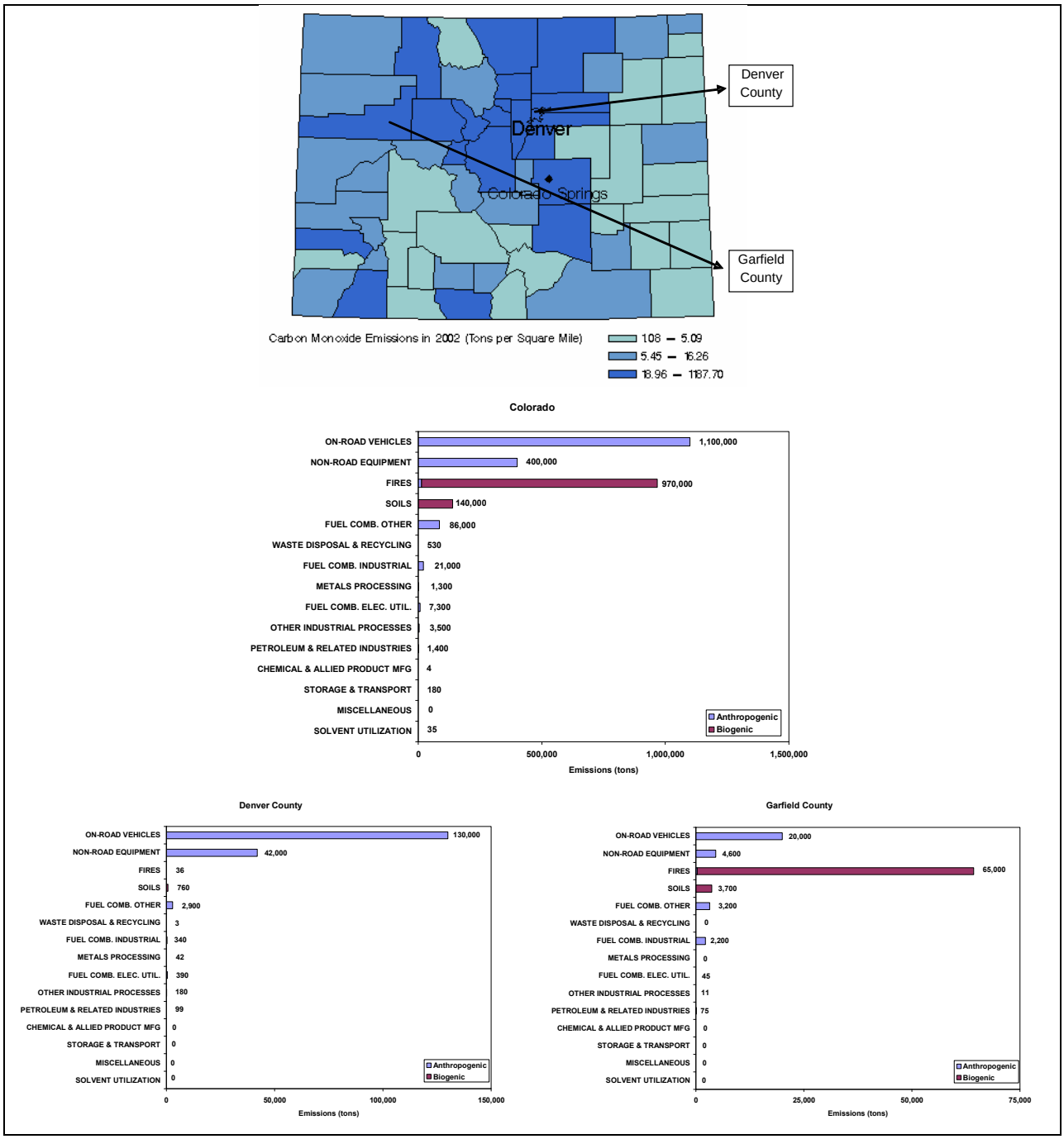
Figure 3-4. CO concentrations centered at ~3,000 m above sea level measured by the MOPITT sensor on the Terra satellite for the period July 15-23, 2004, during intense wildfires in Alaska and the Yukon.



Data are presented for 1990 and 1996-2002, as datasets from these inventory years are all fully up to date. Data are available for inventory years 1991-1995, but these data have not been updated to allow comparison with data from 1990 and 1996-2002.

Source: U.S. EPA (2008, 157076)

Figure 3-5. Trends in subnational CO emissions in the 10 U.S. EPA Regions for 1990 and 1996-2002.



Source:: U.S. EPA (2006, 157070)

Figure 3-6. CO emissions density map and distributions for the state of Colorado and for selected counties in Colorado in 2002, from the NEI and the BEIS. The "fires" category has been extracted from Tier 3 miscellaneous categories of the NEI, and biogenic fires are those attributed to wildfires. The "soils" category comprises the BEIS data. The "roadway vehicles" and "non-road vehicles" categories have been renamed here for clarity.

3.2.2. Secondary CO Emissions and Associated Chemistry

Oxidation of anthropogenic and biogenic VOCs constitute important secondary sources of CO. For example, Hudman et al. (2008, 191253) determined that oxidation of isoprene and other biogenic VOCs contributed 9.1 MT of atmospheric CO (with isoprenes contributing 7.1 MT), and oxidation of anthropogenic VOCs contributed another 2.0 MT of CO emissions during the period July 1-August 15, 2004, for the eastern U.S. In contrast, direct anthropogenic CO emissions were estimated to be 5.1 MT for this time period and location. Hence, secondary biogenic formation was found to be a more important source of CO emissions than direct anthropogenic activities for the study period. Hudman et al. (2008, 191253) noted that biogenic CO emissions were highest in the southeastern U.S., where isoprene emissions are also greatest. These estimates were obtained using aircraft measurements from the ICARTT campaign (Fehsenfeld et al., 2006, 190531) and estimates from the GEOS-Chem model (Bey et al., 2001, 051218), configured as described by Hudman et al.(2007, 089474).

Secondary CO production occurs by photooxidation of methane (CH_4) and other VOCs, including nonmethane hydrocarbons (NMHCs) in the atmosphere and organic molecules in surface waters and soils. CH_4 oxidation is summarized in this reaction sequence:

$$CH_4 + OH \rightarrow CH_3 + H_2O$$
$$CH_3 + O_2\ (+ M) \rightarrow CH_3O_2\ (+ M)$$
$$CH_3O_2 + NO \rightarrow CH_3O + NO_2$$
$$CH_3O_2 + HO_2 \rightarrow CH_3OOH + O_2$$
$$CH_3O + O_2 \rightarrow CH_2O + HO_2$$
$$CH_2O + h\nu \rightarrow H_2 + CO$$
$$or \quad CH_2O + h\nu \rightarrow HCO + H$$
$$or \quad CH_2O + OH \rightarrow HCO + H_2O$$
$$HCO + O_2 \rightarrow CO + HO_2$$

Reaction 3-1

where M is a reaction mediator that is neither created nor destroyed and stabilizes the reaction product.

Photolysis of formaldehyde (CH_2O) proceeds by two pathways. The first produces molecular hydrogen (H_2) and CO with a reaction yield of 55% in conditions of clear skies and low zenith angles; the second yields a hydrogen radical (H) and the formyl radical (HCO). HCO then reacts with O_2 to form hydroperoxy radical (HO_2; OH and HO_2 together are termed HO_X) and CO. Reaction of methyl peroxy radical (CH_3O_2) with HO_2 radicals to form methyl hydroperoxide (CH_3OOH) is also operative, especially in low oxides of nitrogen ($NO+NO_2=NO_X$) conditions. Heterogeneous removal of the partially water-soluble intermediate products, such as CH_3OOH and CH_2O, will decrease CO yields from CH_4 oxidation.

While oxidation of CH_2O nearly always produces CO and some small quantities of formic acid (CH_2O_2) in the reaction of CH_2O with HO_2 (not shown here), oxidation of acetaldehyde (CH_3CHO) does not always yield two CO molecules. Reaction of CH_3CHO with OH can yield acetyl radicals (CH_3CO) which then will participate with O_2 in a termolecular recombination reaction to form peroxyacyl radicals, which then can react with nitric oxide (NO) to form CH_3 and CO_2; or the peroxyacyl radicals can react with NO_2 to form peroxyacetyl nitrate (PAN), $CH_3CO_3NO_2$. In this way, one carbon atom is oxidized directly to CO_2 without passing through CO. The yield of CO from these pathways depends on the OH concentration and the photolysis rate of CH_3CHO, as well as on the abundance of NO, since peroxyacyl radicals also will react with other odd hydrogen radicals like HO_2.

Estimating the CO yield from oxidation of hydrocarbons (HCs) larger than CH_4 requires computing the yields of CH_2O, CH_3CHO, CH_3CO, and analogous radicals from oxidation of the parent molecules. Moreover, the extent of heterogeneous removal of soluble intermediate products also affects oxidation of more complex HCs. However, the detailed gas-phase kinetics for many HCs

with more than a few carbons is still unknown. This is especially the case for several important classes of VOCs, including the aromatics, biogenic HCs including isoprene, and their intermediate oxidation products like epoxides, nitrates, and carbonyls. Mass-balance analyses performed on irradiated smog chamber mixtures of aromatic HCs indicate that only about one-half of the carbon is in the form of compounds that can be identified. In addition, reactions like the oxidation of terpenes that produce condensable products are also significant because these reactions produce secondary organic aerosols, thereby reducing the potential yield of CO. The CO yield from oxidation of CH_4, for example, is ~0.9 on a per carbon basis (Kanakidou and Crutzen, 1999, 011760). Yields from other compounds range from <0.1 for anthropogenic alkanes (Altshuller, 1991, 192375) to ~0.9 for ethane; yields from other compounds are given in Table 3-1 taken from Kanakidou and Crutzen (1999, 011760).

Table 3-1. Literature values for CO yields from hydrocarbons in per carbon units, except as noted. Specific hydrocarbons are noted in parentheses.

Reference	CO Yields
Zimmerman et al. (1978, 010758)	0.3 (hydrocarbons)
Brewer et al. (1984, 194402)	0.22-0.27 (isoprene)
Hanst et al. (1980, 011988)	According to chamber experiments, CO and CO_2 yield:
	~0.85 (ethylene)
	~0.90 (ethane)
	~0.80 (propane)
	~0.58 (n-butane)
	~0.73 (isoprene)
	~0.30 (alpha-pinene)
Crutzen (1987, 002848)	0.9 of CH_4
Kanakidou et al. (1991, 029701)	0.39 (C_2H_6 and C_3H_8)
Jacob and Wofsy (1990, 029668)	@ low NO_X: 0.2 (isoprene)
	@ high NO_X: 0.6 (isoprene)
Crutzen et al. (1985, 194403)	=0.8 (isoprene + OH)
Kirchhoff and Marinho (1990, 194406)	Isoprene oxidation may form 10 ppbv CO/d over the Amazon (3 km deep boundary layer)
Altshuller (1991, 192375)	Conversion factors of 19 (C_2-C_6) anthropogenic alkenes vary between 0.010 and 0.075
Manning et al. (1997, 194401)	CH_4 in the SH: 0.7
Kanakidou and Crutzen (1999, 011760)	Annual tropospheric mean conversion factors:
	CH_4: 0.9
	Isoprene: 0.4
	Other nonmethane hydrocarbons: 0.7

Source: Adapted with Permission of Elsevier Ltd. from Kanakidou and Crutzen (1999, 011760)

The major pathway for removal of CO from the atmosphere is reaction with OH to produce CO_2 and H radicals that rapidly combine with O_2 to form HO_2 radicals, with a rate constant at 1 atm in air of ~2.4×10^{-13} cm^3/molecule/s (Finlayson-Pitts and Pitts, 2000, 055565). The mean tropospheric photochemical lifetime (τ) of CO in the northern hemisphere is ~57 days (Khalil and Rasmussen, 1990, 012352; Thompson and Cicerone, 1986, 019374). Owing to variation in atmospheric water vapor, OH concentration, and insolation, shorter τ are found nearer the tropics and longer ones at higher latitudes. During winter at high latitudes, CO has nearly no photochemical reactivity on urban and regional scales. Because the CO τ is shorter than the ~1 yr characteristic time scale for mixing between the hemispheres and because northern hemisphere CO emissions are higher due to anthropogenic activity (Khalil and Rasmussen, 1990, 012443), a large gradient in concentrations

exists between the hemispheres (Edwards et al., 2004, 199889). In addition, the CO τ at high latitudes is long enough to result in much smaller gradients between 30° latitude and the pole of either hemisphere. The typical residence time of CO in urban areas when assuming a diel-average OH concentration of 3×10^6/cm^3 in urban areas is ~16 days, so CO will not typically be destroyed in urban areas where it is emitted and will likely be mixed on continental and larger scales. OH concentrations are orders of magnitude lower in indoor environments, and so CO will generally not be affected by indoor air reactions.

3.3. CO Climate Forcing Effects

Recent data do not alter the current well-established understanding of the role of urban and regional CO in continental and global-scale chemistry outlined in the 2000 CO AQCD (U.S. EPA, 2000, 000907) and subsequently confirmed in the recent global assessments of climate change by the Intergovernmental Panel on Climate Change (IPCC) (2001, 156587; 2007, 092765). CO is a weak direct contributor to greenhouse warming because its fundamental absorption band near 4.63 μm is far from the spectral maximum of Earth's longwave radiation at ~10 μm. Sinha and Toumi (1996, 193747) estimated the direct RF of CO computed for all-sky conditions at the tropopause, which is the IPCC's preferred form for the calculation (Forster et al., 2007, 092936), to be 0.024 W/m^2 based on an assumed change in CO mean global concentration from 25 to 100 ppb since preindustrial times. The direct RF value similarly projected by Sinha and Toumi (1996, 193747) if the mean global background concentration were to increase from 25 to 290 ppb was 0.057 W/m^2.

However, because reaction with CO is the major sink for OH on a global scale, increased concentrations of CO can lead to increased concentrations of other trace gases whose loss processes also involve OH chemistry. Some of those trace gases, CH_4 and O_3 for example, absorb infrared radiation from the Earth's surface and contribute to the greenhouse effect directly. Others, including hydrochlorofluorocarbons (HCFCs), methyl chloride, and methyl bromide, can deplete stratospheric O_3, increasing the surface-incident UV flux.

This indirect effect of CO on stratospheric O_3 concentrations is opposite in sign to the effect of CO on O_3 in the troposphere where CO reacts in a manner similar to other VOCs in the presence of NO_X and UV to create O_3; see the detailed description of O_3 formation from VOCs and NO_X in the 2006 O_3 ISA (U.S. EPA, 2006, 088089). Because CO's chemical lifetime is longer than those of the VOCs most important for O_3 formation on urban and regional scales and because CO oxidation has one-to-one stoichiometry (whereby one molecule of CO converts only one molecule of NO to NO_2), CO has a significantly lower O_3 forming potential than other VOCs in the troposphere. Carter (1998, 192380) computed a maximum incremental reactivity for CO of 0.06 g O_3 for 1 g CO, as compared to reactivities of total on-road vehicle exhaust emissions typically in the range of 3 to 4 g O_3 per g VOC. However, because the total mass of CO emissions is substantially greater than those of the other VOCs with higher carbon numbers and faster reactivities, CO can contribute significantly to O_3 formation even though its photochemical processing is slow. Using data from instrumented models, including that of Jeffries (1995, 003055), the NRC (1999, 010614) estimated, for example, that CO can contribute 15-25% of the total O_3 forming potential of gasoline exhaust emissions, although this estimate shows strong regionality. The contribution of CO to urban and regional O_3 concentration is often <10% owing to its very slow reactivity on these scales and to locally variable radical concentration ratios.

Emissions of CO and the other O_3 precursors, nonmethane VOCs (NMVOCs) and NO_X, affect the oxidizing capacity of the atmosphere largely by perturbing HO_X concentrations. From a climate perspective, this HO_X perturbation chiefly affects the CH_4 τ and production of O_3 in the troposphere. Changes in the concentration of O_3 and hence in its RF occur mainly in the time of a few months. However, Prather (1996, 193195) showed that changes in CH_4 concentration and its RF extend to the "primary mode" timescale of troposphere chemistry of about 14 yr (Derwent et al., 2001, 047912; Wild et al., 2001, 193196). The primary mode timescale of CH_4 is in part determined by the positive feedbacks in the CH_4-OH-CO system in which even low concentration additions of CH_4 produce additional CO through oxidation by OH. That additional CO then further decreases atmospheric OH concentrations when OH oxidizes it to CO_2. The resulting decreased OH concentration then further increases the CH_4 τ (Daniel and Solomon, 1998, 193235; Isaksen and Hov, 1987, 019490). Atmospheric CH_4 concentrations since 1750 have increased by more than a factor of 2, giving an RF

of ~0.6 W/m^2 (Forster et al., 2007, 092936). Roughly 25% of the global mean tropospheric CO is produced by CH_4 oxidation (Wuebbles and Hayhoe, 2002, 044159). Using a 2-D global model on a coarse grid, Wang and Prinn (1999, 011758) showed that increasing CO and CH_4 concentrations leading to decreased OH concentrations can extend the CO τ as well as the CH_4 τ. Wang and Prinn (1999, 011758) varied the CO emissions and other model inputs and parameters in a matrix of simulations that showed, with increased or even constant 20th century CO concentrations, the CO τ was increased by more than 50% in 100 yr. However, Wang and Prinn (1999, 011758) stated that their simulation omitted NMHCs and therefore likely underestimated CO concentrations while under- or overestimating hydroxyl radical concentrations. Likewise, low spatial resolution of the model likely incurred additional error in the solution.

CH_4 is long-lived and, in general, well mixed in the atmosphere. However, the reaction of CH_4 and OH, and hence the CH_4 τ, is governed by the behavior and location of emissions of the short-lived gases, including CO, VOCs, and NO_X. This produces high regional variability and uncertainty in the concentrations and RFs from CO and its related climate forcing gases (Berntsen et al., 2006, 193244; Fuglestvedt et al., 1999, 047431). NO_X, for example, can produce effects on the combined indirect RF opposite in direction to those of CH_4 since under most global background conditions an increase in NO_X increases the global average OH concentration and decreases CH_4 τ and RF (Berntsen et al., 2005, 193241; Wild et al., 2001, 193196). Wild et al. (2001, 193196) also showed that emissions changes in CO have effects opposite in sign to those of NO_X because increases in CO act to depress OH concentrations and that the combined effect of CO and NO_X emissions yields a positive RF. The results of this study underscore the need to consider the combined effects of pollutants emitted from similar sources.

Using the 3-D global chemistry model MOZART-2 (Horowitz et al., 2003, 057770), Naik et al. (2005, 193194) simulated changes in global tropospheric O_3 concentrations and RF resulting from differing reductions in emissions of NO_X alone or a combination of NO_X, CO, and NMHCs in nine regions of the Earth. For the reductions in Europe, North America, and Southeast Asia, reducing CO and NMHCs in addition to reducing NO_X lowered the spatial inhomogeneity of the O_3 concentration and RF because CO has a longer lifetime than NO_X.

Wild et al. (2001, 193196) used the University of California-Irvine chemical transport model (CTM) (Wild and Prather, 2000, 052402) driven by the NASA GISS II general circulation model (Rind and Lerner, 1996, 193750) to compute changes in O_3 concentrations and RF from regional emissions of NO_X and CO. Changes in O_3 and CH_4 result from increases in global surface NO_X emissions alone and run for 10-yr periods produced negative net RFs, ranging from -0.2 W/m^2 in East Asia to -0.5 W/m^2 in the Tropics owing to the long-term interdependencies in the CO-CH_4-NO_X system described above. When global CO emissions were increased by an 11 MT pulse for 1 yr together with the same 1-yr pulsed NO_X surface emissions and run again for a 10-yr period, the global net RF rose to 1.7 W/m^2 with an estimated 20% uncertainty based on the spatial variability and short-term reactivity of O_3 (Wild et al., 2001, 193196).

Determining whether several species' τ and RF will increase or decrease in response to pulsed or step-wise emissions of the short-lived O_3 precursor species (NMVOC, CO, and NO_X) is complicated by its global location with respect to the O_3 production response surface. See the description of the O_3 production response surface and its dependence on NO_X and radical concentrations in the 2008 NO_X ISA (U.S. EPA, 2008, 157073) for additional details. Fiore et al. (2002, 051221; 2008, 193749) found that O_3 is closely coupled with CH_4 and that their relationship is influenced by regional variation in NO_X concentrations. Using the weighted average results from 12 3-D global chemistry models exercised for the IPCC Third Assessment Report (2001, 156587), Wigley et al. (2002, 047883) confirmed that increases in CO and VOC emissions increased the O_3 RF both directly and indirectly through the CH_4 effects described above. Furthermore, Wigley et al. (2002, 047883) demonstrated that NO_X emissions produced a mix of direct and indirect increases in RF, mostly dominated by the direct effects for all modeled scenarios. Wigley et al. (2002, 047883) concluded that tropospheric O_3 RF influences were larger than CH_4 influences and that the short-lived reactive gases produced 60-80% of that forcing, with the remainder coming from CH_4. Given these chemical interdependencies, calculations of an indirect RF for any of these short-lived O_3 precursor species are most often made for all of the most important ones together.

Figure 3-7 illustrates model estimates of the combined RF of increased short-lived O_3 precursor species relative to long-lived GHGs, aerosols, and other changes (Forster et al., 2007, 092936). The combined effect of increased CH_4, CO, NMVOC, and NO_X emissions for the period 1750-2005 has produced tropospheric O_3 concentrations associated with a net RF of ~0.4 W/m^2 with

±50% uncertainty based on Shindell et al. (2005, 080129). Indirect effects of CO through the GHGs O_3, CH_4, and CO_2 were estimated to contribute RF ~0.2 W/m^2, which is more than a factor of 2 larger than the indirect effect of the shorter-lived NMVOCs on the same three GHGs (Forster et al., 2007, 092936). Of the indirect effects on these three GHGs from CO emissions, the O_3-related component was the largest, accounting for approximately one-half of the forcing (Forster et al., 2007, 092936). In comparison, CO_2 contributed a direct forcing of 1.6 ± 0.2 W/m^2 over this time period.

Integrated RF estimates over longer time horizons may indicate the future climate effects of present-day emissions. Modeled integrated 20-yr and 100-yr time horizon RFs are presented by Forster et al. (2007, 092936) in Figure 3-8 for year 2000 emissions of short-lived and long-lived GHGs. The integrated RF for CO was estimated to be ~0.2 W/m^2·yr with ~50% uncertainty. It can be seen that the integrated RF of CO_2 is much smaller for the 20-yr horizon because the lifetime of CO_2 perturbations is roughly 150 yr. As a result, the RF related to short-lived CO is ~25% of that for CO_2 for the 20-yr horizon (~0.7 W/m^2·yr) but only ~7% of that for longer-lived CO_2 over a 100-yr time horizon (~2.4 W/m^2·yr). This indirect forcing is just slightly lower than the RF of year 2000 black carbon emissions from fossil fuel and biomass burning on the same horizons according to this assessment.

It is also possible to compute individual contributions to the integral RF from CO based on separate emissions sectors. Unger et al. (2009, 193238) used the NASA GISS model for Physical Understanding of Composition-Climate Interactions and Impacts (G-PUCCINI) (Shindell et al., 2006, 193751). Unger et al. (2009, 193238) divided the 1995 global anthropogenic CO emissions total of 933.3 MT/yr into sectors for on-road transport (ORT) and power generation (PG), and then separated contributions from each of these sectors for the U.S. and other large geographic regions of the Earth. ORT CO emissions in the U.S. were 84.1 MT/yr; PG CO emissions were 0.55 MT/yr out of the total U.S. anthropogenic CO emissions of 112.5 MT/yr. Unger et al. (2009, 193238) concluded from analysis of 7-yr runs that the CO indirect CH_4 effects (that is, the CO effects through CH_4 changes as described above) in the 1995 emissions run were -0.004 W/m^2 for the global ORT and -0.022 W/m^2 for the global PG. In the U.S., the indirect CH_4 RF was positive at +0.009 W/m^2 because the positive effects on CH_4 τ from the CO emissions dominated over the negative effects from NO_X through OH. This RF fraction from indirect CH_4 is approximately the same as the direct O_3 RF from ORT in the U.S., 0.010 W/m^2. Because the PG sector emits NO_X but less CO relative to the ORT, the indirect CH_4 RF from the U.S. PG was not dominated by the positive CO effects and remained a net negative at -0.006 W/m^2 (Unger et al., 2009, 193238). The authors acknowledged some uncertainty in this relationship related to the influence of NO_X emissions on CO transformation, but no quantification of uncertainty in these modeled estimates was provided.

These gross emissions sectors can also be subdivided to demonstrate more clearly the localized chemical interdependencies of the CO-CH_4-NO_X system. Fuglestvedt et al. (2008, 193242) used the Oslo CTM2 model to simulate effects from all emissions and changes in all transportation subsectors from 1850-2000. Fuglestvedt et al. (2008, 193242) found that global transport has been responsible for ~15% of the total anthropogenic CO_2 RF and ~15% of the total anthropogenic O_3 RF. Of the total O_3 RF, the largest contributor was the shipping sector at 0.03 W/m^2, because its high NO_X-to-CO and NO_X-to-VOC ratios produced OH increases and hence CH_4 decreases in regions of naturally low NO_X. For the shipping segment of the transport sector, the high NO_X emissions there reduced the CH_4 τ but increased O_3. The global mean effect from these two was small and still smaller than the direct negative effect from SO_4^{2-} aerosols. In the on-road segment of global transportation, emissions of CO and VOCs together with NO_X produce an O_3 RF larger than the negative RF from CH_4.

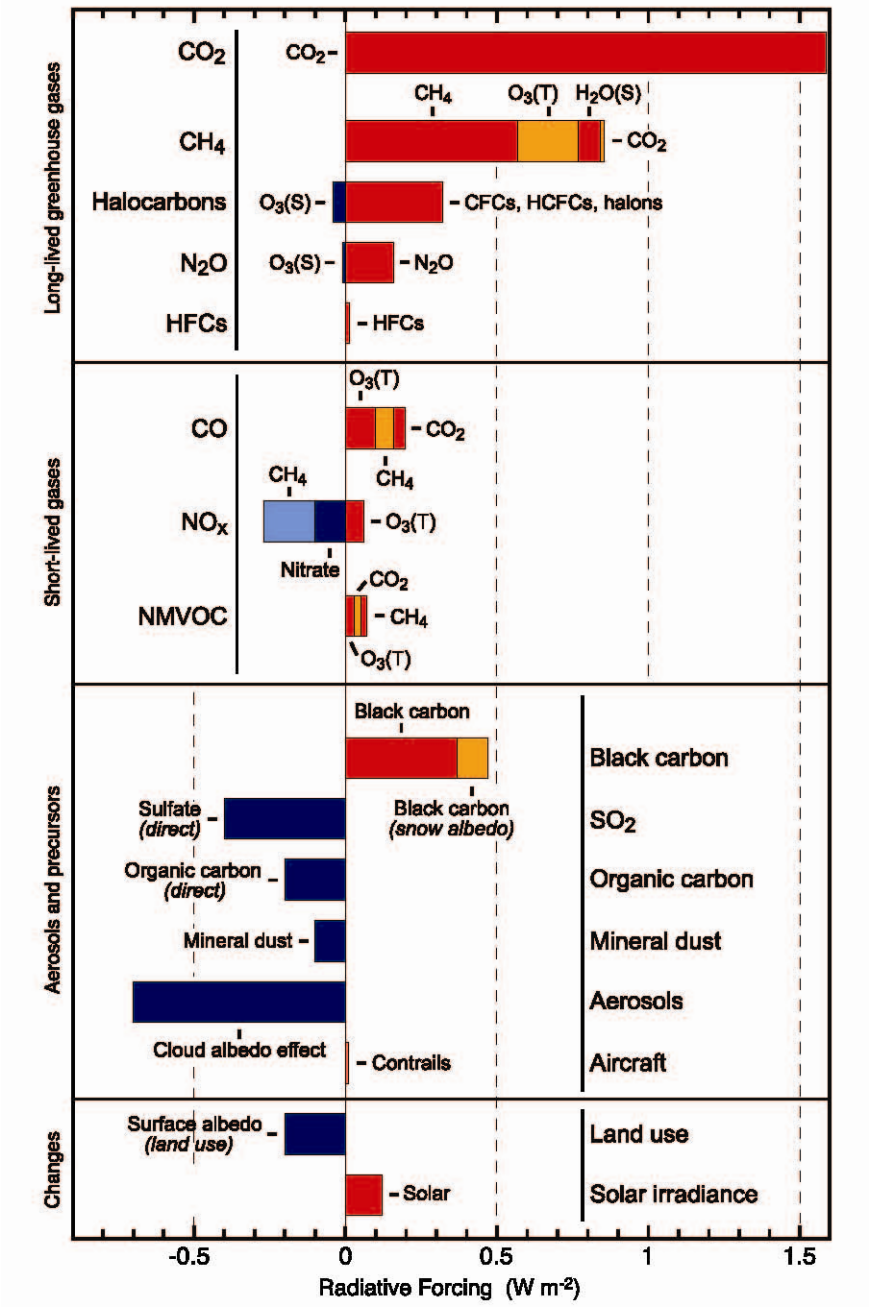


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Figure 3-7. Components of RF in 2005 resulting from emissions since 1750. (S) and (T) indicate stratospheric and tropospheric changes, respectively.

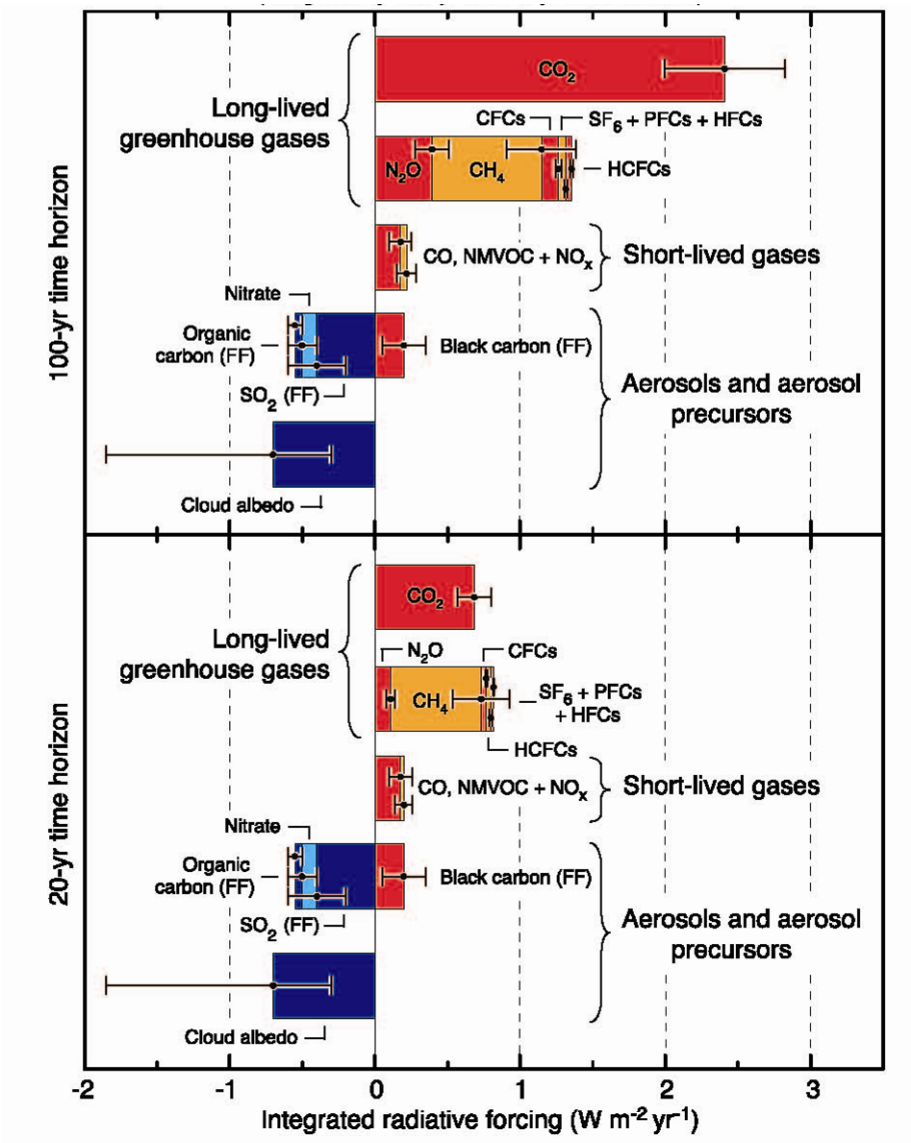

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Figure 3-8. Integrated RF of year 2000 emissions over 20-yr and 100-yr time horizons. The values provided refer to global annual emissions, but effects are expected to vary regionally for short-lived gases.

Caution is warranted in interpreting RF estimates. RF values are global model calculations using the assumption that global climate sensitivities are equal for all forcing mechanisms, whether CO_2, SO_4^{2-} and other aerosols, or the short-lived gases like CO (Berntsen et al., 2005, 193241; Berntsen et al., 2006, 193244). That assumption is under challenge now by GCM results using regionalized RF values separately for different forcing mechanisms and with CO_2, O_3, and solar input changes (Joshi et al., 2003, 193752). Joshi et al. (2003, 193752) found that global climate system sensitivities from non-CO_2 RF varied by ±30% compared to CO_2 RF. Other GCM experiments by Lelieveld et al. (2002, 190361), Rotstayn and Penner (2001, 193754), Menon et al. (2002, 155978), and Kristjansson (2002, 045282) have indicated that regionally changing RF can induce changes in large-scale circulation patterns that control the regionalized cycles of flooding and drought through disruptions in regional temperature and hydrologic cycles. However, such regionalized patterns resulting from GCM experiments are so uncertain and so widely variable across models that even the sign of these regionalized changes can vary with model type and any of

the models' unconstrained assumptions (Berntsen et al., 2006, 193244). Even with such uncertainty and variability, though, the consensus of the climate community is that the climate effects of changes to emissions of the long- and especially the short-lived pollutants, including CO, very likely depend on location.

Global warming potential (GWP) is a widely used relative measure of the potential effect of different emissions on climate, usually defined as the time-integrated RF from an instantaneous pulsed release of 1 kg of a trace gas relative to the effects from a pulsed release of 1 kg of CO_2. Because the greenhouse warming effects from CO are nearly completely indirect and because CO concentrations are spatially heterogeneous, neither the IPCC nor EPA computes direct GWPs for CO, just as they do not for tropospheric O_3, NO, NO_2, or VOCs (U.S. EPA, 2008, 184463). IPCC does estimate indirect GWP for CO using the integrated indirect RF (Forster et al., 2007, 092936). However, the indirect GWP values evaluated and summarized by IPCC are global and cannot reflect effects of localized emissions or emissions changes, making the values for the short-lived species NMVOC, CO, and NO_X more uncertain than the values for the long-lived, well-mixed species as a result of the OH chemistry described above. Moreover, urban- and regional-scale oxidation of CO to CO_2 under current atmospheric conditions proceeds very slowly, and IPCC considers production of CO_2 through this pathway to be double counting of CO effects (Forster et al., 2007, 092936). Variation in the CO GWP range of estimates can be attributed to the unusually large heterogeneity in model type and form, pulsed or stepped emissions increase, time-horizon unit, and integral or differential indirect effects in several combinations (with or without NO_X emissions changes, including or excluding CO_2 effects).

Even with such variability in methods and tools, the CO GWPs have been largely in agreement for approximately 10 yr. The IPCC estimated the indirect GWP of CO to be 1.9 (Forster et al., 2007, 092936). Daniel and Solomon (1998, 193235) used a global box model for changes through CH_4 and O_3 effects from pulsed CO emissions and estimated a CO GWP exclusive of the effect through CO_2 to be between 1 and 4.4. Using the STOCHEM CTM, Derwent et al. (2001, 047912) estimated a pulsed emissions CO GWP, again exclusive of effects through CO_2, to be 1.5. Johnson and Derwent (1996, 193192) had previously computed and integrated GWP of 2.1 for the CH_4 and O_3 effect from a step-wise emissions change using a 2-D and a 100-yr time horizon. Derwent et al. (2001, 047912) and Collins et al. (2002, 044156) subsequently differentiated that integral for each effect and reported GWP for step-wise CO emissions changes on a 100-yr time horizon of 1.0, 0.6, and 1.6 through the effects on CH_4, O_3, and CO_2, respectively. Berntsen et al. (2005, 193241) used the model LMDz v3.3 (Hauglustaine et al., 2004, 193191) to compute 100-yr GWP values for pulsed CO emissions through all indirect effects to be 1.9 as resolved for Europe and 2.4 for Asia, demonstrating the strong regionality in the indirect effects from these short-lived precursors. Most recently, Shindell et al. (2009, 201599) compared GWPs separately for CO, CH_4, and NO_X with and without interactions with aerosols. When including direct and indirect radiative effects related to interaction of CO with aerosols, the GWP for CO was estimated to rise from a range of 1-3 to a range of 3-8.

3.4. Ambient Measurements

3.4.1. Ambient Measurement Instruments

For enforcement of the air quality standards set forth under the Clean Air Act, EPA has established provisions in the Code of Federal Regulations (CFR) under which analytical methods can be designated as federal reference methods or federal equivalent methods (FRM or FEM, respectively). Measurements for determinations of NAAQS compliance must be made with FRMs or FEMs. As of August 2009, 20 automated FRMs and no FEMs had been approved for CO (http://www.epa.gov/ttn/amtic/criteria.html).

All EPA FRMs for CO operate on the principle of nondispersive infrared (NDIR) detection and can include the gas filter correlation (GFC) methodology. NDIR is an automated and continuous method based on the specific absorption of infrared radiation by the CO molecule. Most commercially available analyzers incorporate a gas filter to minimize interferences from other gases and operate near atmospheric pressure. NDIR is based on the physics of CO's characteristic infrared

absorption near 4.63 μm. NDIR methods have several practical advantages over other techniques for CO detection in that they are not sensitive to flow rate changes, require no wet chemicals, are reasonably independent of ambient air temperature changes, are sensitive over wide concentration ranges, and have fast response times. An extensive and comprehensive review of NDIR, GFC, and alternative, non-FRM techniques for CO detection, including tunable diode laser spectroscopy, gas chromatography, mercury liberation, and resonance fluorescence, was made for the 2000 CO AQCD (U.S. EPA, 2000, 000907), and the reader is directed there for additional information. The description here is limited to a brief outline of the FRM NDIR and GFC techniques.

GFC spectroscopy analyzers are used most frequently now in documenting compliance with ambient air standards. A GFC monitor has all of the advantages of an NDIR instrument and the additional advantages of smaller size, no interference from CO_2, and very small interference from water vapor. During operation, air flows continuously through a sample cell. Radiation from the infrared source is directed by optical transfer elements through two main optical subsystems: (1) the rotating gas filter; and (2) the optical multipass (sample) cell. The beam exits the sample cell through an interference filter, which limits the spectral passband to a few of the strongest CO absorption lines. Detection of the transmitted radiation occurs at the infrared detector. The gas correlation cell is constructed with two compartments, one filled with 0.5 atm CO, and a second with pure nitrogen gas (N_2). Radiation transmitted through the CO is completely attenuated at the wavelengths where CO absorbs strongly. The radiation transmitted through the N_2 is reduced by coating the exit window of the cell with a neutral attenuator so that the amounts of radiation transmitted by the two cells are made approximately equal in the passband that reaches the detector. In operation, radiation passes alternately through the two cells as they are rotated to establish a signal modulation frequency. If CO is present in the sample, the radiation transmitted through the CO is not appreciably changed, whereas that through the N_2 cell is changed. This imbalance is linearly related to CO concentrations in ambient air.

Specifications for CO monitoring are designed to help states demonstrate whether they have met compliance criteria; operational parameters required under 40 CFR 53 are provided in Table 3-2. Given the 1-h level of the NAAQS of 35 ppm and the 8-h level of the NAAQS of 9 ppm, a 1.0 ppm limit of detection (LOD) is sufficient for demonstration of compliance, where the LOD is set at three times an instrument's noise level when analyzing a zero air sample to ensure that reported signals are in response to actual ambient CO concentrations. However, with ambient CO levels now routinely at or below 1 ppm, there is greater uncertainty in the monitoring data because a large percentage is below the LOD. For this reason, a new generation of ambient CO monitors has been designed for measurements below 0.5 ppm, with LOD = 0.04 ppm. Additionally, CO measurements at concentrations below 0.5 ppm are needed to support additional objectives, such as validating the inputs to CTMs, improving estimates of low-concentration CO exposure, and assessing differences between CO levels in urban and rural areas, because background CO concentrations are on the order of 0.1 ppm. Effective LOD is influenced by instrumental noise and drift and by the amount of water vapor in the air. Recent improvements in the instruments' optical components and dehumidification of the air stream help to reduce the amount of noise and drift in the CO measurements. Newer GFC instruments have been designed for automatic zeroing to minimize drift (U.S. EPA, 2000, 000907).

Table 3-2. Performance specifications for analytical detection of CO, based on 40 CFR Part 53.

Parameter	Specification
Range	0-50 ppm
Noise	0.5 ppm
LOD	1.0 ppm
Interference equivalent	
Each interfering substance	±1.0 ppm
Total interfering substances	1.5 ppm
Zero drift	
12 h	±1.0 ppm
24 h	±1.0 ppm
Span drift, 24 h	
20% of upper range limit	±10.0%
80% of upper range limit	±2.5%
Lag time	10 min
Rise time	5 min
Fall time	5 min
Precision	
20% of upper range limit	0.5 ppm
80% of upper range limit	0.5 ppm

Currently, 24 models of CO monitors are in use; the models are listed in Annex A, Table A-1. Among them, 20 are older NDIR instruments listed to have an LOD of 0.5 ppm, and 4 are GFC instruments listed to have an LOD of 0.04 ppm. States do not routinely report the operational LOD, precision, and accuracy of the monitors to EPA's Air Quality System (AQS). When the monitored value is below the LOD, some states report the raw monitored data, while others report the concentration as 50% of the LOD (0.25 ppm for high-LOD instruments and 0.02 ppm for low-LOD instruments) when reported data are below the LOD. Among several of the older instruments still in use (Federal Reference Method codes 008, 012, 018, 033, 041, 050, 051, and 054), performance testing has shown effective LODs of 0.62-1.05 ppm, with 24-h drift ranging from 0.044-0.25 ppm and precision ranging from 0.022-0.067 ppm at 20% of the upper range limit of the instrument (Michie et al., 1983, 194043). Among newer GFC instruments, manufacturer-declared LODs range from 0.02-0.04 ppm, with 24-h zero drift varying between 0.5% within 1 ppm and 0.1 ppm and precision varying from 0.5% to 0.1 ppm.

Comparison of older and newer monitors with LOD = 0.5 ppm and 0.04 ppm, respectively, calls attention to several data quality issues with the older monitors; Figure 3-9 illustrates this point with data from two co-located monitors with LODs of 0.5 ppm and 0.04 ppm, in Charlotte, NC. First, the data appearing below the LOD of 0.5 ppm for the older monitor comprise 58% of the data obtained by that monitor. In contrast, no data from the 0.04 ppm LOD monitor are reported below 0.04 ppm. Below 0.5 ppm, observations obtained with the older monitor are on average more than five times higher than those from the newer monitor. Second, the data from the older monitor are reported in units of 0.1 ppm, as seen in the lower resolution of the data with respect to the x-axis. Last, it is possible from the data that the older monitor exhibits some upward drift, since newer models have automatic zeroing functions. Above 0.5 ppm, the slope of the scatterplot is 0.95, suggesting that readings from the older monitor are on average 5% higher than those from the newer monitor. The median data are 0.4 ppm for the older monitor and 0.24 ppm for the newer monitor. However the mean from the older monitor is 0.5 ppm, in contrast with 0.330 ppm for the newer monitor. The 99th percentile is 1.8 ppm for the older monitor, in contrast with the newer monitor, whose 99th percentile level is 1.485 ppm.

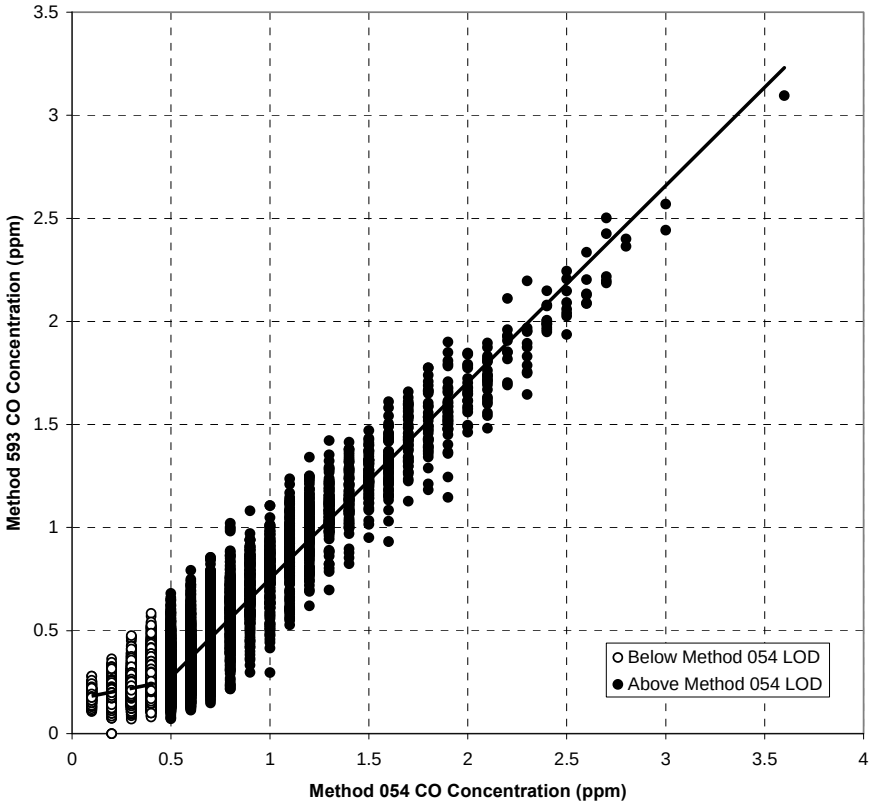


Figure 3-9. Scatterplot comparing data from co-located monitors in Charlotte, NC. Data from Method 054 are from an older model (Thermo Electron Model 48C, Waltham, MA) with LOD = 0.5 ppm, while data from Method 593 are from a newer instrument (Teledyne API Model 300EU, San Diego, CA) with LOD = 0.04 ppm. Above the Method 054 LOD, the methods vary linearly as: [Method 593] = 0.95[Method 054] - 0.20 (R^2 = 0.88, n = 6990); below the Method 054 LOD, the regression changes to [Method 593] = 0.19[Method 054] + 0.16 (R^2 = 0.07, n = 9856).

3.4.2. Ambient Sampling Network Design

3.4.2.1. Monitor Siting Requirements

Minimum monitoring requirements for CO were revoked in the 2006 revisions to ambient monitoring requirements (71 FR 61236, October 17, 2006). This action was made to allow for reductions in measurements of CO and some other pollutants (SO_2, NO_2, and Pb) where measured levels were well below the applicable NAAQS and air quality problems were not expected. CO monitoring activities have been maintained at some State and Local Air Monitoring Stations (SLAMS), and these measurements of CO using FRM are required to continue until discontinuation is approved by the EPA Regional Administrator. CO monitors are typically sited at the following spatial scales (40 CFR Part 58 Appendix D):

- Microscale: Data represent concentrations within a 100 m radius of the monitor. For CO, microscale monitors are sited 2-10 m from a roadway. Measurements are intended to represent the near-road or street canyon environment.

- Middle scale: Data represent concentrations averaged over areas defined by 100-500 m radii. Measurements are intended to represent several city blocks.

- Neighborhood scale: Data represent concentrations averaged over areas defined by 0.5-4.0 km radii. Measurements are intended to represent extended portions of a city.

In 2007, there were 376 CO monitors reporting values to the EPA Air Quality System (AQS) database. Where CO monitoring is ongoing, 40 CFR Part 58 requires at least one CO monitor to capture maximum levels in a given region. This requirement is met with a monitor situated at the CFR-defined microscale distance from the side of a roadway for CO. Microscale monitor locations also have sample inlets mounted at 3 ± 0.5 m above ground level, unlike the monitors sampling for larger scales, whose inlet heights can vary between 2 and 15 m. For the CFR-defined neighborhood scale monitoring, the minimum monitor distance from a major roadway is directly related to the average daily traffic counts on that roadway to ensure that measurements are not substantially influenced by any one roadway. For example, the minimum distance of a neighborhood scale CO monitor from a roadway with an average daily traffic count of 15,000 vehicles per day is 25 m, while the minimum distance is 135 m for a roadway with an average daily traffic count of 50,000 vehicles per day. Occasionally, CO monitors are sited at urban (covering areas of 4-50 km) or regional (covering areas of tens to hundreds of km) scale. More detail on siting requirements can be found in 40 CFR Part 58 Appendices D and E.

In addition to monitoring for determining compliance with the NAAQS, EPA is currently in the process of implementing plans for a new network of multipollutant stations called National Core (NCore) that is intended to meet multiple monitoring objectives. A subset of the SLAMS network, NCore stations are intended to address integrated air quality management needs to support long-term trends analysis, model evaluation, health and ecosystem studies, as well as the more traditional objectives of NAAQS compliance and Air Quality Index reporting. The complete NCore network, required to be fully implemented by January 1, 2011, will consist of approximately 60 urban and 20 rural stations and will include some existing SLAMS sites that have been modified for the additional measurements. Each state will contain at least one NCore station, and 46 of the states plus Washington, DC, will have at least one urban station. CO will be measured using 0.04 ppm LOD monitors at all sites, as will SO_2, NO, and NO_Y[1]; surface meteorology will also be measured at NCore sites. The advantage to the NCore strategy is that time-resolved, simultaneous measurements of multiple pollutants will be obtained at each site. The disadvantage is that the NCore network will be sparse, and so spatial variability will be difficult to ascertain from the data obtained.

3.4.2.2. Spatial and Temporal Coverage

Figure 3-10 depicts the distribution of the 376 regulatory CO monitors operating in the U.S. in 2007. Data from 291 of the 376 CO monitors operating year-round at 290 sites in the years 2005-2007 met the data completeness criteria for inclusion in the multiyear ambient data analyses for this assessment. Completeness criteria require that data be collected for 75% of the hours in a day, 75% of the days in a quarter, and 3 complete quarters for all 3 yr; criteria for Region 10 were relaxed to 2 complete quarters because it contains Alaska. The greatest density of monitors is in the CSAs for Los Angeles, and San Francisco, CA; and along the Mid-Atlantic seaboard. Monitors are also located in regions where biomass burning is more prevalent, such as Anchorage, AK, but not all of these monitors report values from all seasons of all years. The number of monitors per sampling scale is provided in Table 3-3, and locations of monitors with nearby roadway types and traffic counts are provided in Annex A, Tables A-2 through A-7, for each monitoring scale. Twenty-four percent of the monitors meeting completeness criteria are categorized as "Null", meaning that no scale has been identified for those monitors. Furthermore, given the overlap between scales regarding the type of road at which the monitor is sited, it is possible that scale has been misclassified for some of the monitors.

[1] NCore sites must measure, at a minimum, $PM_{2.5}$ particle mass using continuous and integrated/filter-based samplers, speciated $PM_{2.5}$, $PM_{10\text{-}2.5}$ particle mass, speciated $PM_{10\text{-}2.5}$, O_3, SO_2, CO, NO/NO_Y, wind speed, wind direction, relative humidity, and ambient temperature.

Table 3-3. Counts of CO monitors by sampling scale meeting 75% completeness criteria for use in the U.S. during 2005-2007.

Monitoring Scale	Count
Microscale	57
Middle Scale	31
Neighborhood Scale	119
Urban Scale	11
Regional Scale	2
Null	71

Figure 3-10 also shows the locations of the newer 0.04 ppm LOD CO monitors throughout the U.S in 2007, indicated by blue and purple triangles. The newer monitors included in the analysis are located in: Baton Rouge, LA; Boston, MA; Charlotte, NC; Dallas, TX; Decatur, GA; Houston, TX; Portland, OR; Presque Isle, ME; San Jose, CA; and rural locations within Georgia and South Carolina. Other 0.04 ppm LOD monitors not meeting completeness criteria for the 2005-2007 analysis were located in: Beltsville, MD; Cedar Rapids, IA; Davenport, IA; Des Moines, IA; Nederland, TX; Northbrook, IL; Plant City, FL; Seattle, WA; Thomaston, CT; Tulsa, OK; Westport, CT; and rural locations in Maryland and Wisconsin. A listing of 0.04 ppm and 0.5 ppm LOD monitors meeting completeness criteria by state for 2005-2007 is provided in Annex A, Table A-8.

Eleven metropolitan regions were chosen for closer investigation of monitor siting based on their relevance to the health studies assessed in subsequent chapters of this ISA and to demonstrate specific points about geospatial distributions of CO emissions and concentrations. These regions were: Anchorage, AK; Atlanta, GA; Boston, MA; Denver, CO; Houston, TX; Los Angeles, CA; New York City, NY; Phoenix, AZ; Pittsburgh, PA; Seattle, WA; and St. Louis, MO. Core-Based Statistical Areas (CBSAs) and Combined Statistical Areas (CSAs), as defined by the U.S. Census Bureau (http://www.census/gov/), were used to determine which counties, and hence, which monitors, to include for each metropolitan region.[1] As an example, Figure 3-11 through Figure 3-14 display CO monitor density with respect to population density (for total population and elderly adults aged 65 and over) for the Denver and Los Angeles CSAs (Annex A, Figures A-7 through A-22 show analogous plots for the other nine metropolitan regions). Figure 3-18 and Figure 3-21 and additional figures in Annex A show the locations of CO monitors for the 11 CSAs/CBSAs in relation to major roadways, including interstate highways, U.S. highways, state highways, and other major roadways required for traffic network connectivity. In the examples shown for Denver and Los Angeles, the monitors were typically located near high population density neighborhoods within the CSA. The Los Angeles CSA monitors appear to be distributed fairly evenly across the city of Los Angeles, while the Denver CSA had three monitors in the city center and two in the suburbs of the Denver CSA. Regional background sites were not included on the maps unless they lay within the CSA/CBSA.

[1] A CBSA represents a county-based region surrounding an urban center of at least 10,000 people determined using 2000 census data and replaces the older Metropolitan Statistical Area (MSA) definition from 1990. The CSA represents an aggregate of adjacent CBSAs tied by specific commuting behaviors. The broader CSA definition was used when selecting monitors for the cities listed above with the exception of Anchorage and Phoenix, which are not contained within a CSA. Therefore, the smaller CBSA definition was used for these metropolitan areas.

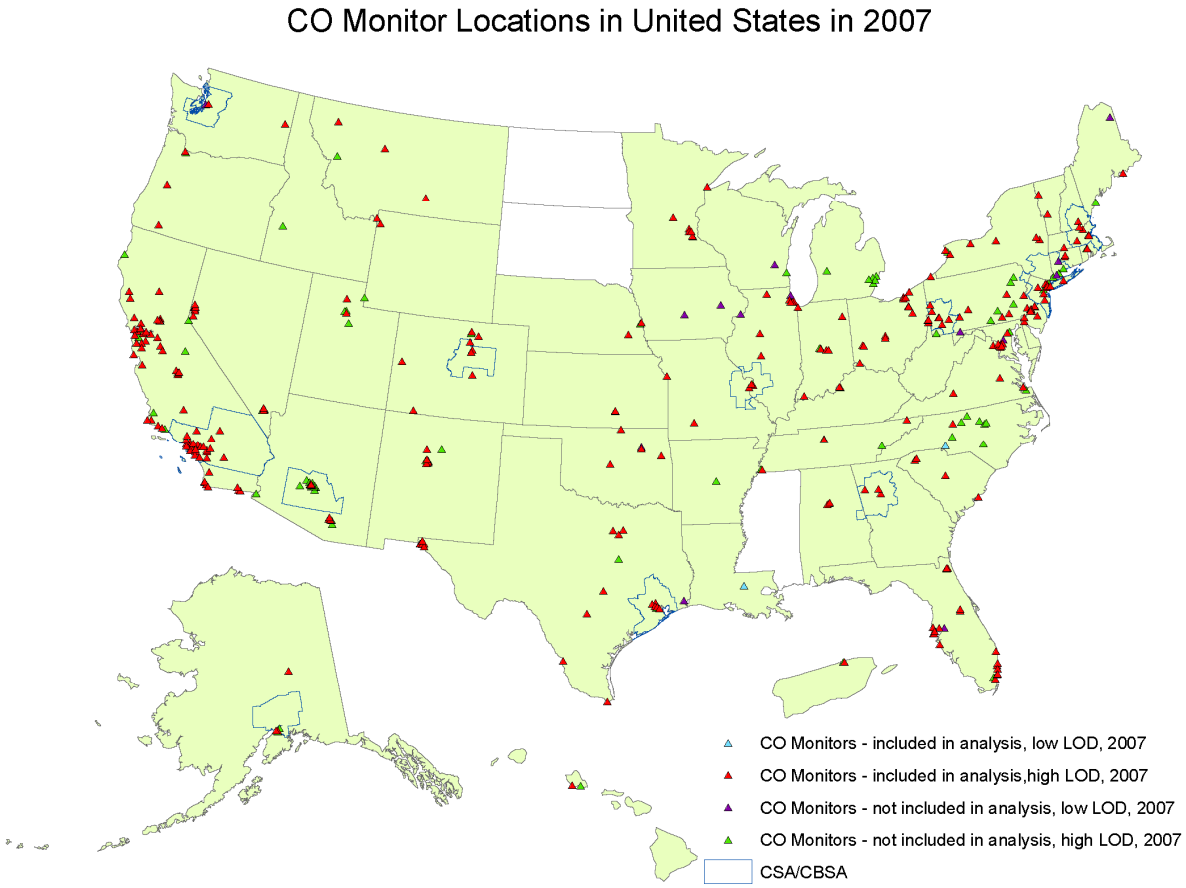


Figure 3-10. Map of CO monitor locations in the U.S. in 2007. Locations are indicated with triangles: blue and red triangles show locations of the sites used in data analysis for this assessment; purple and green triangles are at locations with monitors which did not meet the data completeness requirements for analysis; blue lines mark the boundaries of the 11 CSAs/CBSAs used in the data analysis for this assessment.

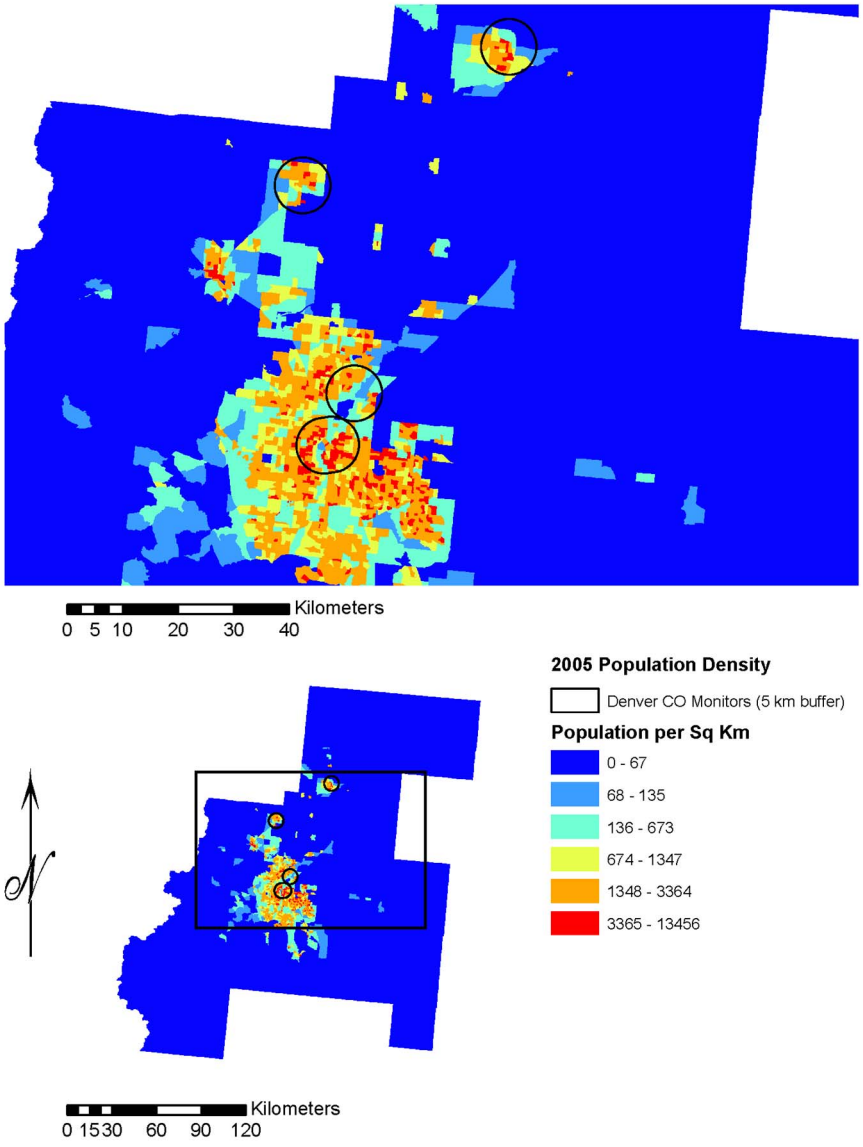


Figure 3-11. Map of CO monitor locations with respect to population density in the Denver, CO CSA, total population. The circles indicate 5 km buffers around the monitors.

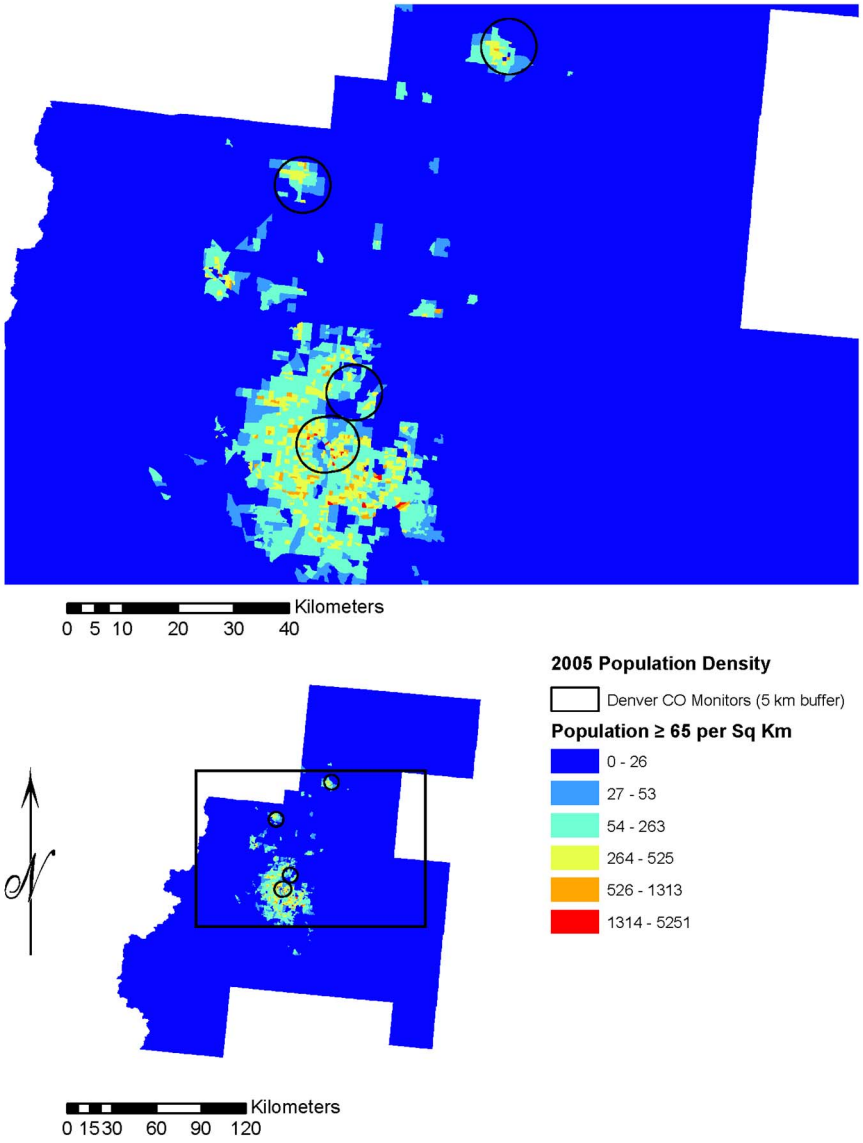


Figure 3-12. Map of CO monitor locations with respect to population density in the Denver, CO CSA, age 65 and older. The circles indicate 5 km buffers around the monitors.

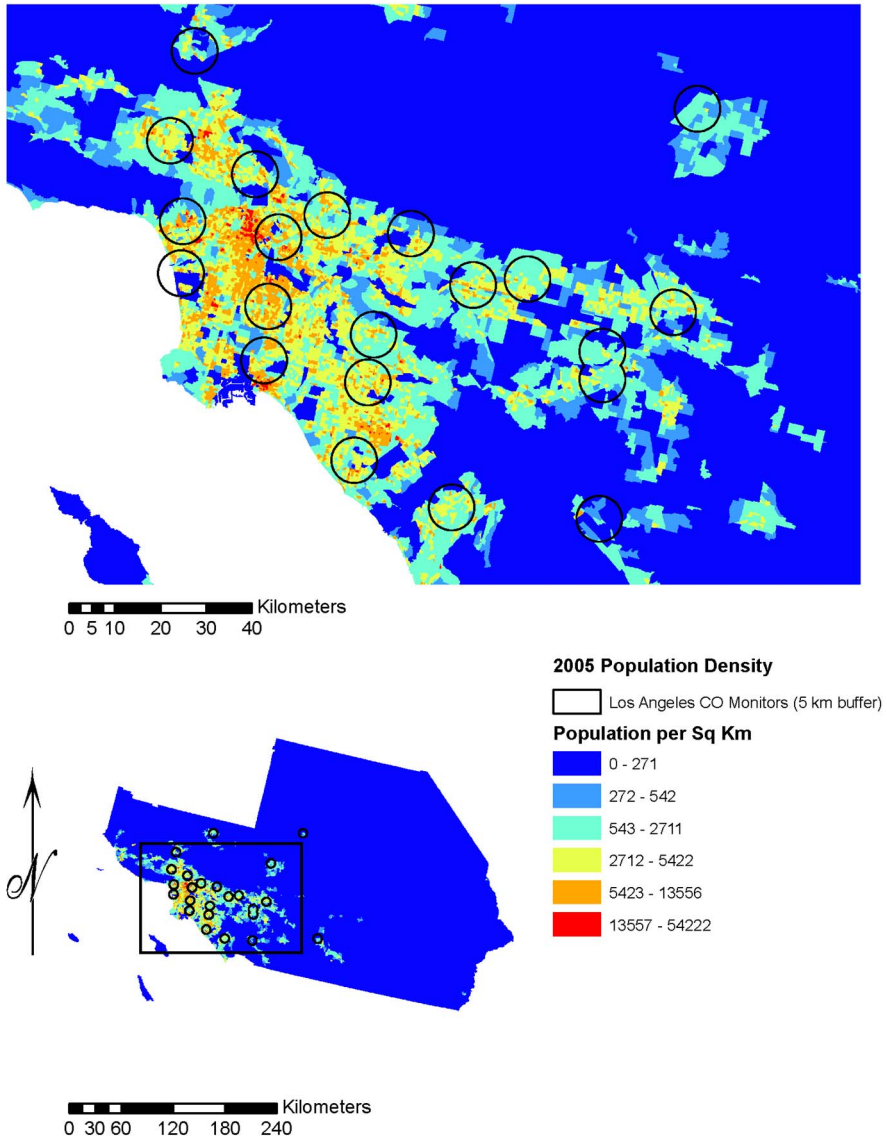


Figure 3-13. Map of CO monitor locations with respect to population density in the Los Angeles, CA CSA, total population. The circles indicate 5 km buffers around the monitors.

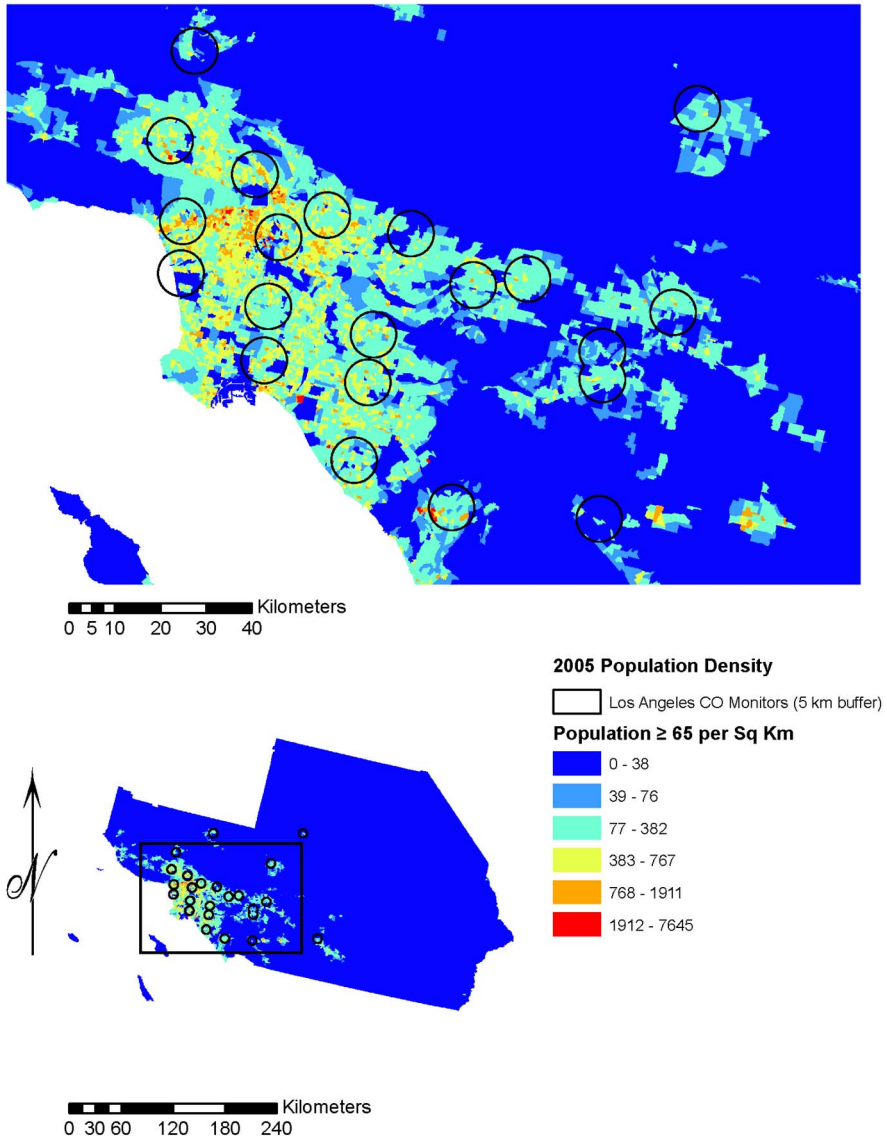


Figure 3-14. Map of CO monitor locations with respect to population density in the Los Angeles, CA CSA, age 65 and older. The circles indicate 5 km buffers around the monitors.

Ambient monitors for CO and other criteria pollutants are located to monitor compliance rather than population exposures. However, CO monitors submitting data to the AQS are often used for exposure assessment. For this reason, data are presented here to assess population density in the vicinity of CO monitors. Table 3-4 and Table 3-5 show the population density around CO monitors for the total population and for elderly adults aged 65 and over for each CSA/CBSA. The percentage of population within specific radii of the monitors for each city was, for the most part, similar between the total and elderly populations. In the cases of Anchorage, Denver, Phoenix, and St. Louis however, the percentage of the elderly population within given radii of the monitors was considerably different compared with the total population. Between-city disparities in population density were larger. Los Angeles, with 85%, and Denver, with 68%, had the largest proportion of the total population within 15 km of a monitor. Seattle, with 18%, had the lowest population coverage in large part because ambient CO concentrations there require only a single CO monitor. For the elderly population, Los Angeles, at 83%, Anchorage, at 73%, and Denver, at 70%, had the greatest population coverage within 15 km of a monitor; Seattle, at 18%, again had the lowest coverage. Proximity to monitoring stations is considered further in Sections 3.5 and 3.6 regarding spatial variability within cities. In combination, these data illustrate that population coverage varies by monitor and across cities.

Table 3-4. Proximity to CO monitors for the total population by city.

Region	Total CSA/ CBSA	≤ 1 km		≤ 5 km		≤ 10 km		≤ 15 km	
	N	N	%	N	%	N	%	N	%
Anchorage, AK	352,225	5,391	1.53	131,608	37.36	212,834	60.43	239,842	68.09
Atlanta, GA	5,316,742	5,480	0.10	149,772	2.82	672,701	12.65	1,444,986	27.18
Boston, MA	7,502,707	95,732	1.28	1,180,054	15.73	2,432,846	32.43	3,418,353	45.56
Denver, CO	2,952,039	26,096	0.88	497,598	16.86	1,091,444	36.97	1,720,360	58.28
Houston, TX	5,503,320	29,068	0.53	599,796	10.90	1,669,117	30.33	2,506,830	45.55
Los Angeles, CA	17,655,319	202,340	1.15	4,064,309	23.02	11,928,427	67.56	15,074,972	85.38
New York, NY	22,050,940	201,350	0.91	3,711,369	16.83	8,385,801	38.03	12,454,837	56.48
Phoenix, AZ	3,818,147	47,478	1.24	503,433	13.19	1,033,102	27.06	1,581,887	41.43
Pittsburgh, PA	2,515,383	29,136	1.16	369,965	14.71	895,252	35.59	1,359,596	54.05
Seattle, WA	3,962,434	4,814	0.12	94,649	2.39	279,976	7.07	699,490	17.65
St. Louis, MO	2,869,955	16,638	0.58	255,499	8.90	886,412	30.89	1,303,636	45.42

Table 3-5. Proximity to CO monitors for adults aged 65 and older by city.

Region	Total CSA/ CBSA	≤ 1 km		≤ 5 km		≤ 10 km		≤ 15 km	
	N	N	%	N	%	N	%	N	%
Anchorage, AK	17,742	361	2.03	8,986	50.65	12,038	67.85	12,990	73.22
Atlanta, GA	362,201	423	0.12	12,758	3.52	54,148	14.95	111,232	30.71
Boston, MA	945,790	8,272	0.87	131,198	13.87	297,392	31.44	430,502	45.52
Denver, CO	232,974	2,541	1.09	42,760	18.35	102,783	44.12	163,682	70.26
Houston, TX	377,586	1,703	0.45	42,312	11.21	130,567	34.58	182,049	48.21
Los Angeles, CA	1,626,663	17,974	1.10	380,079	23.37	1,069,188	65.73	1,355,461	83.33
New York, NY	2,710,675	29,534	1.09	427,601	15.77	940,121	34.68	1,429,215	52.73
Phoenix, AZ	388,150	2,877	0.74	35,839	9.23	77,244	19.90	125,300	32.28
Pittsburgh, PA	449,544	5,383	1.20	66,967	14.90	166,440	37.02	255,220	56.77
Seattle, WA	390,372	556	0.14	12,142	3.11	31,036	7.95	69,858	17.90
St. Louis, MO	358,747	3,203	0.89	42,890	11.96	127,274	35.48	184,491	51.43

3.5. Environmental Concentrations

3.5.1. Spatial Variability

3.5.1.1. National Scale

The current NAAQS designates that the level of the NAAQS is not to be exceeded more than once per year at a given monitoring site. Figure 3-15 and Figure 3-16 show the second-highest 1-h and second-highest 8-h county-average CO concentrations, respectively, over the U.S. along with estimates of the fraction of the U.S. total population exposed to those concentrations. Although 93% of the U.S. counties are not represented in AQS reporting, based on their population densities and proximity to sources, those counties are not expected to have higher concentrations than the ones analyzed here in the absence of extreme events such as wildfires. Continuous hourly averages are reported from U.S. monitoring stations. One-hour (1-h) and 8-h CO data were available for 243 counties and autonomous cities or municipalities (e.g., Anchorage, AK, Washington, DC) where CO monitors met the 75% data completeness criteria used in this analysis for the years 2005-2007. In 2007, no monitored location reported a second-highest 1-h CO concentration above 35 ppm (Figure 3-15). Moreover, only two monitored locations, one in Weber County, UT and the other in Jefferson County, AL (including Birmingham, AL), reported second-highest 1-h CO concentrations between 15.1 and 35.0 ppm. Figure 3-16 shows that only 5 counties reported second-highest 8-h CO concentrations above 5.0 ppm: Jefferson County, AL; Imperial County, CA; Weber County, UT; Philadelphia County., PA; and Anchorage Municipality, AK.

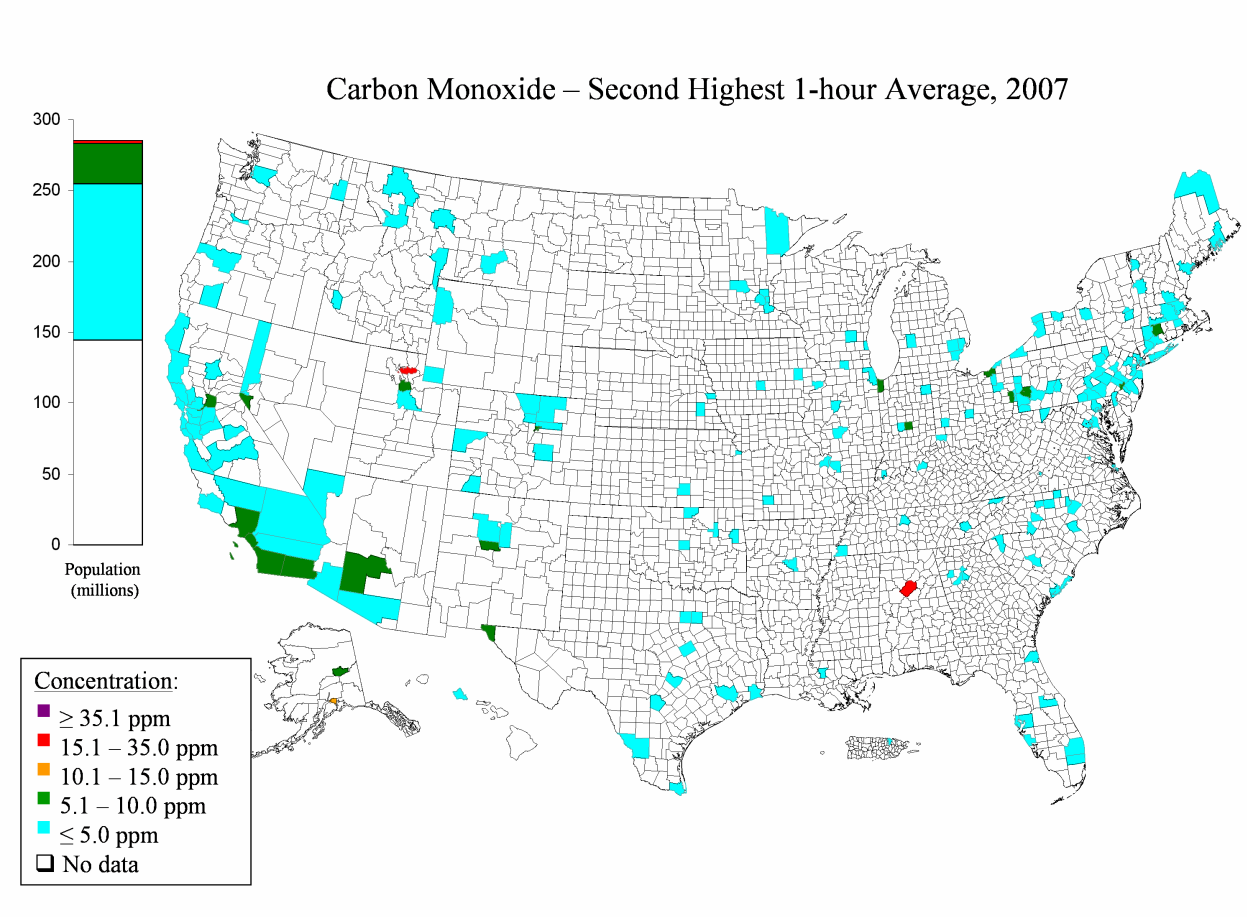


Figure 3-15. County-level map of second-highest 1-h avg CO concentrations in the U.S. in 2007. The bar on the left shows the total U.S. population living in counties with CO concentrations in the range indicated. Note that approximately 150 million people live in counties with no CO monitors.

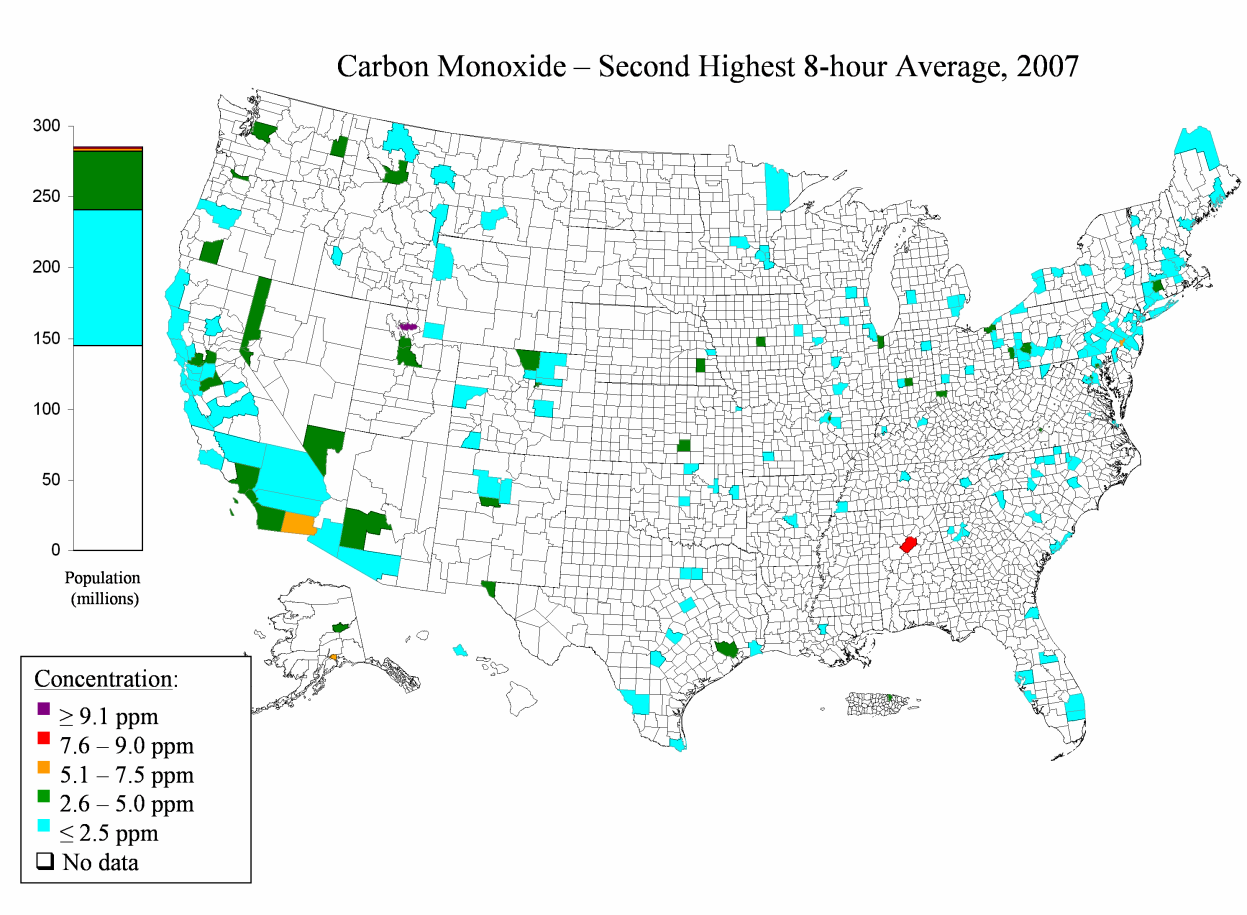


Figure 3-16. County-level map of second-highest 8-h avg CO concentrations in the U.S. in 2007. The bar on the left shows the total U.S. population living in counties with CO concentrations in the range indicated. Note that approximately 150 million people live in counties with no CO monitors.

Table 3-6. Distribution of 1-h avg CO concentration (ppm) derived from AQS data.

				Percentiles									
	N	Mean	Min	1	5	10	25	50	75	90	95	99	Max
NATIONWIDE STATISTICS (N = NUMBER OF OBSERVATIONS)													
2005-2007	7,180,700	0.5	0.0	0.0	0.0	0.1	0.2	0.4	0.6	0.9	1.2	2.1	39.0
2005	2,391,962	0.5	0.0	0.0	0.0	0.1	0.2	0.4	0.6	1.0	1.3	2.3	22.3
2006	2,402,153	0.5	0.0	0.0	0.0	0.1	0.2	0.4	0.6	0.9	1.2	2.1	35.3
2007	2,386,585	0.4	0.0	0.0	0.0	0.1	0.2	0.3	0.5	0.8	1.1	1.9	39.0
Winter (December - February)	1,752,340	0.6	0.0	0.0	0.0	0.1	0.3	0.4	0.7	1.2	1.6	2.7	20.0
Spring (March - May)	1,826,167	0.4	0.0	0.0	0.0	0.1	0.2	0.3	0.5	0.8	1.0	1.7	35.3
Summer (June - August)	1,811,082	0.4	0.0	0.0	0.0	0.0	0.2	0.3	0.5	0.7	0.9	1.5	39.0
Fall (September - November)	1,791,111	0.5	0.0	0.0	0.0	0.1	0.2	0.4	0.6	1.0	1.3	2.2	24.1
NATIONWIDE STATISTICS, POOLED BY SITE (N = NUMBER OF SITES)													
2005-2007	285	0.5	0.0	0.0	0.1	0.2	0.3	0.4	0.6	0.7	0.8	1.0	1.5
2005	285	0.5	0.0	0.0	0.1	0.2	0.4	0.5	0.6	0.8	0.9	1.3	1.6
2006	285	0.5	0.0	0.0	0.1	0.2	0.3	0.4	0.6	0.7	0.8	1.2	1.4
2007	285	0.4	0.0	0.0	0.1	0.2	0.3	0.4	0.5	0.7	0.7	1.1	1.5
Winter (December - February)	285	0.6	0.0	0.0	0.2	0.2	0.4	0.5	0.7	0.9	1.1	1.5	1.6
Spring (March - May)	285	0.4	0.0	0.0	0.1	0.2	0.3	0.4	0.5	0.7	0.7	1.0	1.6
Summer (June - August)	285	0.4	0.0	0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	1.1	1.5
Fall (September - November)	285	0.5	0.0	0.0	0.1	0.2	0.4	0.4	0.6	0.8	0.9	1.1	1.5
STATISTICS FOR INDIVIDUAL CSAS/CBSAS (2005-2007) (N = NUMBER OF OBSERVATIONS)													
Anchorage[a]	25,672	1.1	0.0	0.1	0.2	0.3	0.5	0.7	1.3	2.3	3.1	5.0	13.1
Atlanta	76,683	0.5	0.0	0.0	0.2	0.2	0.3	0.4	0.6	0.8	1.1	1.6	10.8
Boston	171,975	0.4	0.0	0.0	0.0	0.1	0.2	0.4	0.5	0.7	0.9	1.4	10.0
Denver	129,038	0.5	0.0	0.0	0.1	0.2	0.3	0.4	0.6	1.0	1.3	2.2	9.3
Houston	123,925	0.3	0.0	0.0	0.0	0.0	0.2	0.3	0.4	0.6	0.8	1.4	4.6
Los Angeles	592,960	0.5	0.0	0.0	0.0	0.1	0.2	0.3	0.6	1.0	1.4	2.3	8.4
New York	226,673	0.5	0.0	0.0	0.1	0.1	0.3	0.5	0.6	0.9	1.1	1.6	5.8
Phoenix	127,477	0.8	0.0	0.0	0.1	0.2	0.3	0.5	1.0	1.9	2.5	3.6	7.8
Pittsburgh	179,758	0.3	0.0	0.0	0.0	0.0	0.1	0.2	0.4	0.6	0.8	1.2	6.7
Seattle	25,818	0.8	0.0	0.1	0.2	0.3	0.4	0.6	0.9	1.3	1.6	2.5	5.9
St. Louis	77,142	0.4	0.0	0.0	0.1	0.2	0.3	0.4	0.5	0.7	0.9	1.4	5.7
Not in the 11 cities	5,449,251	0.5	0.0	0.0	0.0	0.1	0.2	0.4	0.6	0.9	1.2	2.1	39.0

[a]CO monitoring is only available for quarters 1 and 4; since monitoring data are not available year-round, Anchorage is not included in the nationwide statistics shown in this table.

Table 3-6 contains the distribution of hourly CO measurements reported to AQS for 2005-2007. All monitoring locations meeting the 75% data completeness criteria have been included in this table. Several monitors in EPA Region 10, including four in Alaska, did not meet the data completeness criteria since CO reporting was only required during the first and fourth quarters of each year at these sites. Anchorage was included in the table, however, for an approximate comparison with the other CSAs and CBSAs reporting year-round measurements to AQS. Anchorage and other partial-year monitors were not, however, included in the national statistics shown in the table. AQS site number 371190041, located in Charlotte, NC, was the only site with co-located monitors both meeting the data completeness criteria and, therefore, the nationwide data in the table was derived from 286 monitors located at 285 sites. In Section 3.5.1.3, the nationwide 1-h avg statistics shown in Table 3-6 (along with the nationwide 24-h avg, 1-h daily max and 8-h daily max statistics) are further divided by monitoring scale (microscale, middle scale, etc.) to address issues relating to the near-road environment.

The nationwide mean, median, and interquartile range for 1-h measurements reported for 2005-2007 were 0.5, 0.4 and 0.4 ppm, respectively, and these statistics did not change by more than 0.1 ppm over the 3-yr period. More than 50% of the data nationwide were below the LOD for the majority of monitors in use. The largest recorded second-highest 1-h concentration, 26.3 ppm, for this period was reported in 2006 in Birmingham, AL (AQS site ID: 010736004). The highest 1-h concentration, 39 ppm, between 2005 and 2007, was reported in Ogden, UT (AQS site ID: 490570006) on August 28, 2007. An annual outdoor barbeque festival held in Ogden on that day resulted in a period of elevated CO concentrations. The seasonally stratified concentrations in Table 3-6 are generally highest in the winter (December-February) and fall (September-November) and decrease on average during the spring (March-May) and summer (June-August).

Nationwide statistics pooled by site are listed in the center rows of Table 3-6 and illustrate the distribution of the site average CO concentrations recorded at the 285 monitoring sites for 2005-2007 (Figure 3-10). The site reporting the highest 3-yr pooled 1-h avg CO concentration, 1.5 ppm, was located in San Juan, Puerto Rico (AQS site ID: 721270003). The 11 individual CSAs/CBSAs discussed earlier are included in the table, none of which reported concentrations above the value of the 1-h NAAQS. Four of the 11 cities (Boston, Houston, Pittsburgh and St. Louis) had 95th percentile 1-h CO concentrations below 1 ppm; the 95th percentile concentrations for the remaining cities were below 3.1 ppm. Lack of year-round monitoring in Anchorage prevented a direct comparison with the other metropolitan regions. However, Anchorage exhibited a 1-h CO distribution shifted higher in concentration when compared to the U.S. average during fall or winter. The 99th percentile 1-h avg concentration in Anchorage was 5.0 ppm; the other selected cities with year-round monitoring had 99th percentile concentrations ranging from 0.9 ppm to 2.5 ppm.

Table 3-7. Distribution of 24-h avg CO concentration (ppm) derived from AQS data.

				Percentiles									
	N	Mean	Min	1	5	10	25	50	75	90	95	99	Max
NATIONWIDE STATISTICS (N = NUMBER OF OBSERVATIONS)													
2005-2007	303,843	0.5	0.0	0.0	0.0	0.1	0.3	0.4	0.6	0.9	1.1	1.7	7.0
2005	101,184	0.5	0.0	0.0	0.0	0.1	0.3	0.4	0.6	0.9	1.1	1.8	5.8
2006	101,652	0.5	0.0	0.0	0.0	0.1	0.3	0.4	0.6	0.9	1.1	1.6	7.0
2007	101,007	0.4	0.0	0.0	0.0	0.1	0.2	0.4	0.5	0.8	1.0	1.6	6.9
Winter (December-February)	74,144	0.6	0.0	0.0	0.1	0.2	0.3	0.5	0.7	1.1	1.3	2.0	7.0
Spring (March - May)	77,317	0.4	0.0	0.0	0.0	0.1	0.2	0.4	0.5	0.7	0.9	1.4	6.4
Summer (June - August)	76,562	0.4	0.0	0.0	0.0	0.1	0.2	0.3	0.5	0.7	0.8	1.3	6.9
Fall (September - November)	75,820	0.5	0.0	0.0	0.0	0.1	0.3	0.4	0.6	0.9	1.1	1.7	5.8
NATIONWIDE STATISTICS, POOLED BY SITE (N = NUMBER OF SITES)													
2005-2007	285	0.5	0.0	0.0	0.1	0.2	0.3	0.4	0.6	0.7	0.8	1.0	1.5
2005	285	0.5	0.0	0.0	0.1	0.2	0.4	0.5	0.6	0.8	0.9	1.3	1.6
2006	285	0.5	0.0	0.0	0.1	0.2	0.3	0.4	0.6	0.7	0.8	1.2	1.4
2007	285	0.4	0.0	0.0	0.1	0.2	0.3	0.4	0.5	0.7	0.7	1.1	1.5
Winter (December - February)	285	0.6	0.0	0.0	0.2	0.2	0.4	0.5	0.7	0.9	1.1	1.5	1.6
Spring (March - May)	285	0.4	0.0	0.0	0.1	0.2	0.3	0.4	0.5	0.7	0.7	1.0	1.6
Summer (June - August)	285	0.4	0.0	0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	1.1	1.5
Fall (September - November)	285	0.5	0.0	0.0	0.1	0.2	0.4	0.4	0.6	0.8	0.9	1.1	1.5
STATISTICS FOR INDIVIDUAL CSAS/CBSAS (2005-2007) (N = NUMBER OF OBSERVATIONS)													
Anchorage[a]	1,074	1.1	0.0	0.2	0.2	0.4	0.6	0.9	1.4	1.9	2.4	3.3	4.6
Atlanta	3,229	0.5	0.0	0.1	0.2	0.2	0.3	0.4	0.6	0.8	0.9	1.2	1.6
Boston	7,446	0.4	0.0	0.0	0.1	0.1	0.3	0.4	0.5	0.7	0.8	1.1	2.2
Denver	5,363	0.5	0.0	0.1	0.2	0.2	0.3	0.5	0.6	0.9	1.1	1.5	2.3
Houston	5,188	0.3	0.0	0.0	0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.9	1.9
Los Angeles	25,803	0.5	0.0	0.0	0.1	0.1	0.2	0.4	0.6	1.0	1.2	1.7	3.8
New York	9,513	0.8	0.0	0.0	0.1	0.2	0.4	0.5	0.6	0.8	1.0	1.3	2.5
Phoenix	5,348	0.8	0.0	0.1	0.2	0.3	0.4	0.6	1.1	1.6	1.9	2.5	3.4
Pittsburgh	7,497	0.3	0.0	0.0	0.0	0.0	0.1	0.2	0.4	0.6	0.7	1.0	1.9
Seattle	1,079	0.8	0.1	0.2	0.3	0.4	0.5	0.7	0.9	1.2	1.4	1.8	2.4
St. Louis	3,216	0.4	0.0	0.0	0.1	0.2	0.3	0.4	0.5	0.7	0.8	1.0	1.9
Not in the 11 cities	230,161	0.5	0.0	0.0	0.0	0.1	0.2	0.4	0.6	0.8	1.1	1.6	7.0

[a]CO monitoring is only available for quarters 1 and 4; since monitoring data are not available year-round, Anchorage is not included in the nationwide statistics shown in this table.

Table 3-7 contains the distribution of 24-h avg CO concentrations derived from the 1-h concentrations reported to AQS and summarized in Table 3-6. The nationwide mean, median, and interquartile range for 24-h avg values during 2005-2007 were 0.5, 0.4 and 0.3 ppm, respectively. These were similar to those for the 1-h values and showed more than half the data falling below the LOD for the majority of monitors in the field. The maximum 24-h avg concentration in these years, 7 ppm, was reported in Birmingham, AL (AQS site ID: 010736004). The 99th percentile 24-h avg

concentrations ranged from 0.9 ppm to 2.5 ppm in the selected cities with year-round monitoring; Anchorage had a 99th percentile concentration of 3.3 ppm.

Table 3-8. Distribution of 1-h daily max CO concentration (ppm) derived from AQS data.

				Percentiles									
	N	Mean	Min	1	5	10	25	50	75	90	95	99	Max
NATIONWIDE STATISTICS (N = NUMBER OF OBSERVATIONS)													
2005-2007	303,843	0.9	0.0	0.0	0.1	0.3	0.4	0.7	1.2	1.8	2.4	3.8	39.0
2005	101,184	1.0	0.0	0.0	0.2	0.3	0.5	0.8	1.3	2.0	2.6	4.1	22.3
2006	101,652	0.9	0.0	0.0	0.1	0.3	0.4	0.7	1.2	1.9	2.4	3.9	35.3
2007	101,007	0.8	0.0	0.0	0.1	0.2	0.4	0.7	1.1	1.7	2.1	3.4	39.0
Winter (December - February)	74,144	1.2	0.0	0.0	0.2	0.3	0.5	0.9	1.6	2.5	3.1	4.7	20.0
Spring (March - May)	77,317	0.8	0.0	0.0	0.1	0.3	0.4	0.7	1.0	1.6	2.0	3.0	35.3
Summer (June - August)	76,562	0.7	0.0	0.0	0.1	0.2	0.4	0.6	0.9	1.3	1.6	2.5	39.0
Fall (September - November)	75,820	1.0	0.0	0.0	0.2	0.3	0.5	0.8	1.3	2.0	2.5	3.8	24.1
NATIONWIDE STATISTICS, POOLED BY SITE (N = NUMBER OF SITES)													
2005-2007	285	0.9	0.1	0.1	0.3	0.5	0.6	0.8	1.1	1.5	1.7	2.3	3.9
2005	285	1.0	0.1	0.1	0.4	0.5	0.7	0.9	1.2	1.6	2.0	2.5	3.7
2006	285	0.9	0.1	0.1	0.3	0.5	0.6	0.9	1.1	1.6	1.8	2.3	4.8
2007	285	0.8	0.1	0.1	0.3	0.4	0.6	0.8	1.0	1.4	1.6	2.0	3.1
Winter (December - February)	285	1.2	0.0	0.1	0.4	0.6	0.8	1.0	1.5	2.1	2.5	3.4	4.1
Spring (March - May)	285	0.8	0.1	0.1	0.3	0.4	0.6	0.8	1.0	1.3	1.5	2.1	4.0
Summer (June - August)	285	0.7	0.0	0.1	0.2	0.3	0.5	0.6	0.8	1.1	1.3	2.2	3.3
Fall (September - November)	285	1.0	0.1	0.1	0.3	0.5	0.7	0.9	1.2	1.7	2.0	2.4	4.1
STATISTICS FOR INDIVIDUAL CSAS/CBSAS (2005-2007) (N = NUMBER OF OBSERVATIONS)													
Anchorage[a]	1,074	2.6	0.0	0.3	0.6	0.8	1.3	2.2	3.5	5.0	6.1	7.6	13.1
Atlanta	3,229	0.8	0.0	0.2	0.3	0.3	0.4	0.7	1.1	1.4	1.7	2.2	10.8
Boston	7,446	0.7	0.0	0.1	0.2	0.3	0.4	0.6	0.9	1.2	1.6	2.6	10.0
Denver	5,363	1.2	0.1	0.2	0.4	0.5	0.7	1.0	1.5	2.2	2.7	3.9	9.3
Houston	5,188	0.7	0.0	0.0	0.1	0.2	0.4	0.6	0.8	1.3	1.7	2.6	4.6
Los Angeles	25,803	1.0	0.0	0.1	0.2	0.3	0.5	0.8	1.3	2.0	2.6	4.0	8.4
New York	9,513	0.9	0.0	0.1	0.2	0.4	0.6	0.8	1.1	1.5	1.8	2.5	5.8
Phoenix	5,348	1.9	0.0	0.3	0.5	0.6	0.9	1.6	2.5	3.5	4.1	5.3	7.8
Pittsburgh	7,497	0.6	0.0	0.0	0.0	0.1	0.2	0.5	0.8	1.1	1.4	2.0	6.7
Seattle	1,079	1.5	0.2	0.4	0.5	0.7	0.9	1.3	1.8	2.4	2.9	4.3	5.9
St. Louis	3,216	0.8	0.0	0.1	0.3	0.4	0.5	0.6	0.9	1.3	1.7	2.7	5.7
Not in the 11 cities	230,161	0.9	0.0	0.0	0.1	0.2	0.4	0.7	1.2	1.8	2.4	3.8	39.0

[a]CO monitoring is only available for quarters 1 and 4; since monitoring data are not available year-round, Anchorage is not included in the nationwide statistics shown in this table.

Table 3-8 contains the distribution of 1-h daily max CO concentrations derived from 1-h values reported to AQS for all monitors meeting the inclusion criteria described earlier. The nationwide mean, median, and interquartile range for 1-h daily max concentrations reported for 2005-2007 were 0.9, 0.7 and 0.8 ppm, respectively. Roughly one-third of the 1-h daily max data fall below the LOD for the majority of CO monitors reporting to AQS. The 99th percentile 1-h daily max

concentrations ranged from 2.0 ppm to 5.3 ppm in the selected cities with year-round monitoring; Anchorage had a 99th percentile concentration of 7.6 ppm.

Table 3-9. Distribution of 8-h daily max CO concentration (ppm) derived from AQS data.

				Percentiles									
	N	Mean	Min	1	5	10	25	50	75	90	95	99	Max
NATIONWIDE STATISTICS (N = NUMBER OF OBSERVATIONS)													
2005-2007	303,843	0.7	0.0	0.3	0.3	0.3	0.3	0.5	0.8	1.3	1.7	2.6	10.9
2005	101,184	0.7	0.0	0.3	0.3	0.3	0.3	0.6	0.9	1.4	1.8	2.8	9.7
2006	101,652	0.7	0.0	0.3	0.3	0.3	0.3	0.5	0.8	1.3	1.7	2.6	9.8
2007	101,007	0.6	0.0	0.3	0.3	0.3	0.3	0.5	0.8	1.2	1.5	2.3	10.9
Winter (December - February)	74,144	0.9	0.0	0.3	0.3	0.3	0.4	0.7	1.1	1.7	2.1	3.2	9.8
Spring (March - May)	77,317	0.6	0.0	0.3	0.3	0.3	0.3	0.5	0.7	1.1	1.3	2.0	9.6
Summer (June - August)	76,562	0.5	0.0	0.3	0.3	0.3	0.3	0.4	0.6	0.9	1.1	1.7	10.9
Fall (September - November)	75,820	0.7	0.0	0.3	0.3	0.3	0.3	0.6	0.9	1.4	1.8	2.7	9.0
NATIONWIDE STATISTICS, POOLED BY SITE (N = NUMBER OF SITES)													
2005-2007	285	0.7	0.2	0.3	0.3	0.4	0.5	0.6	0.8	1.0	1.2	1.7	2.1
2005	285	0.7	0.3	0.3	0.3	0.4	0.5	0.6	0.9	1.1	1.4	1.9	2.2
2006	285	0.7	0.2	0.3	0.3	0.4	0.5	0.6	0.8	1.1	1.2	1.8	2.4
2007	285	0.6	0.2	0.3	0.3	0.4	0.5	0.6	0.7	1.0	1.1	1.6	2.0
Winter (December - February)	285	0.9	0.2	0.3	0.4	0.4	0.6	0.8	1.1	1.4	1.7	2.4	2.6
Spring (March - May)	285	0.6	0.2	0.3	0.3	0.4	0.4	0.5	0.7	0.9	1.1	1.6	2.2
Summer (June - August)	285	0.5	0.2	0.3	0.3	0.3	0.4	0.5	0.6	0.8	0.9	1.5	2.0
Fall (September - November)	285	0.7	0.2	0.3	0.3	0.4	0.5	0.6	0.9	1.2	1.3	1.8	2.2
STATISTICS FOR INDIVIDUAL CSAS/CBSAS (2005-2007) (N = NUMBER OF OBSERVATIONS)													
Anchorage[a]	1,074	1.7	0.3	0.3	0.4	0.6	0.9	1.5	2.3	3.3	3.9	5.0	6.5
Atlanta	3,229	0.6	0.0	0.2	0.2	0.3	0.4	0.5	0.8	1.1	1.3	1.7	2.5
Boston	7,446	0.6	0.3	0.3	0.3	0.3	0.3	0.5	0.7	0.9	1.1	1.8	5.8
Denver	5,363	0.8	0.3	0.3	0.3	0.3	0.5	0.7	1.0	1.4	1.8	2.4	3.4
Houston	5,188	0.5	0.3	0.3	0.3	0.3	0.3	0.4	0.6	0.9	1.1	1.7	3.3
Los Angeles	25,803	0.7	0.3	0.3	0.3	0.3	0.3	0.6	0.9	1.5	1.8	2.7	6.2
New York	9,513	0.7	0.3	0.3	0.3	0.3	0.4	0.6	0.9	1.2	1.4	1.8	3.0
Phoenix	5,348	1.3	0.3	0.3	0.3	0.4	0.6	1.0	1.8	2.5	3.0	3.8	5.8
Pittsburgh	7,497	0.5	0.3	0.3	0.3	0.3	0.3	0.3	0.6	0.9	1.0	1.5	3.7
Seattle	1,079	1.1	0.3	0.3	0.4	0.5	0.7	1.0	1.4	1.8	2.2	3.2	4.0
St. Louis	3,216	0.6	0.3	0.3	0.3	0.3	0.3	0.5	0.7	0.9	1.2	1.9	4.2
Not in the 11 cities	230,161	0.7	0.0	0.3	0.3	0.3	0.3	0.5	0.8	1.3	1.6	2.5	10.9

[a]CO monitoring is only available for quarters 1 and 4; since monitoring data is not available year-round, Anchorage is not included in the nationwide statistics shown in this table.

Table 3-9 contains the distribution of 8-h daily max concentrations derived from the 1-h CO concentrations reported to AQS. This was done by first calculating the average concentration for each successive 8-h period, thereby producing 24 8-h avg per day. The maximum of these values for a given monitor within a given day (midnight-to-midnight) was used as the 8-h daily max statistic for that monitor and day. The nationwide mean, median, and interquartile range for 8-h daily max

concentrations reported for 2005-2007 were 0.7, 0.5, and 0.5 ppm, respectively. Half of the 8-h daily max concentrations fell below the LOD for the majority of CO monitors in the field. The highest 8-h daily max concentration, 10.9 ppm, was recorded at a monitor located 5 mi north of Newkirk, OK (AQS site ID: 400719010). The 99th percentile 8-h daily max concentrations ranged from 1.5 ppm to 3.8 ppm in the selected cities with year-round monitoring; Anchorage had a 99th percentile 8-h daily max concentration of 5.0 ppm.

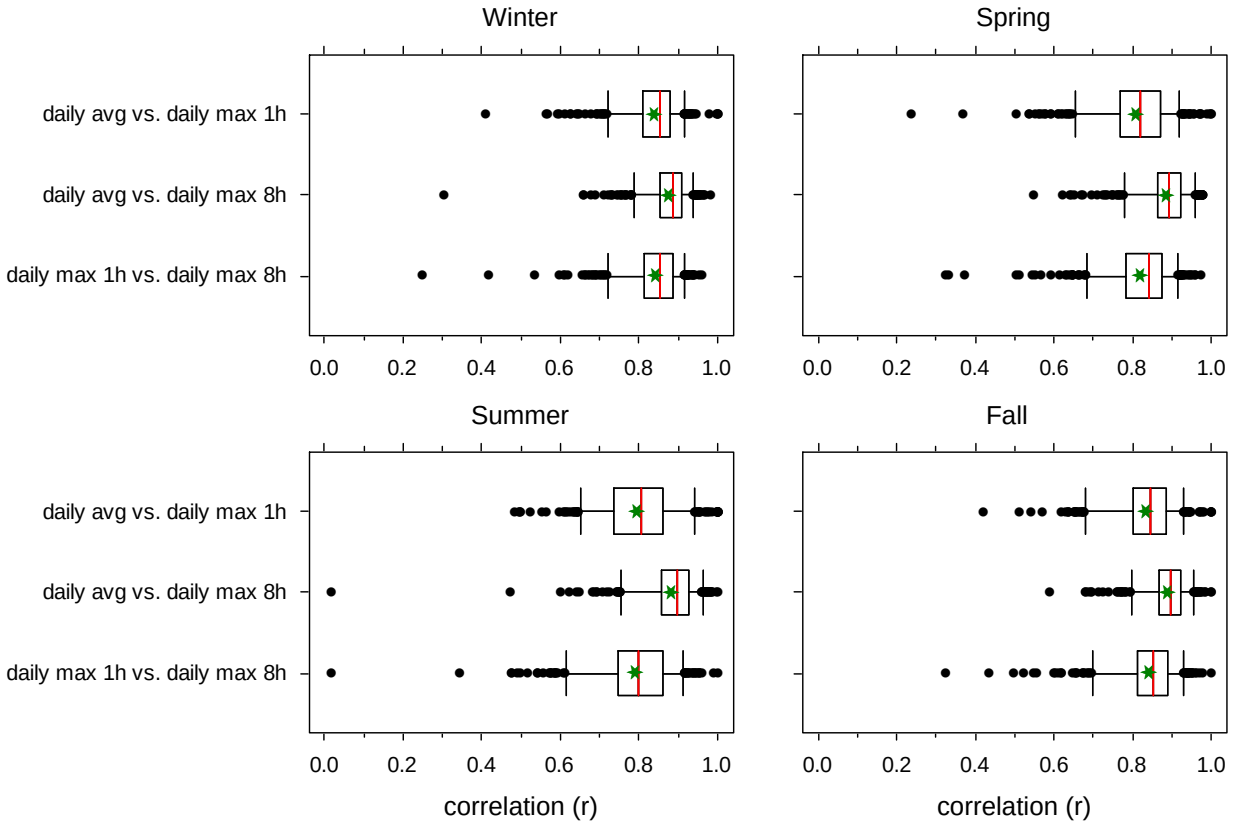


Figure 3-17. Seasonal plots showing the variability in correlations between 24-h avg CO concentration with 1-h daily max and 8-h daily max CO concentrations and between 1-h daily max and 8-h daily max CO concentrations. Red bars denote the median, green stars denote the arithmetic mean, the box incorporates the IQR and the whiskers extend to the 5th and 95th percentiles. Correlations outside the 5th and 95th percentiles are shown as individual points.

Table 3-7 through Table 3-9 show distributions of CO data based on the 24-h avg, 1-h daily max and 8-h daily max concentration. The current standards are based on 1-h and 8-h calculations. While the nationwide concentrations vary in absolute magnitude based on these three statistics, the shape of the distributions are quite similar up to the 99th percentile. The relative increase from the 99th percentile to the max for the 1-h daily max is larger than for the 24-h or 8-h daily max. This is to be expected since this statistic is more sensitive to short-term (less than 8 h) increases in CO concentration. Box plots showing the range in Pearson correlation coefficients (r) between the different statistics are shown in Figure 3-17. Included are the correlation of the 24-h avg with the 1-h daily max and 8-h daily max, as well as the correlation between the 1-h daily max and 8-h daily max, all calculated using the same 2005-2007 data set stratified by season. Correlations are generally quite high across all seasons and all comparisons, with median $r > 0.8$. Correlations are higher on average in the wintertime compared to the summertime for the two comparisons involving the 1-h daily max

statistic. The correlations between the 24-h avg and the 8-h daily max are the highest in all seasons, which is in agreement with the distributional similarities shown in the preceding tables.

3.5.1.2. Urban Scale

This section describes urban variability in CO concentrations reported to AQS at the individual CSA/CBSA level. Denver, CO, and Los Angeles, CA, were selected for this assessment to illustrate the variability in CO concentrations measured across contrasting metropolitan regions. Information on the other nine cities evaluated for this assessment is included in Appendix A. Maps of the Denver CSA and the Los Angeles CSA shown in Figure 3-18 and Figure 3-21, respectively, illustrate the location of all CO monitors meeting the inclusion criteria described earlier. Letters on the maps identify the individual monitor locations and correspond with the letters provided in the accompanying concentration box plots (Figure 3-19 and Figure 3-22) and pair-wise monitor comparison tables (Table 3-10 and Table 3-11). The box plots for each monitor include the hourly CO concentration median and interquartile range with whiskers extending from the 5th to the 95th percentile. Data from 2005-2007 were used to generate the box plots, which are stratified by season as follows: 1 = winter (December-February), 2 = spring (March-May), 3 = summer (June-August), and 4 = fall (September-November). The comparison tables include the Pearson correlation coefficient (r), the 90th percentile of the absolute difference in concentrations (P90) in ppm, the coefficient of divergence (COD) and the straight-line distance between monitor pairs (d) in km. The COD provides an indication of the variability across the monitoring sites within each CSA/CBSA and is defined as follows:

$$COD_{jk} = \sqrt{\frac{1}{p}\sum_{i=1}^{p}\left(\frac{X_{ij} - X_{ik}}{X_{ij} + X_{ik}}\right)^2}$$

Equation 3-1

where X_{ij} and X_{ik} represent the observed hourly concentrations for time period i at sites j and k, and p is the number of paired hourly observations. A *COD* of 0 indicates there are no differences between concentrations at paired sites (spatial homogeneity), while a *COD* approaching 1 indicates extreme spatial heterogeneity. Pearson correlation is also plotted as a function of distance for Denver and Los Angeles in Figure 3-20 and Figure 3-23, respectively. Similar maps, box plots, and comparison tables for the nine remaining CSAs/CBSAs are included in Annex A.

The information contained in these figures and tables should be used with some caution since many of the reported concentrations for the years 2005-2007 are near or below the monitors' stated LOD. Because ambient concentrations are now in large part very near or below the 0.5 ppm LOD for the majority of FRMs and the coarsely reported measurement resolution is 0.1 ppm, the comparison statistics shown in these tables might be biased to exhibit specious heterogeneity in the box plots.

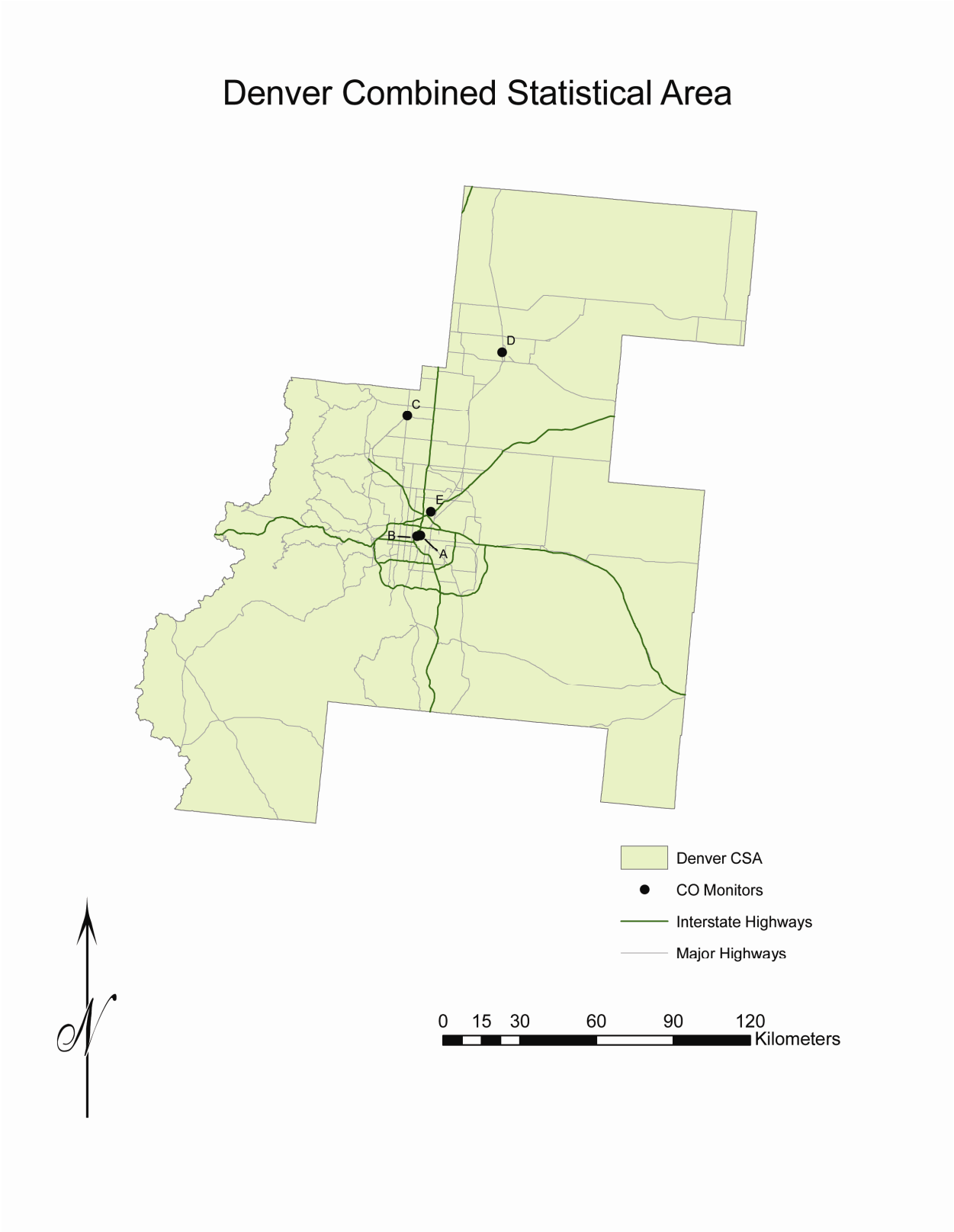


Figure 3-18. Map of CO monitor locations and major highways for Denver, CO.

	A	B	C	D	E
Site ID	08-031-0002	08-031-0019	08-013-0009	08-123-0010	08-001-3001
Mean	0.65	0.52	0.42	0.55	0.52
SD	0.42	0.46	0.38	0.46	0.36
Obs	25959	25552	25559	26048	25920
Scale	Micro	Micro	Micro	Neighbor-hood	Neighbor-hood

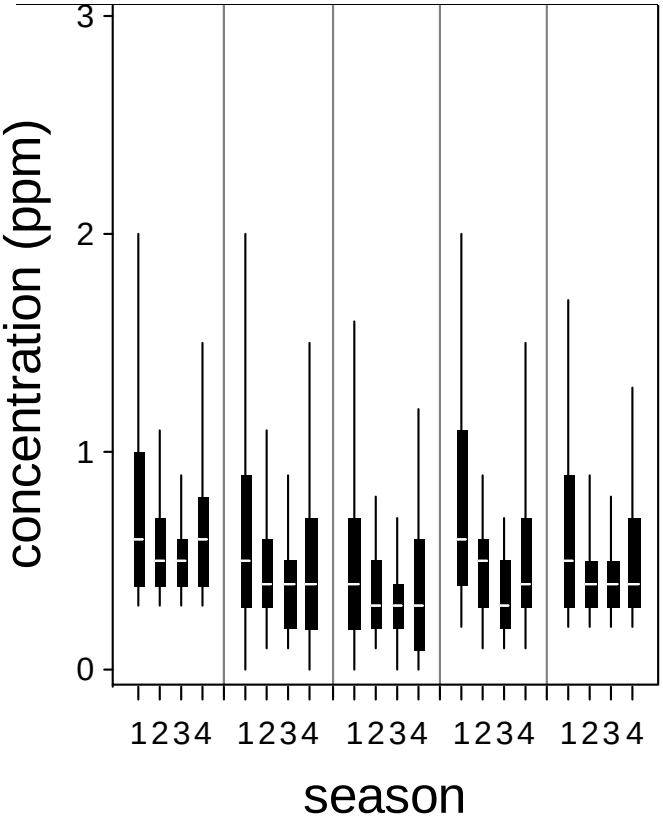


Figure 3-19. Box plots illustrating the distribution of 2005-2007 hourly CO concentrations in Denver, CO. The data are stratified by season along the x-axis where 1 = winter, 2 = spring, 3 = summer, and 4 = fall. The box plots show the median and interquartile range with whiskers extending from the 5th to the 95th percentile. Identifiers and statistics for each site are shown at the top of the figure.

Table 3-10. Table of intersampler comparison statistics, as defined in the text, including Pearson r, P90 (ppm), COD and d (km) for each pair of hourly CO monitors reporting to AQS for 2005-2007 in Denver, CO. The table is grouped and identified by monitoring scale.

		Micro			Neighborhood	
		A	B	C	D	E
Micro	A	1.00	0.76	0.46	0.45	0.59
		0.0	0.5	0.7	0.7	0.6
		0.00	0.34	0.44	0.36	0.29
		0	1.3	46.9	78.3	10.1
	B		1.00	0.49	0.46	0.64
			0.0	0.7	0.7	0.5
			0.00	0.47	0.42	0.37
			0	47.0	79.0	10.9
	C			1.00	0.54	0.53
				0.0	0.6	0.6
				0.00	0.43	0.43
				0	44.6	38.5
Neighborhood	D				1.00	0.52
					0.0	0.6
					0.00	0.34
			Legend		0	68.2
	E		r			1.00
			P90			0.0
			COD			0.00
			d			0

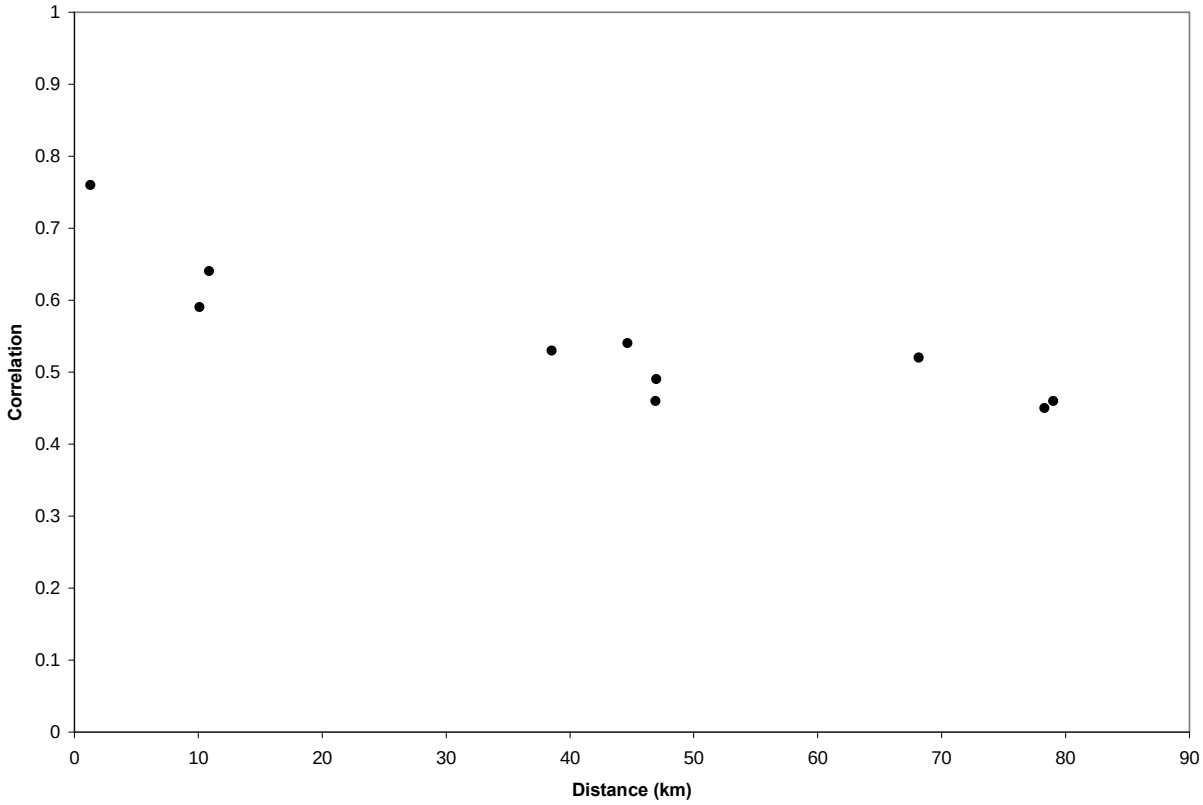


Figure 3-20. Intersampler correlation versus distance for monitors located within the Denver CSA.

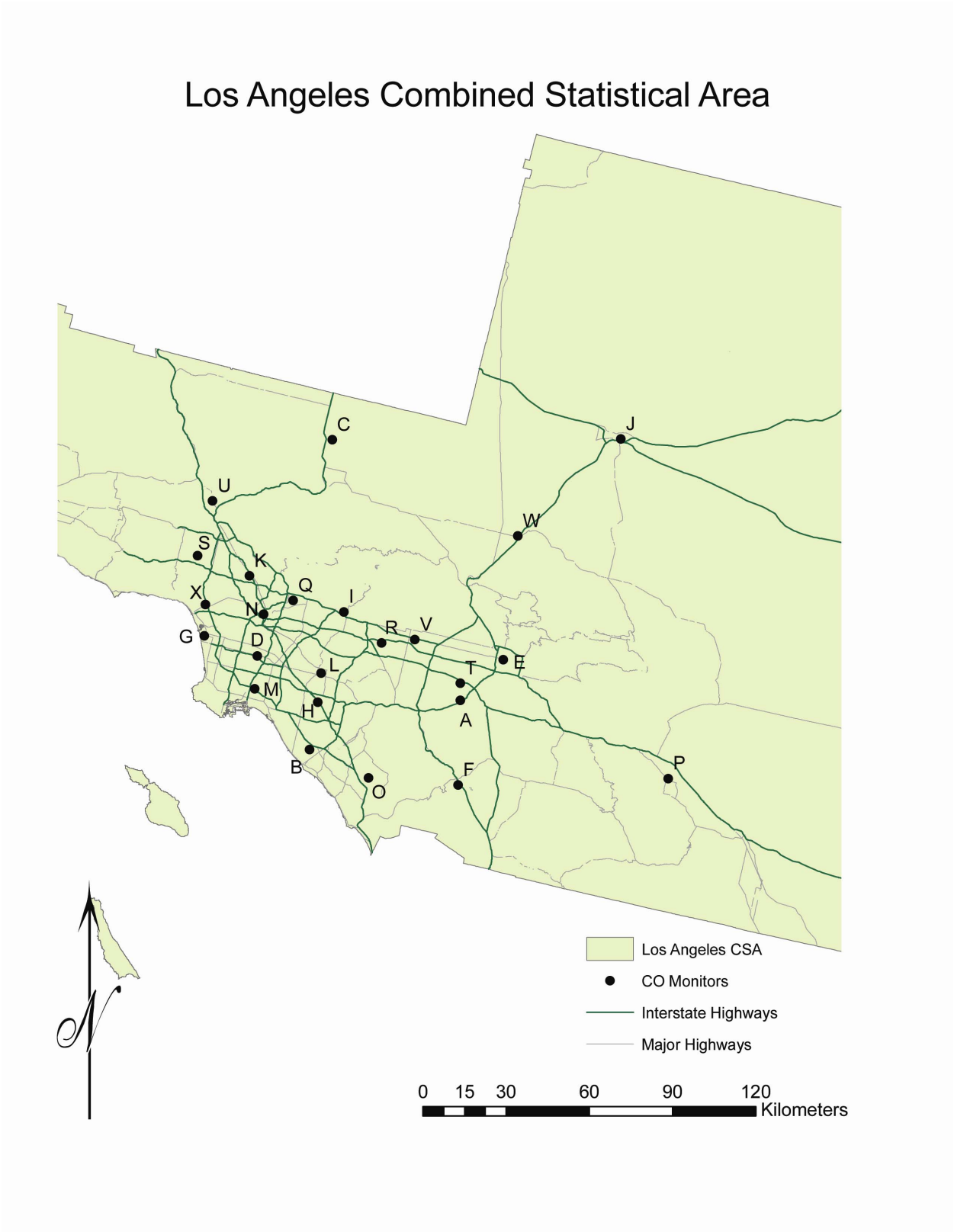


Figure 3-21. Map of CO monitor locations and major highways for Los Angeles, CA.

	A	B	C	D	E	F	G	H
Site ID	06-065-1003	06-059-1003	06-037-9033	06-037-1301	06-071-9004	06-065-9001	06-037-5005	06-059-0007
Mean	0.67	0.31	0.23	0.98	0.53	0.29	0.24	0.42
SD	0.42	0.47	0.29	0.89	0.38	0.20	0.37	0.46
Obs	24885	24760	24135	24825	24844	24792	24965	24264
Scale	Micro	Middle	Middle	Middle	Middle	Neighbor-hood	Neighbor-hood	Urban

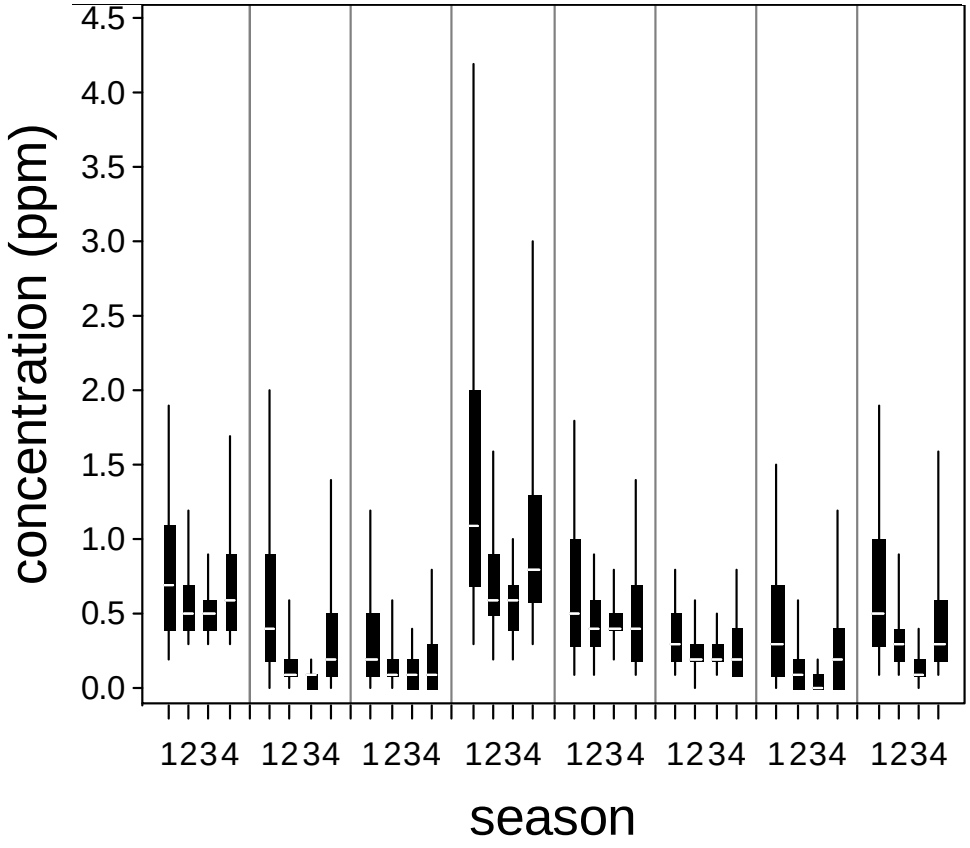
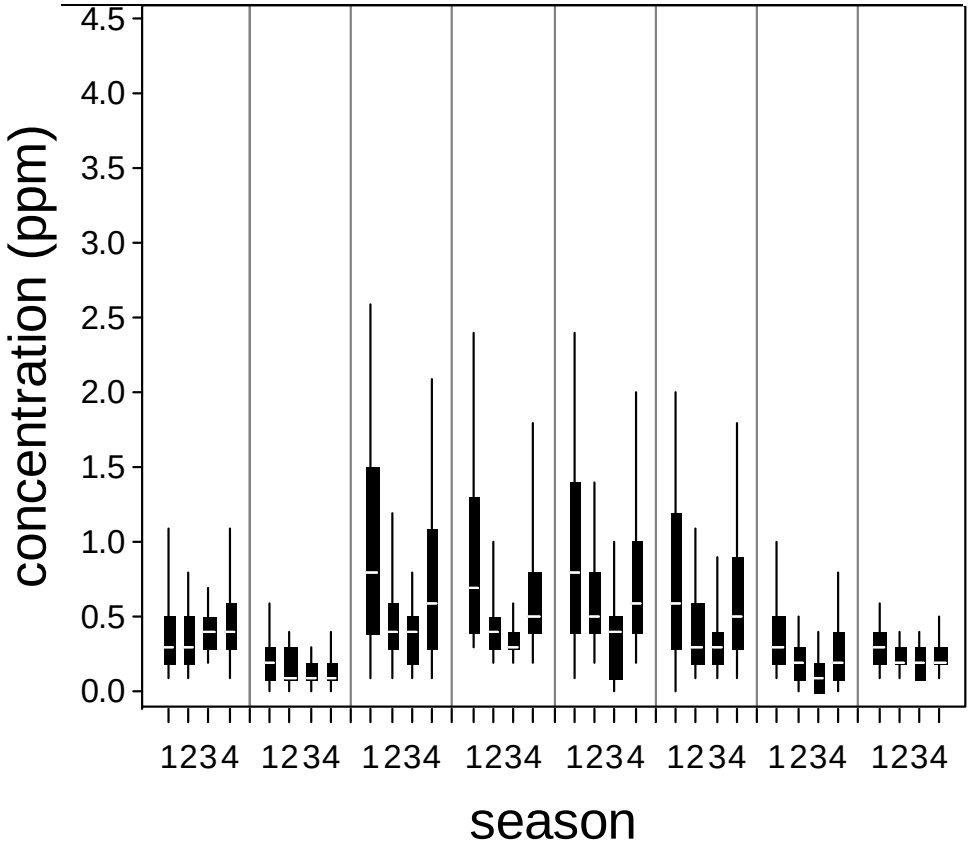


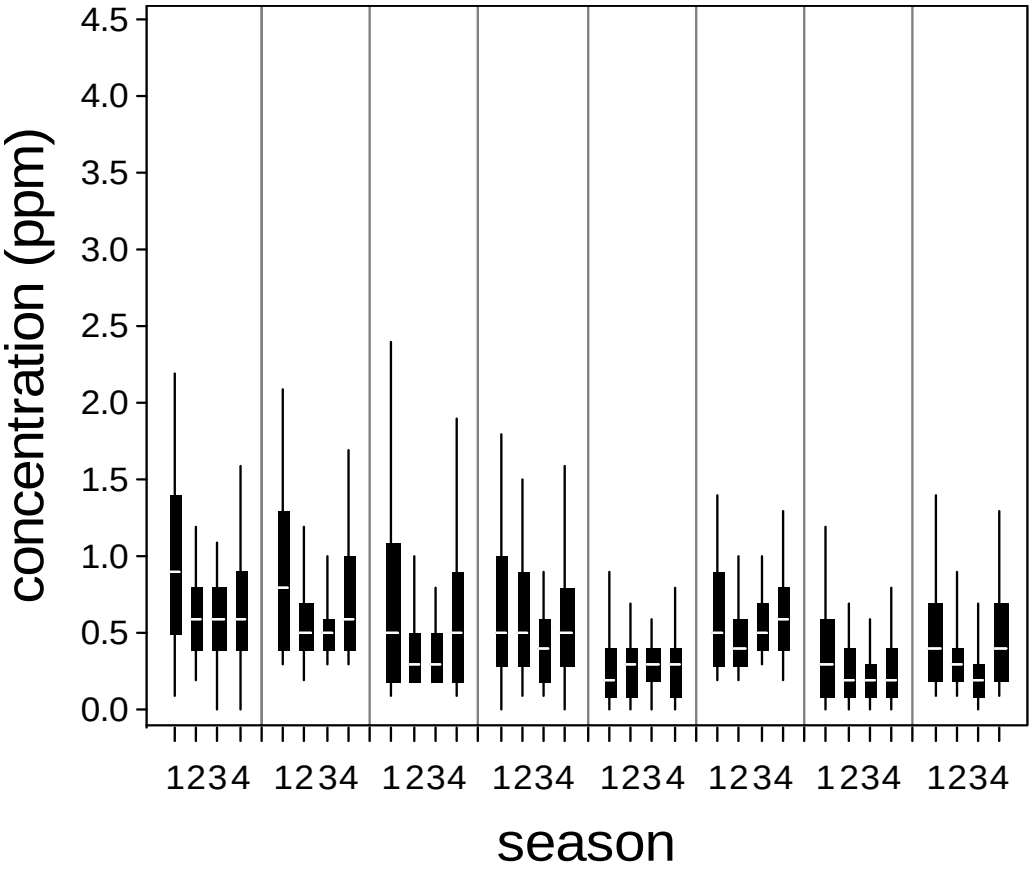
Figure 3-22. Box plots illustrating the distribution of 2005-2007 hourly CO concentrations in Los Angeles, CA. The data are stratified by season along the x-axis where 1 = winter, 2 = spring, 3 = summer, and 4 = fall. The box plots show the median and interquartile range with whiskers extending from the 5th to the 95th percentile. Identifiers and statistics for each site are shown at the top of the figure (monitors without scale designations in AQS are labeled Null). Part 1 of 3 of Figure 3-22. See the next two pages for parts 2 and 3 of Figure 3-22.

	I	J	K	L	M	N	O	P
Site ID	06-037-0002	06-071-0001	06-037-1002	06-059-5001	06-037-4002	06-037-1103	06-059-2022	06-065-5001
Mean	0.42	0.17	0.66	0.62	0.69	0.56	0.26	0.25
SD	0.27	0.17	0.59	0.55	0.56	0.50	0.25	0.14
Obs	2,5001	24105	24892	24705	24259	24645	24831	24938
Scale	Null	Null	Null	Null	Null	Null	Null	Null



Part 2 of 3 for Figure 3-22

	Q	R	S	T	U	V	W	X
Site ID	06-037-2005	06-037-1701	06-037-1201	06-065-8001	06-037-6012	06-071-1004	06-071-0306	06-037-0113
Mean	0.72	0.69	0.57	0.60	0.30	0.59	0.30	0.41
SD	0.48	0.45	0.54	0.46	0.25	0.32	0.28	0.36
Obs	24804	24912	24281	24778	24860	24767	24796	24916
Scale	Null	Null	Null	Null	Null	Null	Null	Null



Part 3 of 3 for Figure 3-22

Table 3-11. Table of intersampler comparison statistics, as defined in the text, including Pearson r, P90 (ppm), COD and d (km) for each pair of hourly CO monitors reporting to AQS for 2005-2007 in Los Angeles, CA. The table is grouped and identified by monitoring scale (monitors without scale designations in AQS are labeled Null).

		Micro	Middle				Neighborhood		Urban	Null															
		A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X
Micro	A	1.00	0.56	0.56	0.54	0.73	0.72	0.45	0.62	0.54	0.35	0.70	0.66	0.46	0.62	0.61	0.48	0.53	0.78	0.73	0.67	0.54	0.70	0.55	0.57
		0.0	0.8	0.9	1.1	0.5	0.7	0.9	0.7	0.7	1.0	0.6	0.6	0.8	0.6	0.8	0.9	0.7	0.4	0.6	0.6	0.8	0.5	0.8	0.7
		0.00	0.66	0.67	0.30	0.30	0.46	0.73	0.46	0.33	0.68	0.29	0.24	0.39	0.37	0.58	0.47	0.35	0.19	0.29	0.37	0.53	0.20	0.54	0.42
		0	57.1	104.6	74.8	21.3	30.5	95.0	51.3	52.6	110.6	88.2	51.0	74.1	77.4	43.3	80.1	70.1	35.0	108.0	6.1	114.5	27.4	62.8	98.1
Middle	B		1.00	0.55	0.67	0.50	0.46	0.60	0.75	0.14	0.28	0.70	0.72	0.64	0.58	0.62	0.34	0.50	0.60	0.57	0.40	0.25	0.36	0.55	0.47
			0.0	0.6	1.3	0.7	0.5	0.5	0.5	0.7	0.7	0.9	0.7	0.9	0.8	0.5	0.6	0.9	0.9	0.8	0.9	0.7	0.8	0.6	0.7
			0.00	0.66	0.70	0.64	0.59	0.69	0.55	0.64	0.69	0.63	0.62	0.64	0.63	0.56	0.59	0.68	0.66	0.62	0.67	0.67	0.65	0.62	0.59
			0	112.0	38.6	76.9	55.1	55.8	17.3	51.2	158.5	66.3	27.9	29.5	51.6	23.7	129.6	54.0	46.3	80.7	59.3	96.2	54.9	107.5	64.4
	C			1.00	0.55	0.50	0.50	0.39	0.56	0.27	0.45	0.59	0.63	0.43	0.53	0.51	0.41	0.45	0.61	0.53	0.41	0.40	0.49	0.67	0.42
				0.0	1.6	0.7	0.4	0.6	0.7	0.6	0.4	1.1	0.9	1.1	0.9	0.4	0.4	1.0	0.9	0.9	0.9	0.5	0.7	0.4	0.7
				0.00	0.72	0.64	0.57	0.74	0.60	0.62	0.62	0.65	0.64	0.69	0.63	0.61	0.56	0.70	0.66	0.62	0.67	0.62	0.65	0.57	0.60
				0	82.5	100.4	132.5	84.4	94.7	62.2	104.0	57.4	84.2	94.0	67.5	122.7	171.9	59.6	75.4	64.0	99.2	48.4	77.9	75.4	74.9
	D				1.00	0.44	0.39	0.63	0.71	0.21	0.33	0.70	0.78	0.70	0.74	0.57	0.28	0.53	0.65	0.49	0.35	0.23	0.39	0.51	0.50
					0.0	1.3	1.6	1.5	1.1	1.5	1.7	0.9	0.9	1.0	1.0	1.5	1.7	1.0	1.0	1.2	1.2	1.6	1.3	1.5	1.3
					0.00	0.42	0.56	0.76	0.51	0.44	0.73	0.35	0.30	0.39	0.41	0.65	0.56	0.39	0.29	0.41	0.45	0.60	0.35	0.61	0.50
					0	88.6	86.0	20.4	27.4	35.0	152.6	29.1	23.8	11.8	15.3	59.5	154.5	23.8	45.0	42.1	73.7	58.2	57.0	103.4	26.4
	E					1.00	0.69	0.43	0.55	0.48	0.31	0.65	0.55	0.39	0.58	0.51	0.46	0.52	0.68	0.71	0.64	0.50	0.64	0.51	0.53
						0.0	0.6	0.8	0.6	0.6	0.8	0.7	0.7	0.9	0.6	0.6	0.7	0.7	0.6	0.6	0.6	0.6	0.5	0.6	0.6
						0.00	0.42	0.72	0.46	0.35	0.65	0.35	0.33	0.46	0.39	0.56	0.43	0.41	0.31	0.32	0.41	0.51	0.29	0.52	0.41
						0	48.0	108.0	68.5	59.9	90.2	96.3	65.7	90.1	87.9	64.6	73.3	78.6	44.2	116.3	17.7	119.3	32.7	44.9	109.1
Neighborhood	F						1.00	0.43	0.53	0.56	0.30	0.58	0.55	0.36	0.53	0.51	0.49	0.47	0.69	0.66	0.66	0.56	0.68	0.49	0.55
							0.0	0.5	0.6	0.4	0.4	1.0	0.8	1.1	0.8	0.3	0.3	0.9	0.8	0.8	0.8	0.3	0.6	0.4	0.5
							0.00	0.70	0.42	0.38	0.58	0.46	0.43	0.54	0.46	0.50	0.32	0.53	0.46	0.40	0.49	0.47	0.43	0.47	0.39
							0	106.1	58.7	74.8	137.8	106.5	63.7	81.1	93.4	32.4	75.7	89.2	58.1	125.1	36.6	135.3	54.8	92.3	112.0
	G							1.00	0.58	0.19	0.18	0.64	0.59	0.59	0.59	0.42	0.26	0.40	0.51	0.52	0.43	0.24	0.27	0.41	0.59
								0.0	0.6	0.7	0.6	1.0	0.8	1.0	0.8	0.5	0.5	1.0	1.0	0.9	0.9	0.6	0.9	0.6	0.6
								0.00	0.71	0.72	0.75	0.72	0.72	0.75	0.73	0.73	0.70	0.75	0.73	0.72	0.74	0.73	0.73	0.72	0.69
								0	47.4	51.0	166.0	27.0	44.2	26.4	22.7	78.3	174.8	34.4	63.9	29.1	93.7	48.7	75.8	118.6	11.4
Urban	H								1.00	0.29	0.31	0.72	0.81	0.63	0.70	0.67	0.37	0.54	0.69	0.61	0.49	0.29	0.47	0.54	0.59
									0.0	0.6	0.8	0.7	0.5	0.8	0.6	0.5	0.7	0.8	0.7	0.7	0.8	0.7	0.7	0.6	0.5
									0.00	0.43	0.62	0.41	0.38	0.48	0.40	0.46	0.41	0.52	0.44	0.41	0.49	0.53	0.45	0.50	0.39
									0	33.9	144.7	51.8	10.5	23.2	37.3	32.9	129.2	37.7	31.4	68.3	51.7	81.8	41.6	93.7	53.7
Null	I									1.00	0.17	0.43	0.34	0.17	0.46	0.42	0.33	0.41	0.57	0.44	0.47	0.43	0.61	0.24	0.45
										0.0	0.6	1.0	0.8	1.1	0.8	0.5	0.5	0.8	0.8	0.7	0.8	0.5	0.5	0.6	0.5
										0.00	0.62	0.35	0.33	0.47	0.38	0.52	0.36	0.43	0.33	0.33	0.43	0.47	0.30	0.50	0.38
										0	117.7	36.5	23.6	42.4	29.0	60.6	131.4	18.7	17.7	56.5	49.2	61.9	27.4	68.4	50.0
	J										1.00	0.35	0.34	0.24	0.34	0.33	0.29	0.31	0.40	0.31	0.19	0.25	0.36	0.43	0.25
											0.0	1.2	1.0	1.3	1.0	0.4	0.3	1.1	1.1	1.0	1.1	0.5	0.8	0.4	0.7
											0.00	0.67	0.66	0.70	0.66	0.63	0.55	0.71	0.68	0.64	0.69	0.62	0.66	0.59	0.62
											0	142.7	137.1	159.7	143.4	152.3	123.6	131.7	113.3	158.2	105.4	148.8	103.7	51.0	161.1
	K											1.00	0.75	0.62	0.84	0.69	0.40	0.67	0.78	0.74	0.52	0.39	0.59	0.58	0.69
												0.0	0.6	0.8	0.5	1.0	1.2	0.7	0.5	0.6	0.8	1.1	0.7	1.0	0.8
												0.00	0.26	0.41	0.29	0.56	0.46	0.39	0.26	0.28	0.42	0.52	0.29	0.53	0.38
												0	43.6	40.8	14.7	84.6	167.7	18.1	53.5	20.0	85.3	30.1	63.8	97.8	18.9
	L												1.00	0.62	0.74	0.67	0.40	0.58	0.77	0.61	0.50	0.34	0.54	0.58	0.59
													0.0	0.7	0.5	0.8	1.0	0.7	0.5	0.7	0.8	0.9	0.6	0.8	0.6
													0.00	0.37	0.31	0.54	0.42	0.37	0.20	0.29	0.38	0.52	0.25	0.51	0.37
													0	24.6	29.8	41.5	130.6	28.1	24.3	61.5	50.2	73.4	35.8	86.4	48.5
	M													1.00	0.60	0.48	0.24	0.41	0.52	0.44	0.31	0.15	0.28	0.43	0.43
														0.0	0.8	1.1	1.2	0.9	0.8	0.9	1.0	1.2	0.9	1.1	0.9
														0.00	0.45	0.58	0.53	0.46	0.38	0.44	0.48	0.60	0.41	0.59	0.48
														0	27.1	52.1	152.4	34.7	48.6	52.3	74.0	69.4	60.3	109.6	35.2
	N														1.00	0.63	0.32	0.67	0.77	0.64	0.49	0.34	0.57	0.51	0.71
															0.0	0.8	1.0	0.7	0.5	0.7	0.8	0.9	0.6	0.8	0.6
															0.00	0.55	0.46	0.44	0.33	0.34	0.45	0.52	0.36	0.53	0.38
															0	70.2	157.4	11.7	43.8	31.8	75.1	44.7	55.2	95.9	21.2
	O															1.00	0.44	0.55	0.70	0.55	0.43	0.28	0.57	0.45	0.57
																0.0	0.3	0.9	0.9	0.8	0.9	0.5	0.7	0.4	0.6
																0.00	0.47	0.62	0.58	0.54	0.59	0.59	0.56	0.56	0.50
																0	107.9	69.5	48.9	101.2	47.5	114.6	52.6	102.5	85.9

Legend
r
P90
COD
d

		Micro	Middle	Neighborhood	Urban	Null								
Null	P					1.00	0.39	0.47	0.42	0.40	0.40	0.47	0.38	0.35
						0.0	1.0	1.0	0.9	0.9	0.4	0.7	0.4	0.6
						0.00	0.54	0.47	0.40	0.50	0.45	0.43	0.44	0.38
						0	149.6	114.2	187.6	82.4	192.2	104.2	102.8	178.1
	Q						1.00	0.65	0.54	0.39	0.32	0.53	0.46	0.49
							0.0	0.6	0.8	0.8	1.0	0.7	0.9	0.8
							0.00	0.34	0.42	0.46	0.58	0.35	0.59	0.49
							0	35.4	38.0	67.2	46.2	46.0	84.3	31.6
	R							1.00	0.70	0.60	0.47	0.78	0.58	0.63
								0.0	0.6	0.7	0.9	0.5	0.9	0.7
								0.00	0.30	0.38	0.53	0.18	0.54	0.41
								0	73.4	31.8	79.6	12.0	62.4	65.0
	S								1.00	0.62	0.53	0.58	0.55	0.64
									0.0	0.7	0.8	0.6	0.8	0.7
									0.00	0.40	0.49	0.30	0.50	0.34
									0	105.2	20.4	83.8	115.6	17.8
	T									1.00	0.46	0.54	0.38	0.55
										0.0	0.9	0.6	0.9	0.7
										0.00	0.56	0.37	0.58	0.46
										0	110.8	22.8	57.0	96.1
	U										1.00	0.53	0.39	0.36
											0.0	0.6	0.5	0.6
											0.00	0.51	0.54	0.50
											0	88.3	110.7	37.4
	V											1.00	0.47	0.50
												0.0	0.7	0.6
												0.00	0.52	0.40
												0	52.7	76.4
	W												1.00	0.41
													0.0	0.6
													0.00	0.50
													0	115.3
	X													1.00
														0.0
														0.00
														0

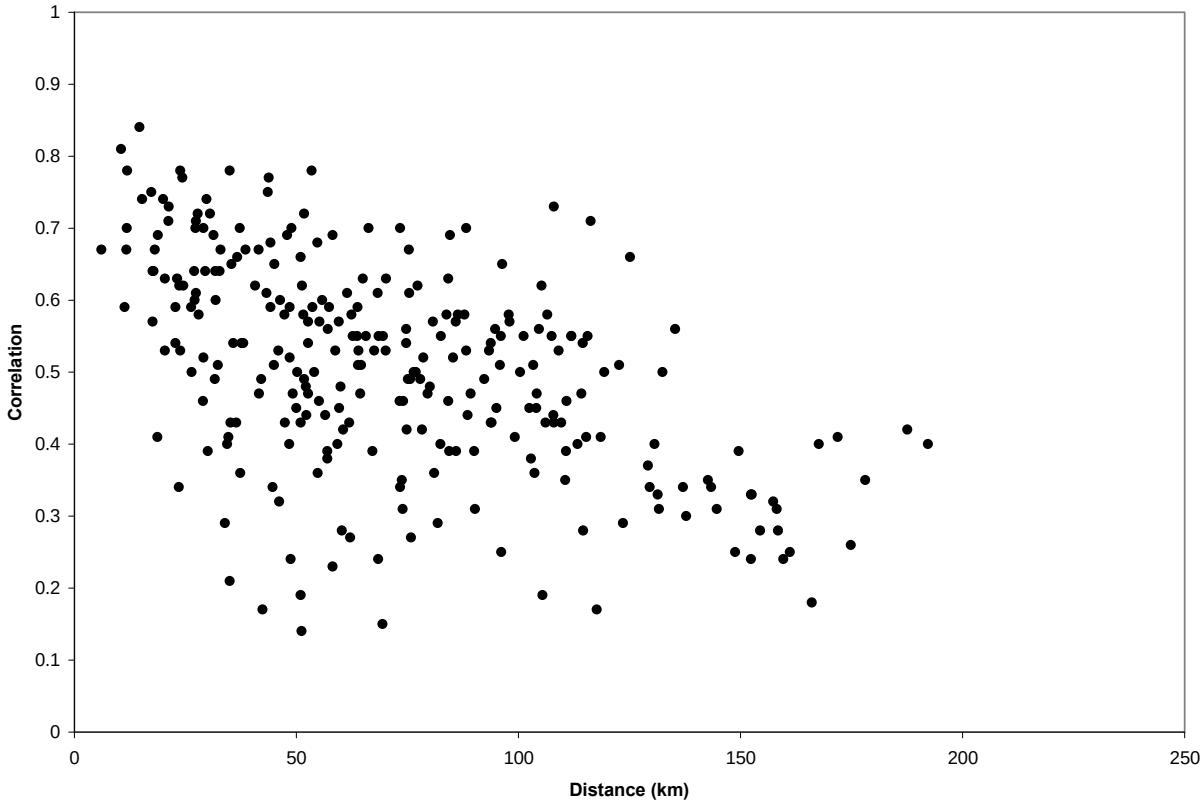


Figure 3-23. Intersampler correlation versus distance for monitors located within the Los Angeles CSA.

The Denver CSA in Figure 3-18 incorporates an area of 33,723 km^2 with a maximum straight-line distance between CO monitors of 79 km. Of the five CO monitors meeting the inclusion criteria, three were sited for microscale monitoring and two were sited for neighborhood scale monitoring. Sites A and B are located in downtown Denver while Site E is located in an industrial region north of town and surrounded on three sides by three heavily-traveled interstate highways. Sites C and D are located in two smaller towns (Longmont and Greeley, respectively) north of Denver. The means and seasonal patterns shown in Figure 3-19 are similar for all five monitors within this CSA. The highest annual mean concentration (0.7 ppm) was observed at Site A, a downtown microscale monitor, while the lowest annual mean concentration (0.4 ppm) was observed at Site C, a microscale monitor in Longmont. The step-wise nature of the box plots is attributed to the 0.1 ppm resolution of the CO monitors used in the Denver CSA. Because these monitors have LOD of 0.5 ppm, it is also likely that the means and statistical distributions are biased as well.

The Los Angeles CSA in Figure 3-21 incorporates an area of 88,054 km^2 and a maximum straight-line distance between monitors of 192 km, making it more than twice the size of the Denver CSA. Of the 11 CSAs/CBSAs investigated, Los Angeles had the largest number of CO monitors (N = 24) meeting the inclusion criteria. One monitor was sited for microscale, four for middle scale, two for neighborhood scale, and one for urban scale. The remaining 16 monitors did not contain a siting classification in AQS. The monitors were evenly distributed around the Los Angeles and Riverside areas, with outlying monitors in Santa Clarita (Site U), Lancaster (Site C), Victorville (Site W), Barstow (Site J) and Palm Springs (Site P). A large amount of variability is present in the means and seasonal patterns displayed in Figure 3-22. Generally speaking, lower annual mean concentrations (<0.3 ppm) were measured in the outlying towns including those listed above as well as Lake Elsinore (Site F) and Mission Viejo (Site O). In addition, a neighborhood scale upwind background site (Site G) located on the grounds of the Los Angeles International Airport and 1.5 km from the

Pacific Ocean reported a relatively low mean annual concentration of 0.2 ppm. The highest annual mean concentration (1.0 ppm) was observed at Site D, a middle scale maximum concentration site located 25 m from a busy surface street and adjacent to the Imperial Shopping Mall. This site is also 180 m from a major highway intersection and 350 m from Interstate 105. The step-wise nature of the box plots is attributed to the 0.1 ppm resolution of the CO monitors used in the Los Angeles CSA. Because these monitors have LOD of 0.5 ppm, it is also likely that the means and statistical distributions are biased as well.

The pair-wise comparisons for measurements at the monitors in each of the 11 CSAs/CBSAs included in this analysis reveal a wide range of response between monitors in each city and among the cities judged against each other (Table 3-10, Table 3-11 and Annex Tables A-9 through A-16). While this wide range is produced by the interactions of many physical and chemical elements, the location of each monitor and the uniqueness of its immediate surroundings can often explain much of the agreement or lack thereof.

For the monitor comparisons within the Denver CSA (Table 3-10 and Figure 3-20), the correlations tend to be inversely related to the monitor separation distance, with the highest correlation ($r = 0.76$) for the two downtown Denver monitors (Sites A and B) separated by 1.3 km and the lowest correlations ($r \leq 0.46$) between the downtown Denver monitors and the Greeley monitor (Site D) located roughly 80 km north. While Sites A and B have a high correlation, the comparative magnitudes of the concentrations measured at these two sites, as determined by the P90 and COD, is comparable to comparisons with much less proximal monitors. This is likely caused by the location of these two monitors on opposite sides of downtown Denver, as illustrated by the aerial view of monitors A and B in Figure 3-24. While there is no prevailing wind direction in Denver, the wind comes from the south-southwest with a slightly higher frequency than other directions, making Site A downwind of the urban core more frequently than Site B. Assuming traffic within the urban core is a major source of CO, this would explain the higher mean concentrations measured at Site A relative to Site B despite their close proximity.

Greater variability in the pair-wise comparison statistics is observed in the Los Angeles CSA compared to the Denver CSA, partially due to the greater number of monitors spread over a larger area. Factors other than the distance between monitors, however, can contribute substantially to concentration disparities observed between monitors. To illustrate this point, Site S (located in Reseda, a suburb in the Simi Valley northwest of Los Angeles) correlates well ($r = 0.73$) with Site A (located 108 km to the southeast in Riverside). In fact, Site S correlates well ($r > 0.62$) with Sites A, E, F and T, all east of Los Angeles and all over 100 km away. Site S is located in a densely populated urban area with a mixture of commercial and residential land whereas the other four sites are located in less densely populated regions with commercial, residential and undeveloped land. Sites S and T contain no monitoring scale information in AQS, but Sites A, E and F are classified as microscale, middle scale and neighborhood scale, respectively. In contrast to the above example, Sites I and Q are located only 19 km apart in Azusa and Pasadena, respectively, and they correlate less well ($r = 0.41$). While these two locations are relatively close in proximity with similar topography, the siting of the two monitors is quite different. Site I in Azusa is located 700 m from I-210 in a mixed use community containing warehouses, small industry, housing and a gravel operation (Figure 3-25) while Site Q in Pasadena is located between a large residential neighborhood and the California Institute of Technology campus (Figure 3-26). Neither of these sites has monitoring scale designations reported in AQS. The contrasting CO emission sources surrounding these two monitors result in disparate concentrations with poor correlations despite their close proximity. Topography and micrometeorology can also play an important role in the correlation between monitors. For example, Sites C and P are isolated from the other sites in the Los Angeles CSA by the San Gabriel Mountains and the San Bernardino Mountains, respectively, resulting in lower than average concentrations (Figure 3-22) and relatively low pair-wise correlations (Table 3-11) for these two sites. This analysis demonstrates that agreement between monitors on an urban scale is a complex function of monitor siting, location relative to sources, geography, and micrometeorology.

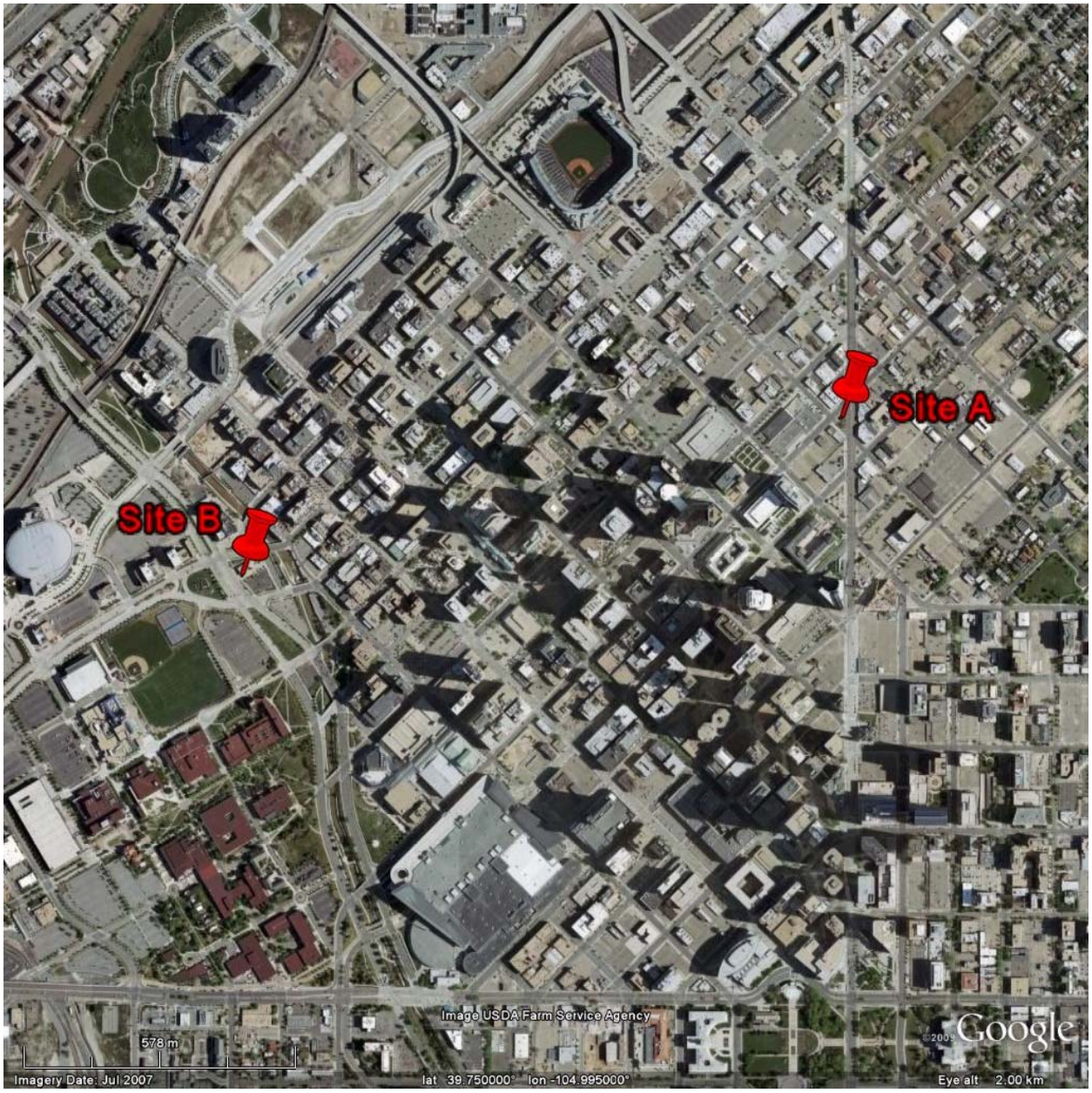


Figure 3-24. Aerial view of the location of CO monitors A and B (marked by the red pins) in Denver, CO, depicting their proximity to the urban core. Scale: 1 cm = 145 m.

Figure 3-25. Aerial view of the location of CO monitor I (marked by the red pin) in Azusa, CA (Los Angeles CSA), depicting its proximity to mixed use land. Scale: 1 cm = 145 m.

Figure 3-26. Aerial view of the location of CO monitor Q (marked by the red pin) in Pasadena, CA (Los Angeles CSA), depicting its proximity to a residential neighborhood. Scale: 1 cm = 145 m.

3.5.1.3. Micro- to Neighborhood Scale and the Near-Road Environment

Table 3-12 shows the 2005-2007 nationwide distributional data for all hourly, 1-h daily max, 1-h daily avg, and 8-h daily max CO concentrations broken down by spatial sampling scale. The different sampling scales included in the table (microscale, middle scale, neighborhood scale and urban scale) were defined in Section 3.4.2.1. While monitors classified under all four scales are used for highest concentration monitoring and regulatory compliance, individual monitors are classified by spatial scale to be used for addressing more particular monitoring objectives. Microscale, middle scale, and neighborhood scale monitors are used to quantify source impacts while neighborhood scale and urban scale monitors are used for population-oriented monitoring (40 CFR Part 58 Appendix D). For CO, traffic is the major source in an urban setting and therefore microscale data are sited "to represent distributions within street canyons, over sidewalks, and near major roadways" with at least one monitor sited to capture maximum concentrations, while middle scale monitors are sited to represent "air quality along a commercially developed street or shopping plaza, freeway corridors, parking lots and feeder streets" (40 CFR Part 58 Appendix D). The data used to create Table 3-12 were subject to the same 75% completeness criteria described in Section 3.5.1.1. More than 50% of the reported hourly data fell below the reported LOD (reported as 0.5 ppm for the majority of monitors reporting to AQS).

Table 3-12. National distribution of all hourly observations, 1-h daily max, 1-h daily average, and 8-h daily max concentration (ppm) derived from AQS data, based on monitor scale designations, 2005-2007.

				PERCENTILES									
Time Scale	**n**	**Mean**	**Min**	**1**	**5**	**10**	**25**	**50**	**75**	**90**	**95**	**99**	**Max**
ALL HOURLY													
Microscale	1,428,745	0.6	0.0	0.0	0.1	0.2	0.3	0.5	0.8	1.1	1.4	2.2	19.6
Middle Scale	771,941	0.5	0.0	0.0	0.0	0.1	0.2	0.4	0.6	1.0	1.3	2.3	18.9
Neighborhood Scale	2,878,993	0.4	0.0	0.0	0.0	0.0	0.2	0.3	0.5	0.8	1.1	2.1	35.3
Urban Scale	279,311	0.3	0.0	0.0	0.0	0.0	0.1	0.3	0.5	0.7	0.9	1.6	10.8
1-H DAILY MAX													
Microscale	59,905	1.2	0.0	0.2	0.3	0.4	0.7	1.0	1.5	2.1	2.5	3.9	19.6
Middle Scale	32,659	1.0	0.0	0.1	0.2	0.3	0.5	0.8	1.2	2.0	2.5	4.0	18.9
Neighborhood Scale	121,328	0.9	0.0	0.0	0.1	0.2	0.4	0.6	1.1	1.8	2.4	4.0	35.3
Urban Scale	11,784	0.7	0.0	0.0	0.0	0.1	0.3	0.5	0.9	1.3	1.8	3.1	10.8
1-H DAILY AVERAGE													
Microscale	59,905	0.6	0.0	0.0	0.1	0.2	0.4	0.5	0.8	1.0	1.2	1.7	4.0
Middle Scale	32,659	0.5	0.0	0.0	0.1	0.1	0.3	0.4	0.6	0.9	1.2	1.9	5.5
Neighborhood Scale	121,328	0.4	0.0	0.0	0.0	0.1	0.2	0.3	0.5	0.8	1.0	1.6	7.0
Urban Scale	11,784	0.3	0.0	0.0	0.0	0.0	0.2	0.3	0.5	0.7	0.8	1.2	2.5
8-H DAILY MAX													
Microscale	59,905	0.8	0.3	0.3	0.3	0.3	0.5	0.7	1.1	1.5	1.8	2.6	5.8
Middle Scale	32,659	0.7	0.1	0.3	0.3	0.3	0.3	0.6	0.9	1.4	1.9	2.8	6.2
Neighborhood Scale	121,328	0.6	0.0	0.3	0.3	0.3	0.3	0.4	0.8	1.2	1.6	2.7	10.9
Urban Scale	11,784	0.5	0.0	0.2	0.3	0.3	0.3	0.4	0.7	1.0	1.3	2.1	4.0

The median hourly CO concentration across the U.S. obtained at microscale monitors was 25% higher than at middle scale and 67% higher than at neighborhood scale. However, measurements at or below the median hourly concentration were almost entirely below the LOD for all scales, thereby limiting the usefulness of hourly median comparisons. The upper percentiles (90% and above), however, were all above the LOD and reveal consistently lower hourly concentrations for the urban scale monitors relative to the other monitors. For example, the 99th percentile of reported hourly values was 2.2, 2.3, and 2.1 ppm for microscale, middle scale and neighborhood scale, respectively, compared to 1.6 ppm for urban scale. Similar patterns were present in the 1-h daily max, 1-h daily average, and 8-h daily max distributions. Overall, the urban scale nationwide distributions tended to have lower concentrations relative to neighborhood scale, middle scale and microscale distributions (Table 3-12).

Distributions categorized by spatial scale and CSA/CBSA are provided in Figure 3-27 for hourly data and in Figure 3-28 for 1-h daily max data for the select CSAs/CBSAs where data were available at multiple scales (not all scales were reported by each CSA/CBSA studied). Tables A-17 through A-26 of Annex A contain tabular distributions for all CSAs/CBSAs except Anchorage. On a city-by-city basis, there was considerable variability when comparing distributions at the available spatial scales. With a few exceptions, however, the distribution of microscale and middle scale monitors tended to be higher than those obtained from neighborhood and urban scale monitors. For example, in CSAs/CBSAs containing both microscale and neighborhood scale monitors (Boston, Denver, Houston, Los Angeles, New York and Phoenix), median hourly concentrations at monitors sited for microscale were 20-40% higher than for middle scale and 0-150% greater than those sited for neighborhood scales. At the 99th percentile, microscale concentrations ranged from 31% less than to 59% greater than middle scale concentrations and from 14% less than to 67% greater than neighborhood scale. For most cities, the median hourly data are near or below the 0.5 ppm LOD reported for most monitors in use. In general, these data suggest that CO concentrations measured with monitors sited at micro- and middle scales, typically near roads, were somewhat elevated compared with neighborhood and urban scale monitor locations. However, the magnitude of these differences varies by city and is difficult to discern given the predominance of CO concentrations near or below the LOD.

Despite differences in concentrations observed at different scales (Figure 3-27 and Figure 3-28), intersampler correlations do not follow a distinct trend with respect to spatial monitoring scale (Table 3-10 and Table 3-11). For instance, intersampler correlation in Denver ranged from 0.46 to 0.76 among microscale monitors and was 0.52 for the correlation between the two neighborhood scale monitors (no monitors in Denver reporting to the AQS are sited at middle scale). Intersampler correlation in Los Angeles ranged from 0.44 to 0.73 for middle scale, and the one pair of neighborhood scale monitors had a correlation of 0.43. Only one monitor was sited each at microscale and urban scale, and 16 of the 24 CO monitors in Los Angeles are not declared to sample at any spatial scale (scale designation = “null”). In Denver, the distribution of hourly CO data obtained at microscale was nearly identical to that obtained at neighborhood scale. In Los Angeles, the microscale data was typically higher than middle, neighborhood, or urban scale data except at the upper end of the distribution, where middle scale data were higher for both hourly and 1-h daily max data (Figure 3-27 and Figure 3-28).

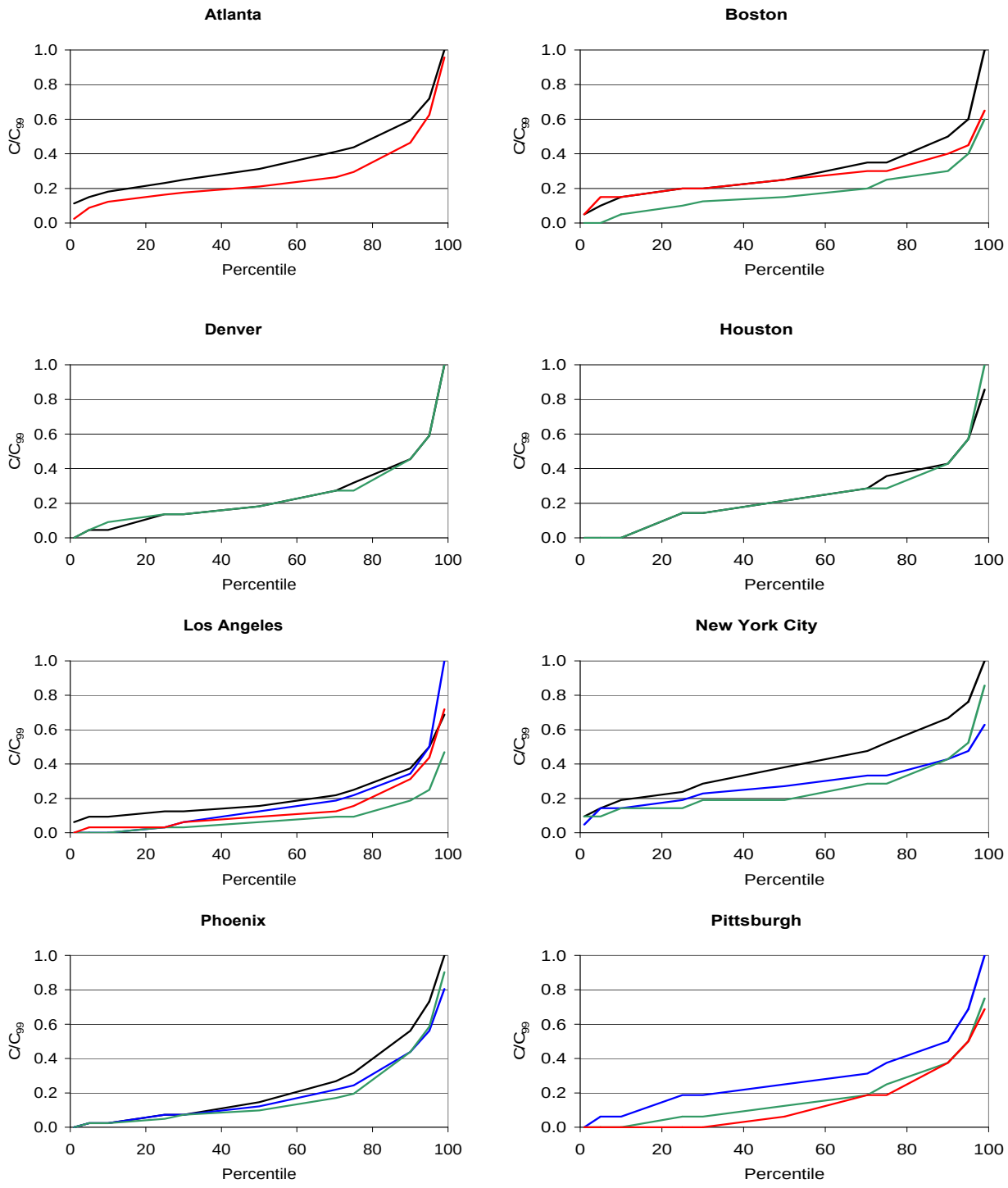


Figure 3-27. Distribution of hourly CO concentration data by city and monitoring scale. For comparison purposes, the y-axis has been scaled to the city-specific 99th percentile concentration. Note that Anchorage, Seattle, and St. Louis CSAs are not included here because these cities do not have monitors sited at different scales.

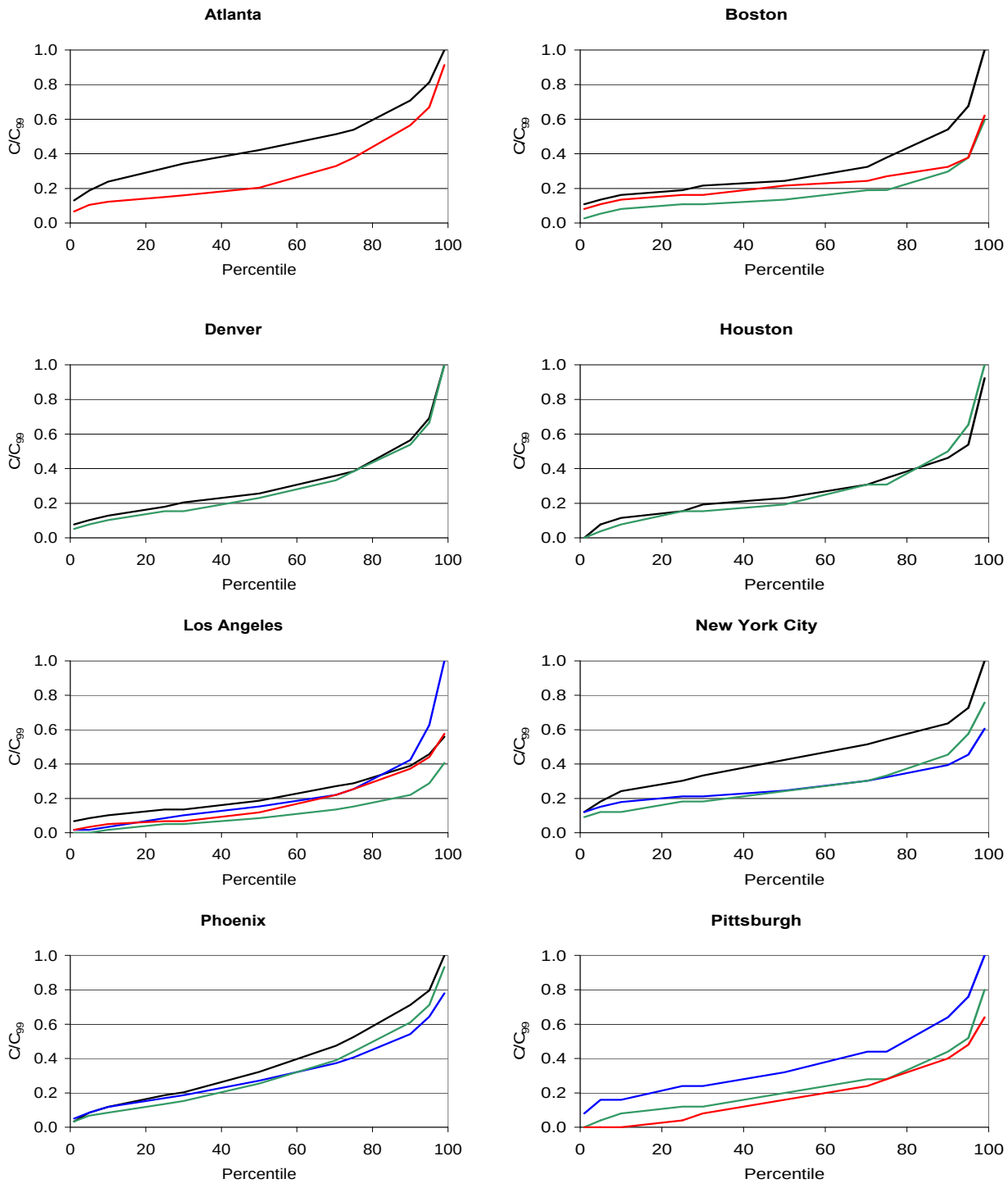
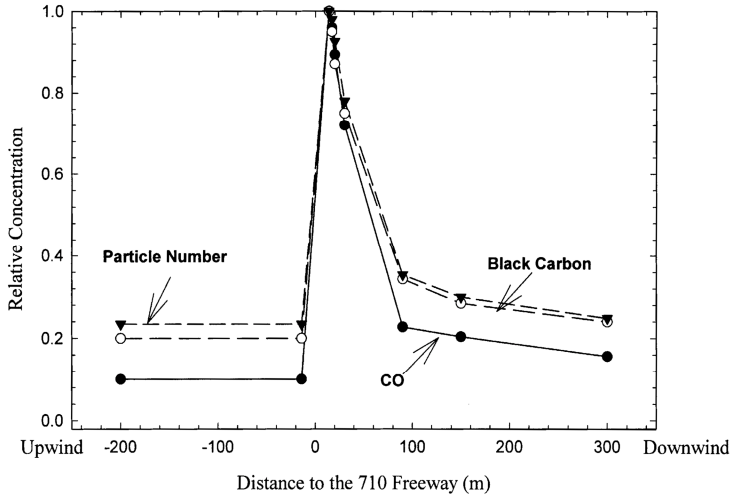


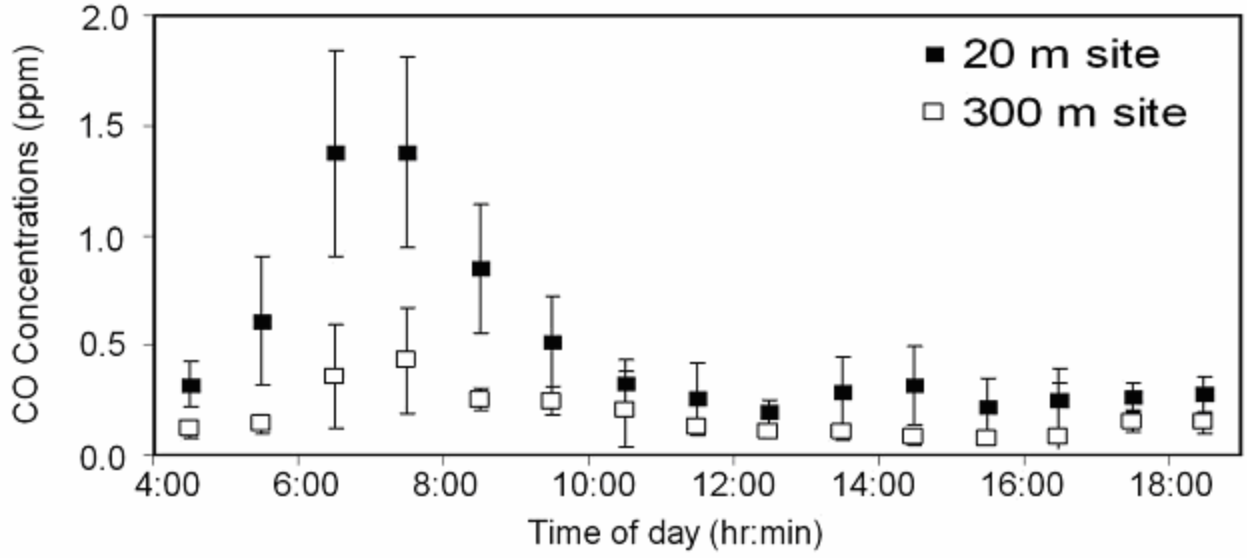
Figure 3-28. Distribution of 1-h daily max CO concentration data by city and monitoring scale. For comparison purposes, the y-axis has been scaled to the city-specific 99th percentile concentration. Note that Anchorage, Seattle, and St. Louis CSAs are not included here because these cities do not have monitors sited at different scales.

The microscale and middle scale CO data reported here are consistent with hourly concentrations reported in the literature for the near-road environment within the U.S. Baldauf et al. (2008, 190239) reported CO concentrations obtained 20 m from an interstate highway in Raleigh, NC, to have a median around 0.25 ppm and with maximum concentration <4.0 ppm. Zhu et al. (2002, 041553) reported CO concentration of 1.9-2.6 ppm at a distance of 17 m from an interstate highway in Los Angeles, with concentration decreasing exponentially with distance from the highway. Zhu et al. (2002, 041553) observed on-road CO concentrations to be approximately 10 times higher than at an upwind monitoring site, as shown in Figure 3-29. Concentrations continued to decrease and were still two times higher than upwind levels at a monitoring site 300 m away. Baldauf et al. (2008, 190239) also reported a drop in concentration at a monitoring site 300 m from the road compared with the 20 m site. Figure 3-30 illustrates the distribution of measurements taken throughout a day. In this plot, the near-road (20 m distance) CO concentrations tended to be significantly higher than those obtained at 300 m, and the daily variability in the CO concentration time series was greater at the 20 m site than at the 300 m site. The ratio of 20 m to 200 m concentrations was higher for the Zhu et al. (2002, 041553) paper. This was likely due to the fact that the 300 m site was always downwind in Zhu et al. (2002, 041553), whereas winds were more variable in Baldauf et al. (2008, 190239). Other near-road measurements reported in the literature are similar to those from the Zhu et al. (2002, 041553) and Baldauf et al. (2008, 190239) studies. Chang et al. (2000, 001276) reported near-road ambient CO measurements obtained in downtown Baltimore (distance to road not specified) in the range of 0.5-1.3 ppm. Riediker et al. (2003, 043761) reported measurements of CO concentration obtained near one of four heavily-trafficked roads in Wake County, NC, to average 1.1 ppm (range: 0.4-1.7 ppm). Neighborhood scale measurements reported in the literature were also consistent with if not slightly lower than those reported by AQS. Gentner et al. (2009, 194034) reported CO concentrations ranging from roughly 0.4-0.9 ppm in Riverside, CA, 1 km east of an interstate highway. Singh et al. (2006, 190136) reported 24-h avg CO concentrations, obtained with a 0.04 ppm LOD CO monitor in Long Beach, CA, within 0.5 km and 1.5 km of two interstate highways, to range from 0.2-1.4 ppm.



Source: Reprinted with Permission of Elsevier Ltd. from Zhu et al. (2002, 041553)

Figure 3-29. Relative concentrations of CO and copollutants at various distances from the I-710 freeway in Los Angeles.



Source: Reprinted with Permission of Air and Waste Management Association from Baldauf et al. (2008, 190239)

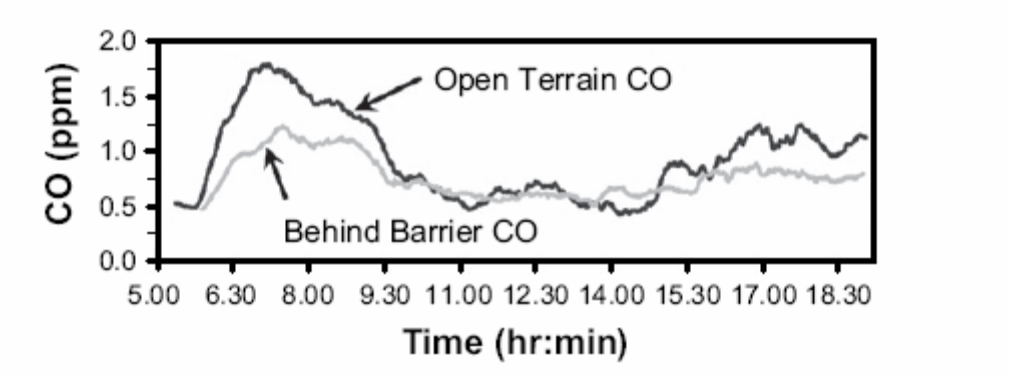
Figure 3-30. CO concentration time series 20 m and 300 m from the I-440 highway in Raleigh, NC. Symbols denote the mean concentration, and whiskers denote standard deviations.

Determinants of spatial variability in ambient CO concentration include roadway density, traffic counts, meteorology, and natural and urban topography. Mobile sources are the largest single source of CO, and their abundance and density affect the magnitude of CO production. Rodes et al. (1998, 010611) compared traffic volume, roadway type, and concentrations of CO and several copollutants in Los Angeles and Sacramento, CA, in a study of on-road traffic emissions. They noted that there was little difference in CO concentration between arterial roads and freeways for Los Angeles. Rodes et al. (1998, 010611) found that traffic was also much more congested throughout Los Angeles. This finding was not surprising given that Los Angeles is a much larger city with substantially higher traffic volumes than Sacramento. Under similar wind conditions, morning concentrations were much higher in Los Angeles than Sacramento. Rodes et al. (1998, 010611) observed that high afternoon winds ventilate Los Angeles, but Sacramento is not as well ventilated. As a result, Sacramento has nearly the same concentrations as Los Angeles in the afternoon. This observation is consistent with measurements by Gentner et al. (2009, 194034), showing that CO concentrations varied inversely with wind speed.

Measured on-road and road-side CO concentrations may also relate to the traffic volume. Among the 291 active sites where monitors met completeness criteria during 2005-2007, 57 were declared by state agencies as microscale with average annual daily traffic (AADT) counts on the nearby roads ranging from 500 vehicles per day at one site in Denver, CO to 133,855 vehicles per day in Tampa, FL with a geometric mean of 17,462 vehicles per day and a geometric standard deviation of 2.5 (Table A-2 of Annex A). Within a geometric standard deviation, the data range from 6,576-40,000 vehicles per day. Only two monitors were sited at roads with 100,000 vehicles per day or more. In contrast, the site where Zhu et al. (2002, 041553) collected data had 160,000-178,000 vehicles per day in 2001 (CalTrans, 2009, 194036). Microscale sites near roads in the mid-range of the traffic count data may record data that are not substantially different from those obtained from neighborhood scale measurements, as indicated in Table 3-12. Likewise, with little microscale data at roads with AADT of more than 100,000 vehicles per day, there is still much uncertainty regarding the magnitude of concentrations in the near-road environment.

Field measurements, computational modeling, and wind tunnel experiments have shown that roadway design, roadside structures and vegetation, and on-road traffic levels can affect concentrations of CO and other pollutant concentrations near roadways. Field measurements reported by Baldauf et al. (2008, 191017) indicated that noise barriers could reduce near-road pollutant concentrations by as much as 50%, although this effect was highly dependent on

meteorological conditions; these results are illustrated in Figure 3-31. This study also showed that the presence of mature vegetation further reduced concentrations and flattened the concentration gradient away from the road. Urban dispersion and wind-field modeling by Bowker et al. (2007, 149997) also demonstrated the influence of noise barriers and vegetation on the concentrations and spatial variability of nonreactive pollutants emitted from traffic sources. Heist et al. (2009, 194037) ran wind tunnel experiments using a model of a road with different roadside features and a tracer gas line source emitted from the simulated road to study how concentrations of gaseous traffic emissions vary spatially in the near-road environment. They demonstrated that noise barriers and roadway design characteristics, such as the presence of embankments and elevated roadway segments, can alter airflow and contaminant dispersion patterns in the near-road environment. For example, their results indicated that roadway design having below-grade sections of road and embankments reduced concentrations away from the road. These results showed similar concentrations as those of Zhu et al. (2002, 041553), both for roadway segments at-grade with no obstructions to air flow and for elevated roadway segments with different road fill conditions. Additionally, Khare et al. (2005, 194016) illustrated in a wind tunnel study that vertical dispersion of a nonreactive gas increased with increasing simulated traffic volume; this effect was also sensitive to changes in approaching wind direction. These studies taken together suggest that localized turbulence induced by roadside structures, roadway design, and traffic provide some mixing and resulting dilution of the CO concentration in the near-road environment; the extent of mixing effects varies by meteorological conditions and the specific roadway design and traffic loading.

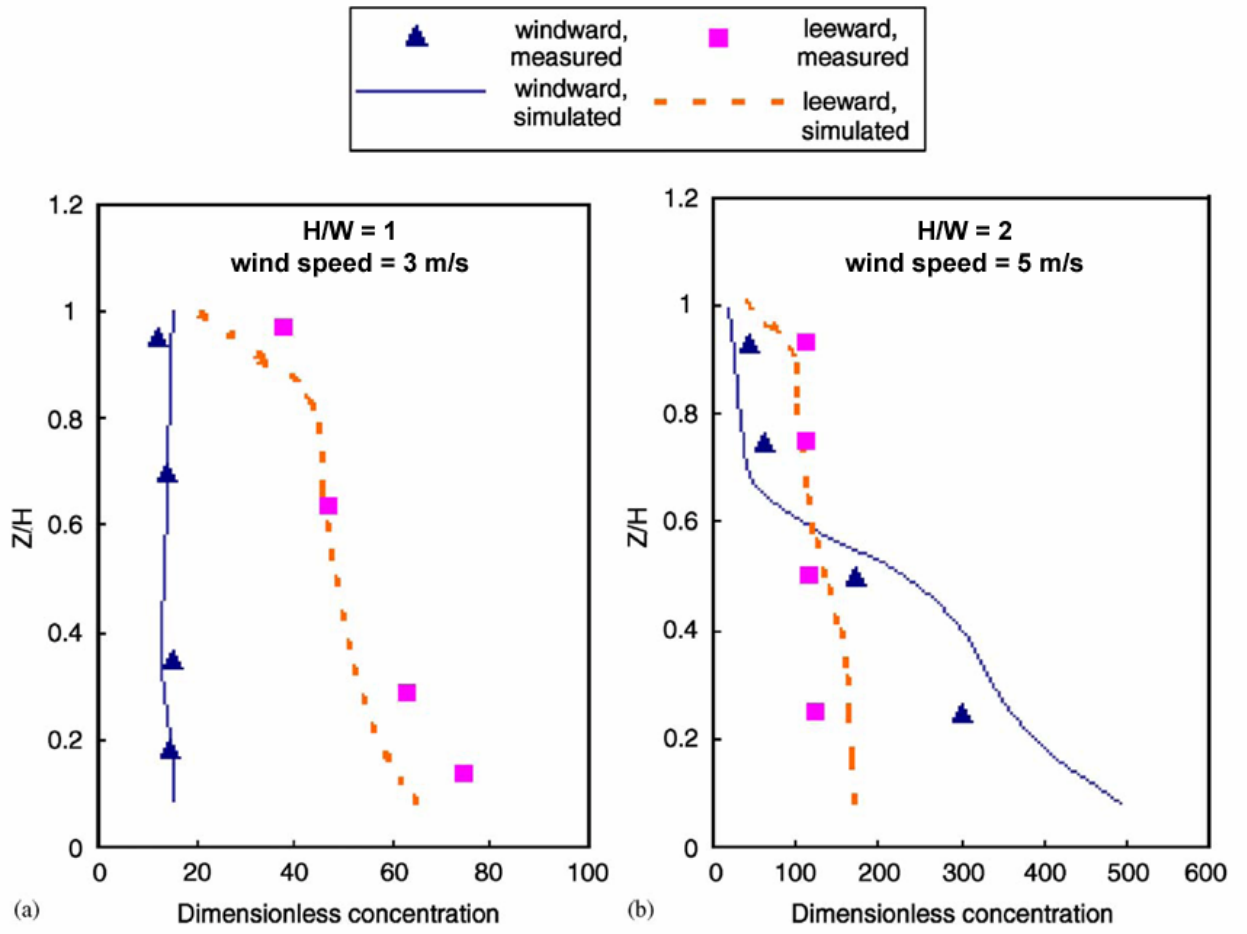


Source: Reprinted with Permission of Elsevier Ltd. from Baldauf et al. (2008, 191017)

Figure 3-31. CO concentration profile 10 m from I-440 in Raleigh, NC, behind a noise barrier and in open terrain.

The geometry of urban street canyons has a profound effect on the distribution of CO concentrations on a microscale. A number of studies have performed computational and wind tunnel modeling of street canyons using nonreactive tracers and demonstrated the potential variability in concentration within a canyon (e.g., Borrego et al., 2006, 155697; Chang and Meroney, 2003, 090298; Kastner-Klein and Plate, 1999, 001961; So et al., 2005, 110746; Xiaomin et al., 2006, 156165). Because CO is a pollutant with very low reactivity on urban and regional scales, results from these models are directly relevant to CO concentration distributions in street canyons. Parameters influencing street canyon dispersion include canyon height to width ratio (H/W), source positioning, wind speed and direction, building shape, and upstream configuration of buildings. Figure 3-32 shows dimensionless concentrations obtained from wind tunnel and computational fluid dynamics simulations of tracer gas transport and dispersion in an infinitely long street canyon with a line source centered at the bottom of the canyon (Xiaomin et al., 2006, 156165). When the canyon height was equal to the street width (typical of moderate density suburban or urban fringe residential neighborhoods) and lower background wind speed existed, concentrations on the leeward (downwind) canyon wall were four times those of the windward (upwind) wall near ground level.

When the canyon height was twice the street width (typical of higher-density cities) and background winds were somewhat higher, near ground-level concentrations on the windward canyon wall were roughly three times higher than those measured at the leeward wall. These results suggest that the magnitude of microscale CO concentrations may vary by factors of three or four times at different locations within a street canyon and are heavily influenced by wind speed and street canyon topography. The relationship between in-canyon concentration and wind speed and turbulence is well established with concentration varying inversely with the magnitude of wind speed and turbulence (Britter and Hanna, 2003, 090295). When studying the effect of wind direction on street canyon concentration levels for a continuous "line source" of traffic exhaust, concentration levels were at local maxima under two conditions: wind perpendicular to or parallel to the street canyon. Wind gusts at the turbulence interface at the top of the canyon or traffic-based turbulence can also cause dilution of the exhaust concentration within the canyon (Kastner-Klein et al., 2000, 194035).

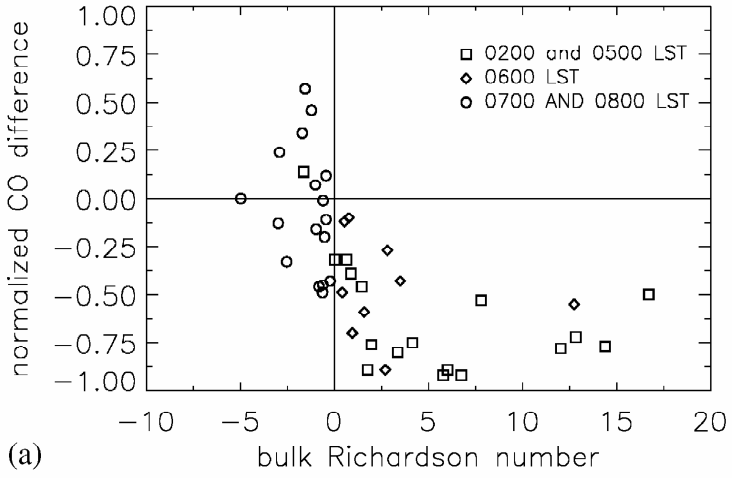


Source: Reprinted with Permission of Elsevier Ltd. from Xiaomin et al. (2006, 156165)

Figure 3-32. Dimensionless tracer gas concentration on the windward and leeward sides of the canyon plotted against the elevation of the measurement (Z) scaled by building height (H) under two different H/W and wind speed conditions. Shown are measurements obtained in a wind tunnel (symbols) and model simulations using computational fluid dynamics (lines).

Street canyon field studies support the computational and wind tunnel modeling results described above. In a multisite survey of curbside CO concentration in London, U.K., Croxford and Penn (1998, 087176) observed up to threefold differences in concentration related to the side of the

street on which the monitor was positioned relative to the wind direction, with H/W varying between 0.7 and 1.7 depending on position within the canyon. Bogo et al. (2001, 192378) measured CO concentrations in a street canyon with H/W of 1 in Buenos Aires, Argentina, using a continuous CO monitor. Similar to the Xiaomin et al. (2006, 156165) simulation results for H/W of 1, Bogo et al. (2001, 192378) observed slightly higher leeward concentrations than windward concentrations within the canyon, where recirculating airflow inside the canyon causes pollutants to collect in higher concentration on one side. However, for the case of a deep street canyon (H/W of 5.7) in Naples, Italy, Murena et al. (2008, 194038) observed that the concentrations on two sides of the canyon differed by <15%, with wind direction varying between 10° and 80° from the street axis. Doran et al. (2003, 143352) measured CO concentration in a street canyon in Phoenix, AZ, during the morning hours and observed that CO concentration decreases with elevation above the ground if turbulent mixing is small, but that the difference between ground level and 39th-floor (50 m AGL) measurements of CO concentration decreases when turbulent mixing increases (with maximum measurements at any elevation not exceeding 2 ppm). As shown in Figure 3-33, the larger difference in concentration as a function of turbulent mixing can occur when there are meteorologically stable conditions in the lower boundary layer. These results support findings from the modeling studies that CO concentration can vary by several times within a street canyon and is greatly influenced by local meteorology and building topography.



Source: Reprinted with Permission of Elsevier Ltd. From Doran et al. (2003, 143352)

Figure 3-33. Normalized difference between CO measurements taken at ground level and from the 39th floor of a building in a Phoenix, AZ street canyon as a function of bulk Richardson number (Ri). Bulk Ri is a dimensionless number that describes the ratio of potential to kinetic energy, and it is used here as a measure of stability within the street canyon, with greater Ri corresponding to greater stability and values near or less than zero indicating greater mixing.

Research by Kaur and Nieuwenhuijsen (2009, 194014) and Carslaw et al. (2007, 148210) suggests that CO exposures are related to traffic volume and fleet mix in the street-canyon environment. Kaur and Nieuwenhuijsen (2009, 194014) used multiple linear regression to model CO concentration data from central London as a function of mode of transport (broken down by vehicle type), traffic count, wind speed, and temperature. They added each variable successively and found traffic count, temperature, wind speed, and walking to be significant parameters in the model, with traffic count being the strongest determinant. Analysis of variance showed variability in traffic count to explain 78% of the variability in CO levels for these data, and variability in mode of transport explained 6% of the variability. Likewise, Carslaw et al. (2007, 148210) used a generalized additive model to determine how CO concentration data (log-transformed) obtained in central London varied as a function of light- and heavy-duty traffic counts, along-street and cross-street components of

wind, temperature, year, and Julian day. Light-duty vehicle count was a more important determinant of CO concentration than heavy-duty (i.e., diesel) vehicle count in this study. They found that the CO declined steadily with year and that wind was the most significant covariate. In addition to showing meteorology to be an important determinant of concentration, these modeling exercises also suggest a linear or log-linear relationship between concentration and traffic.

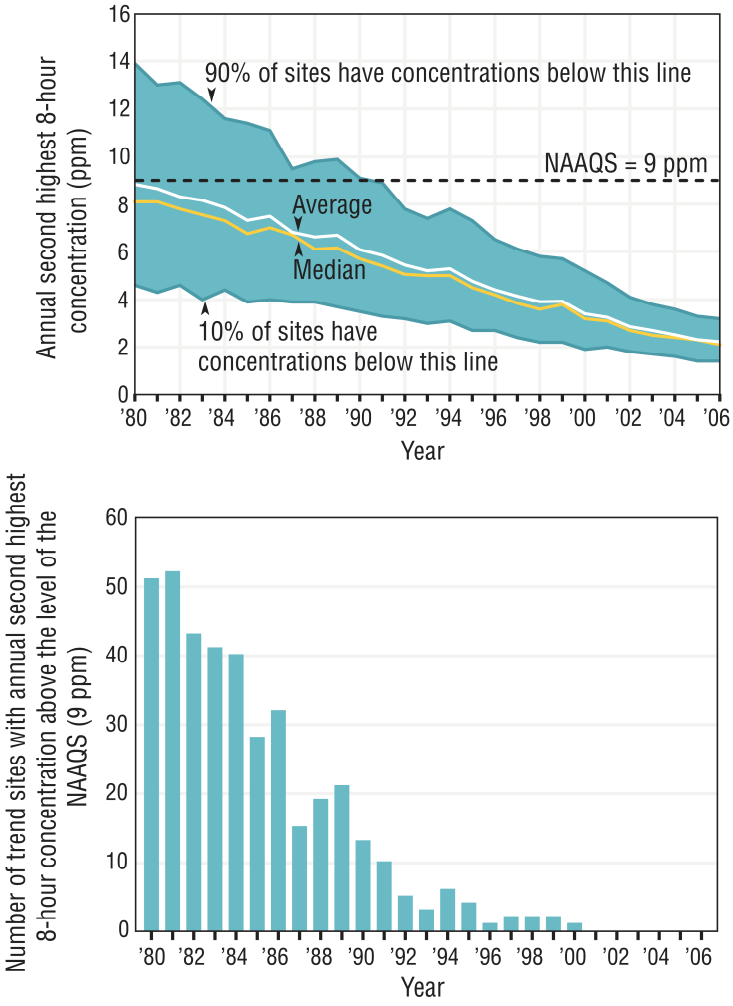
3.5.2. Temporal Variability

3.5.2.1. Multiyear Trends

Figure 3-34 (top) shows ambient CO concentrations in ppm from 1980 to 2006 based on continuous measurements averaged over 8-h time segments. Figure 3-34 (bottom) depicts trends in the annual second-highest 8-h CO concentrations for 144 sites in 102 counties nationwide having data either in the SLAMS network or from other special purpose monitors.

The 2006 annual second highest 8-h CO concentration averaged across 144 monitoring sites nationwide was 75% below that for 1980 and is the lowest recorded during the past 27 yr (Figure 3-34 [top]). Since 1992, more than 90% of these sites have reported second highest CO concentrations below the 8-h NAAQS of 9 ppm. The mean annual second highest 8-h ambient CO concentration has been below 5 ppm since 2004. The downward trend in CO concentrations in the 1990s parallels the downward trend observed in CO emissions, attributed largely to decreased mobile source emissions. In addition, of the 144 sites used to determine this trend, from a total of 375 monitoring sites operating in 2006, the number reporting second-highest 8-h CO concentrations above the level of the NAAQS declined to zero over the same period (Figure 3-34 [bottom]).

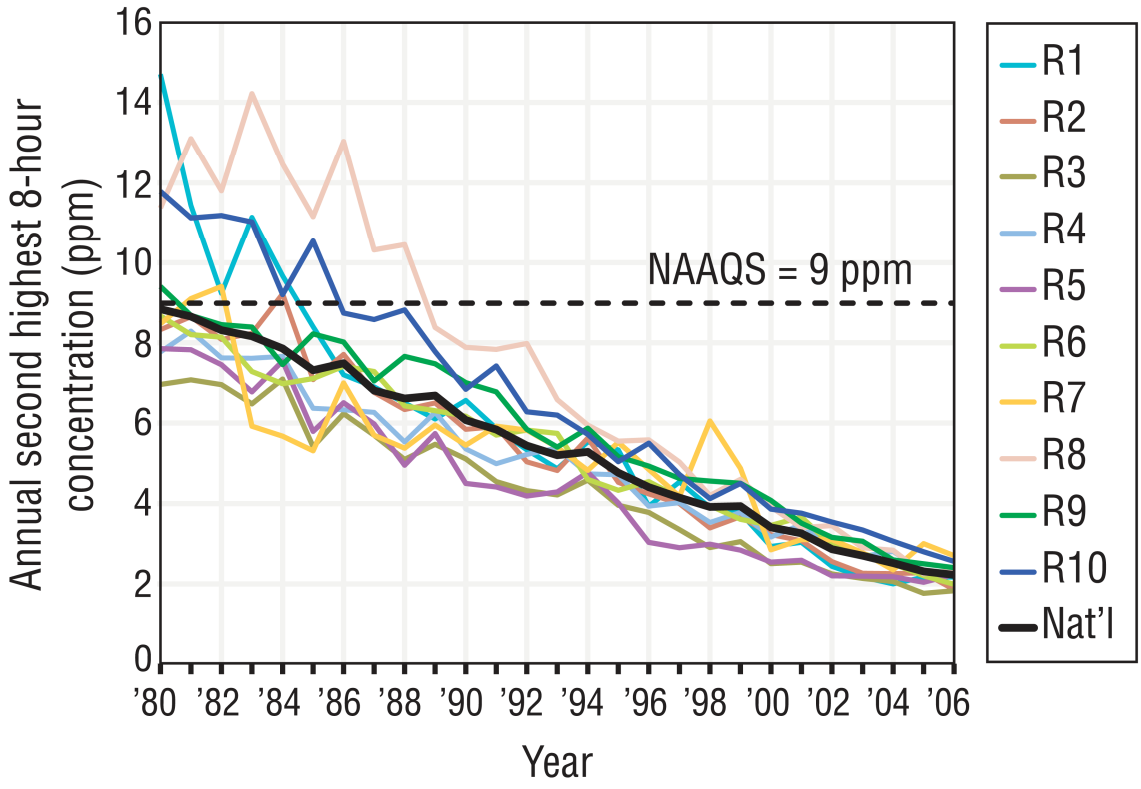
Consistent with the nationwide trends in emissions and concentrations, CO concentrations in all 10 EPA Regions have steadily decreased since 1980, with reductions over this period ranging from 68% in Region 7 to 85% in Region 1 (Figure 3-35). This is also consistent with declining emissions seen in many regions of the U.S., shown in Figure 3-5.



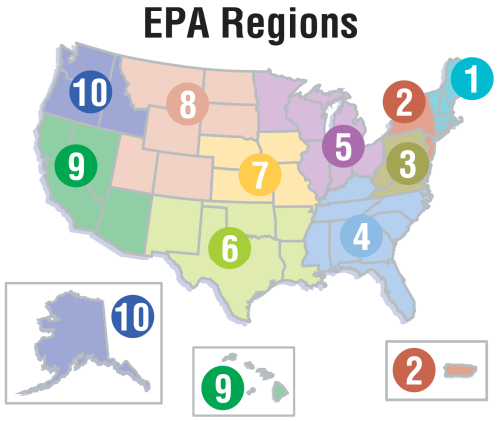
Coverage: 144 monitoring sites in 102 counties nationwide (out of a total of 375 sites measuring CO in 2006) that have sufficient data to assess CO trends since 1980.

Source: U.S. EPA (2008, 157076)

Figure 3-34. (Top) Trends in ambient CO in the U.S., 1980-2006, reported as the annual second highest 8-h concentrations (ppm) for the mean, median, 10% and 90% values. (Bottom) Trends in ambient CO in the U.S., 1980-2006, reported as the number of trend sites (y-axis) with annual second highest 8-h concentrations above the level of the NAAQS (9 ppm).



Coverage: 141 monitoring sites in the EPA Regions (out of a total of 375 sites measuring CO in 2006) that have sufficient data to assess CO trends since 1980.



Source: U.S. EPA (2008, 157076)

Figure 3-35. Trends in ambient CO in the U.S., 1980-2005, reported as the annual second highest 8-h concentrations (ppm) for the EPA Regions 1 through 10, along with a depiction of the geographic extent of those Regions.

3.5.2.2. Hourly Variation

Weekday and weekend diel variation for the mean, median, 5th, 10th, 90th, and 95th percentiles of hourly CO concentration over 2005-2007 are shown in Figure 3-36 and Figure 3-37, respectively, for the 11 CSAs and CBSAs examined in this assessment. Since these figures represent the distribution of hourly observations over a 3-yr period, any fluctuations or changes in the timing of the daily peaks would result in a broadening of the curves shown in the diel plot compared to the actual daily temporal behavior on any specific day measured by an individual monitor. However, these figures are useful for comparing the general hourly variation in CO concentrations across cities and by day of the week (i.e., weekday versus weekend). The weekday data showed that the Anchorage mean, median, 5th and 10th percentile CO concentration curves exhibit pronounced morning and evening rush hour peak CO levels. Boston, Denver, Houston, Los Angeles, Phoenix, Pittsburgh, and St. Louis all exhibited similar trends, although the magnitude of the concentrations shown was roughly twice as high for Anchorage as the other cities. The curves had less overall variability for Boston, Pittsburgh, and St. Louis. The Atlanta plot shows that the median concentration was fairly constant throughout the 24-h period, with a slightly elevated mean during the morning hours. The 90th and 95th percentile curves exhibit stronger morning and evening CO concentration peaks. New York City shows fairly constant CO mean and median concentration throughout the day, with slight elevations throughout the morning rush hour and a slight trough between 1:00 and 5:00 a.m. The Seattle plot shows a daytime plateau beginning around 5:00 a.m. and lasting until roughly 10:00 p.m., with higher concentrations during morning and afternoon rush hour. Differences in hourly variation among the 11 CSAs and CBSAs reflect city-to-city variation in source characteristics and meteorology. For instance, the rush hour peaks in many cities likely correspond to increased mobile source emissions during those periods. Local meteorology and topography, which influence mixing heights, can also affect hourly variation in CO concentration.

Figure 3-37 illustrates weekend diel trends for the 11 CSAs and CBSAs considered in this assessment. For Anchorage during the period 2005-2007, the mean and median concentration curves peaked during the morning and evening hours. A daytime concentration trough is evident. The 90th and 95th percentiles of concentration were similar but more pronounced. The shape of this plot is also characteristic of Atlanta, Boston, Denver, Houston, Los Angeles, Phoenix, Pittsburgh, Seattle, and St. Louis, although the Anchorage CO concentrations are nearly 100% higher than concentrations in the other cities. The weekend diel plot for New York City shows that the mean and median CO concentrations remain fairly constant throughout the day, with a slight reduction between 2:00 and 7:00 a.m. The 90th and 95th percentile curves illustrate more diel variation.

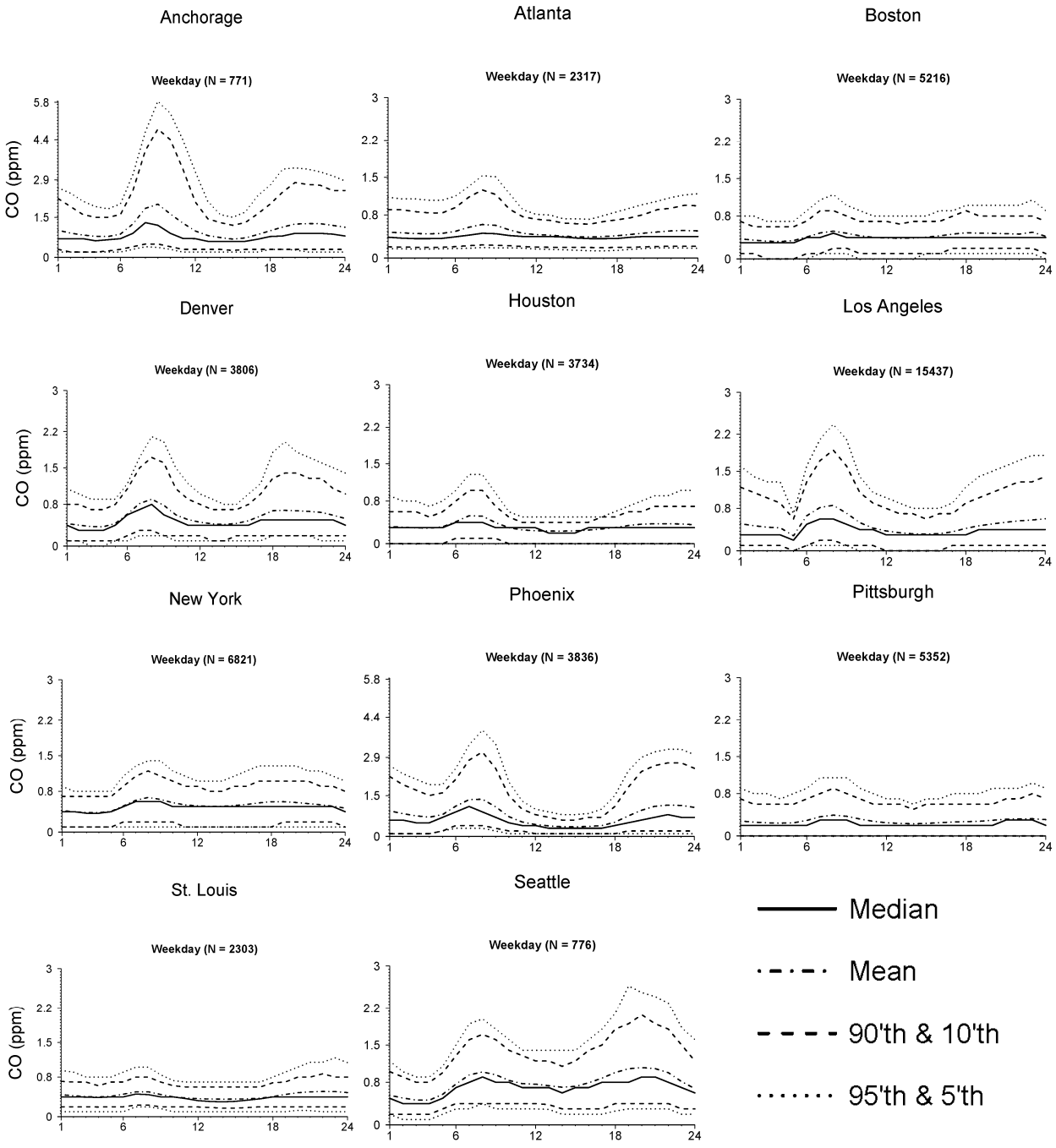


Figure 3-36. Diel plot generated from weekday hourly CO data (ppm) for the 11 CSAs and CBSAs, 2005-2007. Included are the number of monitor days (N) and the median, mean, 5th, 10th, 90th and 95th percentiles of composite CO concentrations plotted by time of day. Note that the y-axis of the Anchorage and Phoenix plots are scaled to 5.8 ppm while the other plots are scaled to 3.0 ppm.

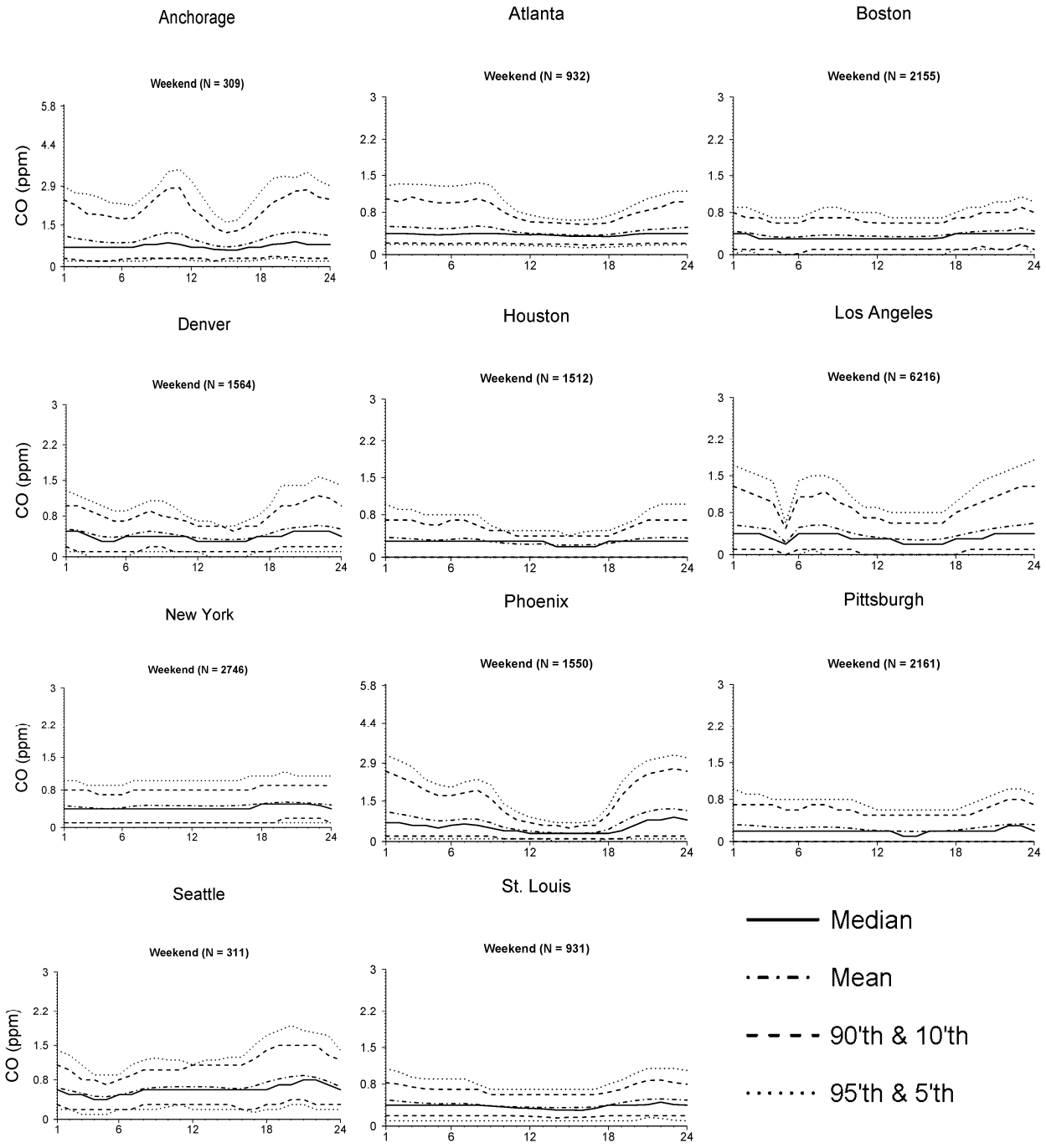


Figure 3-37. Diel plot generated from weekend hourly CO data (ppm) for the 11 CSAs and CBSAs, 2005-2007. Included are the number of monitor days (N) and the median, mean, 5th, 10th, 90th and 95th percentiles of composite CO concentrations plotted by time of day. Note that the y-axis of the Anchorage and Phoenix plots are scaled to 5.8 ppm while the other plots are scaled to 3.0 ppm.

3.5.3. Associations with Copollutants

Associations between hourly CO and other copollutants, including SO_2, NO_2, O_3, PM_{10}, and $PM_{2.5}$ are provided in box plots in Figure 3-38 using AQS data across the U.S. AQS data were obtained from all available co-located monitors across the U.S. after application of the 75% completeness criteria described earlier in Section 3.5.1.1. Pearson correlation coefficients (r) were calculated using 2005-2007 data stratified by season. Correlation plots analogous to Figure 3-38 for select individual cities are provided in Annex A, Figures A-43 to A-48.

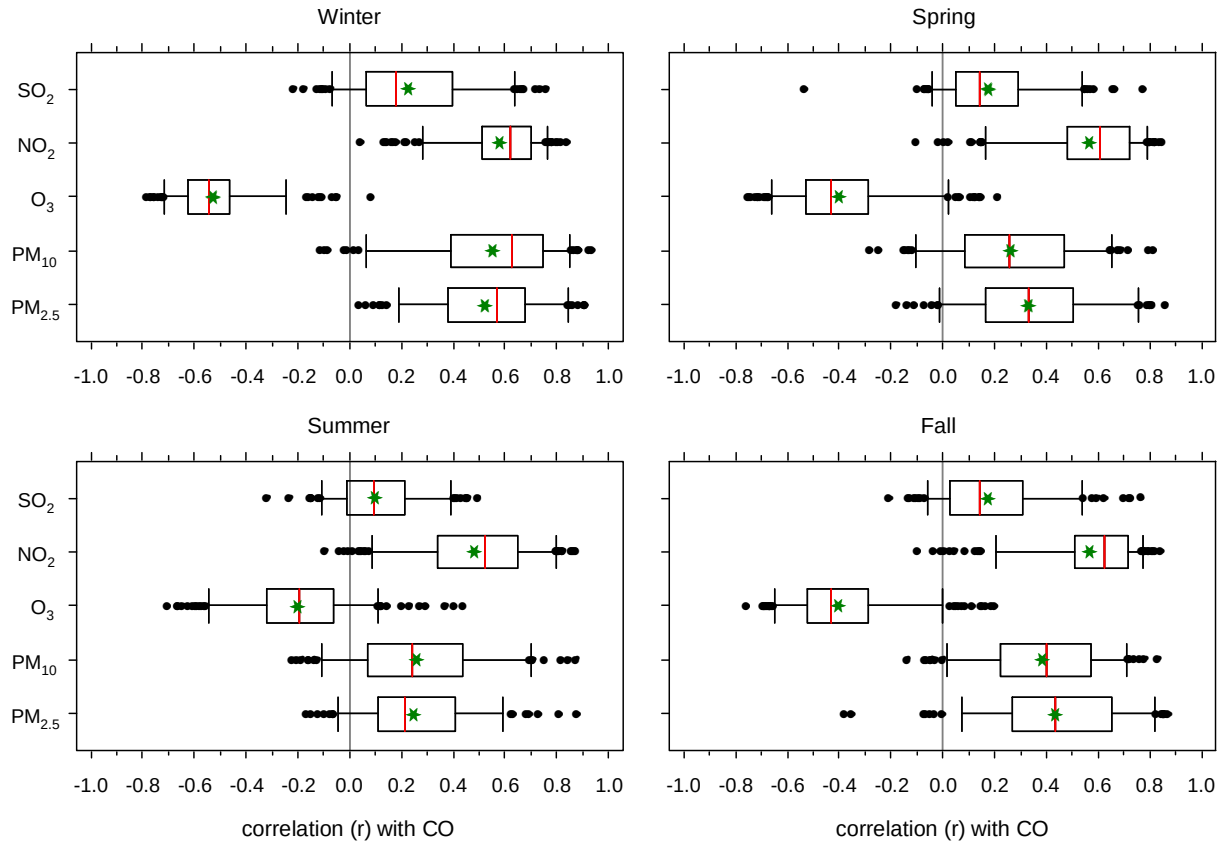


Figure 3-38. Seasonal plots showing the variability in correlations between hourly CO concentration and co-located hourly SO_2, NO_2, O_3, PM_{10} and $PM_{2.5}$ concentrations. Red bars denote the median, green stars denote the arithmetic mean, the box incorporates the IQR, and the whiskers extend to the 5th and 95th percentiles. Correlations outside the 5th and 95th percentiles are shown as individual points.

In all cases, a wide range of correlations existed between CO and copollutants as illustrated in Figure 3-38. The mean and median correlation between CO and copollutants were positive for NO_2, PM_{10}, and $PM_{2.5}$; near zero for SO_2; and negative for O_3. These findings reflect common combustion sources for CO, NO_2, and PM. CO is highly correlated with NO_2 and $PM_{2.5}$ because they are both emitted directly during incomplete combustion and because secondary nitrate PM comes from NO_X, which is largely produced from mobile sources. Among those copollutants with positive associations, NO_2 had the highest mean and median correlations, followed by $PM_{2.5}$ and PM_{10} (correlations vary by season). The IQR of correlations with SO_2 spanned from positive to negative for all seasons; SO_2 would not be expected to correlate well with CO because SO_2 emanates primarily from industrial sources. Correlations between CO and O_3 were almost entirely negative for

winter, when CO emissions tend to be high and O_3 formation is low. During the other three seasons, most of the CO-O_3 correlations were also negative. Given the role of CO in O_3 chemistry, cross-correlation functions were also computed by season for the CO-O_3 relationship (Annex A, Figure A-50). The data showed negative correlations at all lags with minima at zero lag for winter, spring, and fall. During the summer, a small positive peak correlation (r = 0.071) was centered at a lag of -8 h and a minima occurred at a lag of 1 h, r = -0.272. It is not known whether the positive lagged correlations in summertime are related to interaction of CO with O_3 through chemistry, coinciding independent effects such as peak times for rush hour CO emissions and afternoon O_3 formation, or some combination of interactive and independent effects. However, given the very low magnitude of these correlations, it is clear that many other factors influence the O_3 and CO time series.

Within and between individual metropolitan areas, the distribution of copollutant correlations varied substantially. Figure 3-39 and Figure 3-40 illustrate the correlations between CO and copollutants for Denver, CO, and Los Angeles, CA, to exemplify these differences. Copollutant correlation plots are also shown for other cities in Annex A, Figures A-44 through A-49. For instance, correlations between CO and copollutants are all positive for SO_2, NO_2, PM_{10}, and $PM_{2.5}$ and are all negative for O_3 in Denver. In contrast, the correlations in Los Angeles span from negative to positive for O_3, PM_{10}, and $PM_{2.5}$, in various seasons. The larger span of correlations for Los Angeles in comparison with Denver could result from several factors. For example, more variation in meteorology, topography, or source distribution with respect to monitor placement in Los Angeles may cause the distribution of copollutant correlations to be wider. In addition, fewer co-located monitors in Denver compared with Los Angeles may be causing some of the observed differences.

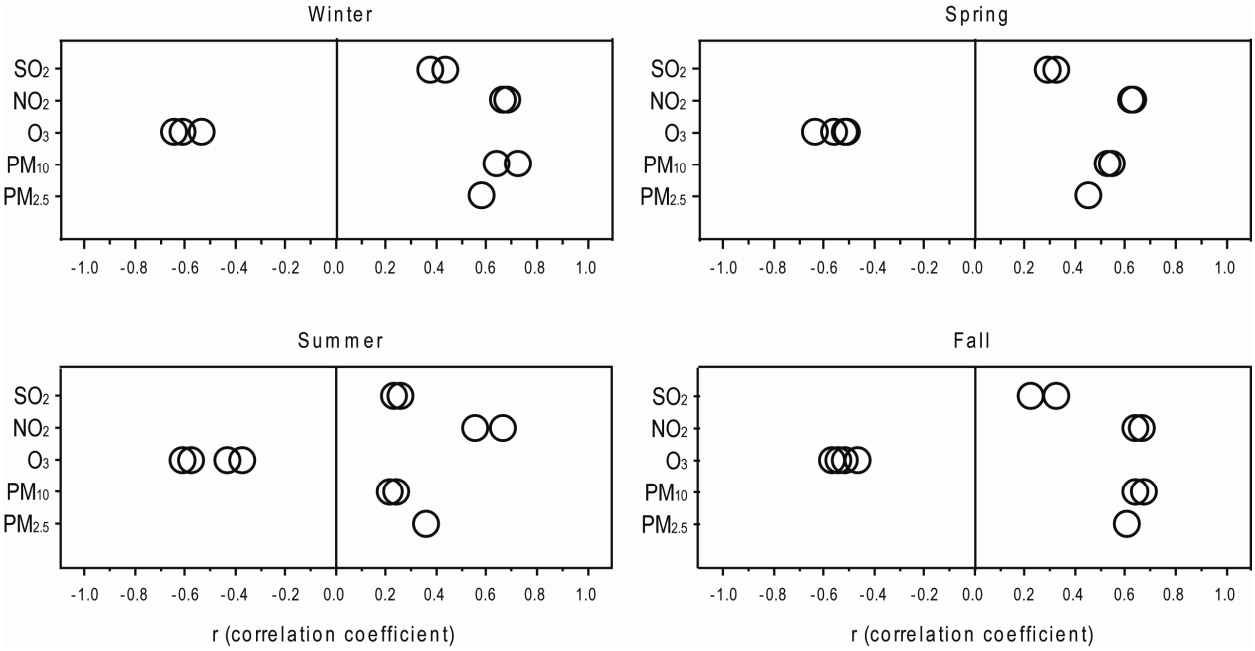


Figure 3-39. Seasonal plots showing the variability in correlations between hourly CO concentration and co-located hourly SO_2, NO_2, O_3, PM_{10} and $PM_{2.5}$ concentrations for Denver, CO.

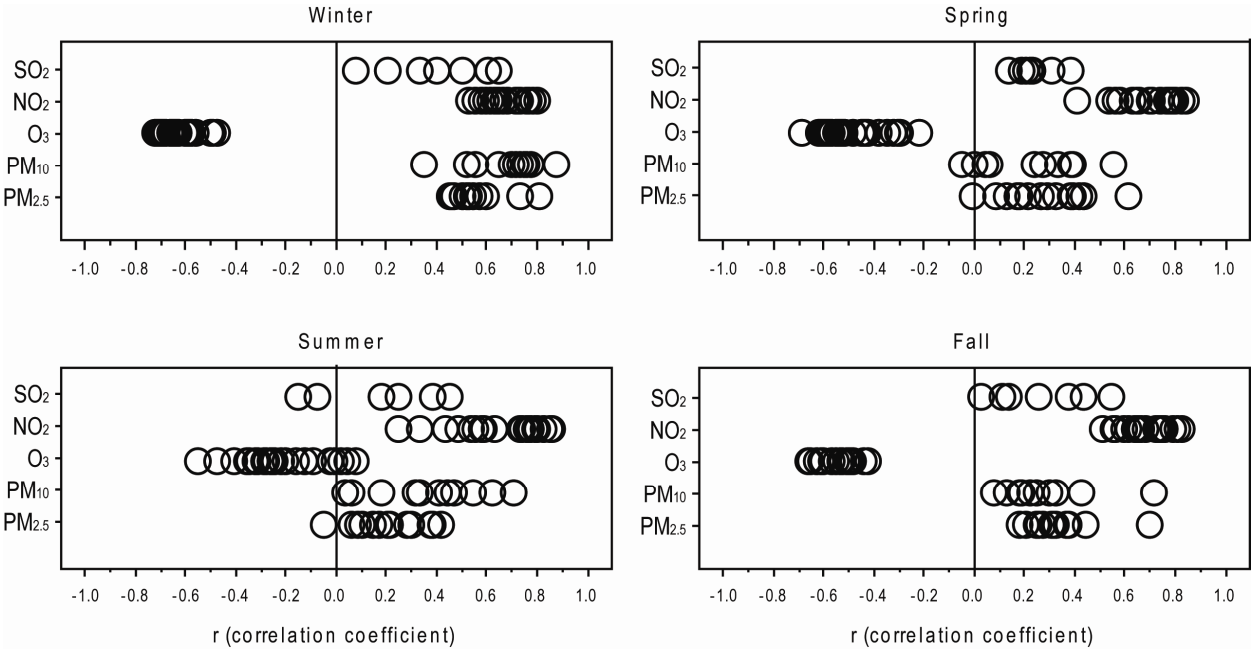
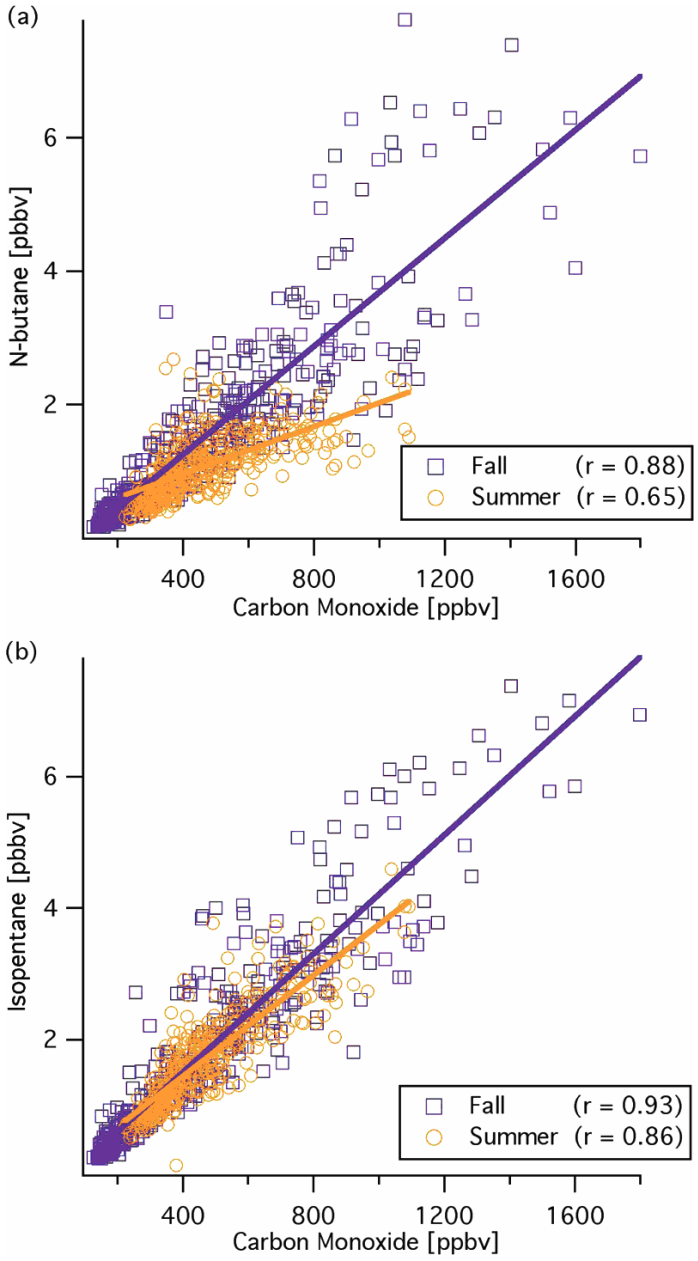


Figure 3-40. Seasonal plots showing the variability in correlations between hourly CO concentration and co-located hourly SO_2, NO_2, O_3, PM_{10} and $PM_{2.5}$ concentrations for Los Angeles, CA.

Several recent studies reported correlations between ambient CO and other pollutants. Reported relationships were generally consistent with the correlations shown above using AQS data. Sarnat et al. (2001, 019401) reported significant positive Spearman's correlations between CO and NO_2 (r = 0.76) and $PM_{2.5}$ (r = 0.69) and significant negative correlations between CO and O_3 (r = -0.67) in Baltimore (concentration averaging periods not specified). Correlation of CO with SO_2 was insignificant (r = -0.12). The Sarnat et al. (2001, 019401) study focused on correlations of ambient and personal $PM_{2.5}$ with gaseous copollutants, so seasonal information is only available for the correlation between $PM_{2.5}$ and CO. High correlation of ambient CO with NO_2 is expected given that both are closely related to mobile source combustion emissions. Sarnat et al (2005, 087531) also reported significant year-round association between CO and $PM_{2.5}$ and significant associations between CO and SO_4^{2-} aerosols. Kim et al. (2006, 089820) measured CO, NO_2, and $PM_{2.5}$ at ambient fixed sites in Toronto, Canada, and found associations, averaged over monitoring stations, of CO with $PM_{2.5}$ (Spearman's r = 0.38, nonsignificant) and of CO with NO_2 (r = 0.72, significant). Tolbert et al. (2007, 090316) reported correlations between multiple pollutants in Atlanta and also showed the highest Spearman's correlation for CO with NO_2 (r = 0.70). CO was also reported to have fairly high correlation with $PM_{2.5}$ elemental carbon (EC) (r = 0.66), $PM_{2.5}$ organic carbon (OC) (r = 0.59), and $PM_{2.5}$ total carbon (TC) (r = 0.63). Correlations were reported to be much lower for CO with O_3 (r = 0.27) and $PM_{2.5}$ SO_4^{2-} (r = 0.14). The higher correlations of CO with EC, OC, and TC are likely related to the fact that CO and carbonaceous PM are both emitted by mobile sources. Gentner et al. (2009, 194034) analyzed the relationship between ambient CO and VOC concentrations, serving as markers of gasoline vehicle emissions in Riverside, CA. Correlations of CO with two compounds, n-butane and isopentane, are shown in Figure 3-41 for summer and fall. Higher concentrations of n-butane per unit of CO were observed for fall, as well as higher correlation (fall: r = 0.88; summer: r = 0.65). For isopentane, the slopes of regression are much closer for fall and summer, with higher correlations between isopentane and CO (fall: r = 0.93; summer: r = 0.86). Gentner et al. (2009, 194034) noted that isopentane vapor fraction was higher in summer than winter and that the n-butane vapor fraction increases in winter. This reflects the higher volatility of n-butane compared with isopentane. In this work, Gentner et al. (2009, 194034) used emissions modeling to estimate that overall VOC emissions from gasoline varies with CO emissions with a ratio of 0.086 with a correlation of r = 0.80 in summer. Gentner et al. (2009, 194034) suggest that the near-road slope of

ambient VOC to CO concentration might be influenced by upwind CO concentration and secondary CO production by oxidation of VOCs.



Source: Reprinted with Permission of ACS from Gentner et al. (2009, 194034)

Figure 3-41. Linear regression of n-butane and isopentane concentration as a function of CO concentration, Riverside, CA.

3.5.4. Policy-Relevant Background

Background concentrations of pollutants used for informing policy decisions about national standards in the U.S. are commonly referred to at EPA as PRB concentrations. In this assessment, PRB concentrations include contributions from natural sources everywhere in the world and from anthropogenic sources outside the U.S., Canada, and Mexico.

3.5.4.1. Surface-Based Determinations

For this assessment, PRB concentrations of CO were determined from the extensive and long-running network of remote-site baseline CO measurements conducted by NOAA's Earth System Research Laboratory (ESRL), Global Monitoring Division (GMD), as part of their Carbon Cycle Greenhouse Gases Group (CCGG) Cooperative Air Sampling Network (CASN); see http://www.esrl.noaa.gov/gmd/ccgg/iadv. Surface-based CO measurements have been made for more than 10 yr with exceptionally high sensitivity and selectivity at locations significantly away from local sources. In this assessment, for example, CO data through December 2007 are available with extensive quality assurance and control information from the worldwide network of 72 stations active in December 2008. ESRL GMD uses the highly sensitive gas chromatography-mercury liberation photometric detection technique with precision to 1 ppb in 50 ppb or 2 ppb in 200 ppb and accuracy to 1.5 ppb in 500 ppb or 2 ppb in 200 ppb.

In order to smooth interannually changing meteorological and emissions effects, data from 2005-2007 at 12 remote sites in the U.S. were used to determine PRB. A map of these sites is shown in Figure 3-42; they are: Cold Bay, AK; Barrow, AK; Shemya Island, AK; Cape Kumukahi, HI; Mauna Loa, HI; Trinidad Head, CA; Point Arena, CA; Wendover, UT; Niwot Ridge, CO; Park Falls, WI; Southern Great Plains, OK; and Key Biscayne, FL. These sites are affected by anthropogenic emissions in North America to varying degrees. Average concentrations for each month and for each of the 3 yr are shown for each site in Figure 3-43. All sites demonstrate the well-known seasonality in background CO with minima in the summer and fall and maxima in the winter and spring in the Northern Hemisphere. Northern Hemisphere summer-time minima are related in large measure to the enhanced photochemical reaction of CO with OH, as described in Section 3.2.2. Analysis for North American PRB is made here by segregating the three Alaska sites (owing to their high latitude) and the two Hawaii sites (owing to their distance from the continent) and treating the remaining seven sites as being more representative of the CONUS surface-level background concentrations. Outside the defined CONUS domain used here, the 3-yr avg CO PRB in Alaska ranged from 127 to 135 ppb with an average of 130 ppb, and from 95.3 to 103.1 ppb with an average of 99.2 ppb in Hawaii. Over the CONUS domain the 3-yr avg CO PRB concentration ranged from 118 to 146 ppb with an average of 132 ppb.

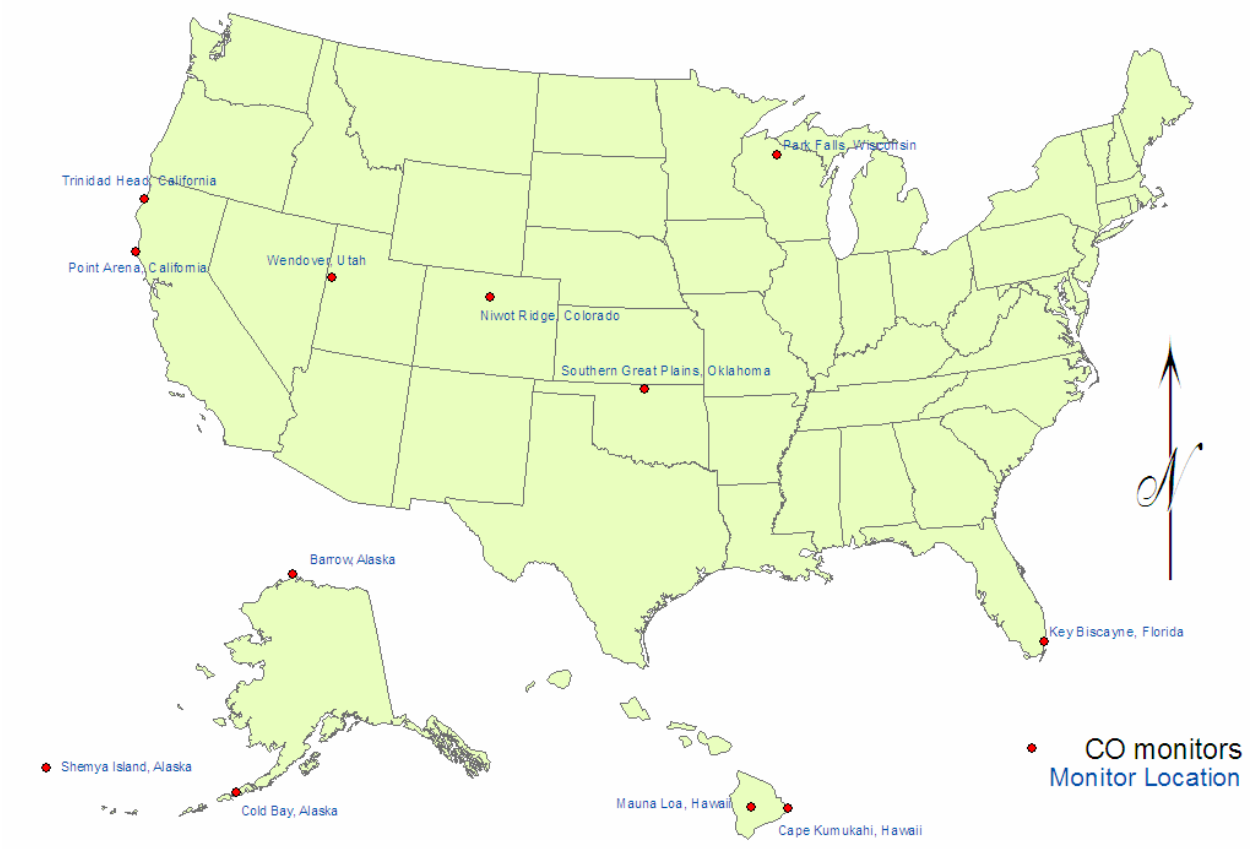


Figure 3-42. Map of the baseline monitor sites used in this assessment to compute PRB concentrations.

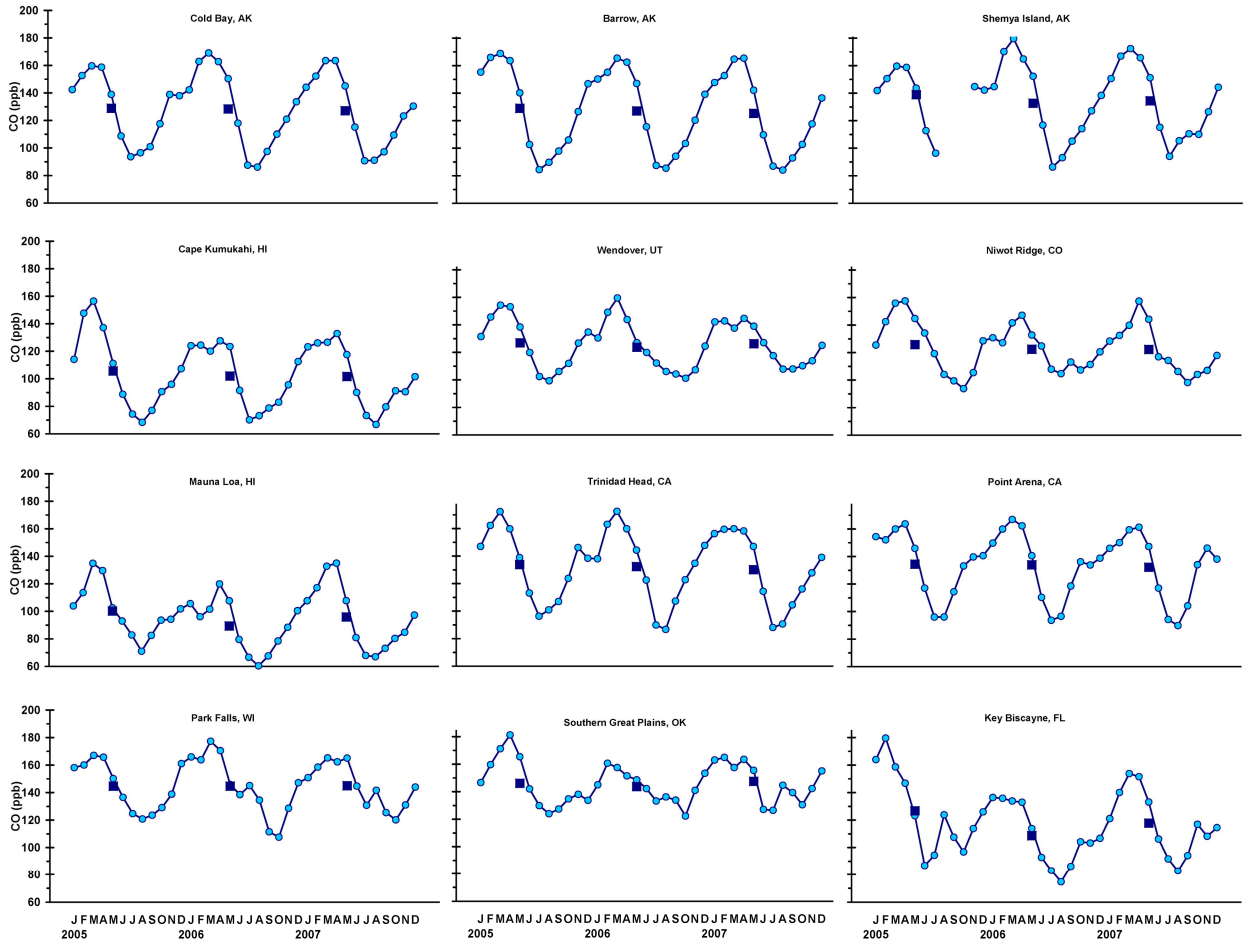


Figure 3-43. Monthly (circles) and annual (squares) average CO concentrations (ppb), 2005-2007. Cold Bay, AK; Barrow, AK; Shemya Island, AK; Cape Kumukahi, HI; Wendover, UT; Niwot Ridge, CO; Mauna Loa, HI; Trinidad Head, CA; Point Arena, CA; Park Falls, WI; Southern Great Plains, OK; and Key Biscayne, FL.

3.5.4.2. Limitations of Other Possible Methods

The significance of CO for surface-level air quality and for its indirect climate forcing effects through CH_4, O_3, and CO_2 as described previously in this chapter, and its long τ relative to that of other primarily urban and regional pollutants make it an important species for measurement and evaluation on multiple spatial, temporal, and chemical scales.

In addition to the ESRL GMD surface network used in this assessment's determination of CO PRB, CO concentrations away from local sources can be measured from space. So, for example, CO has been observed from space by the Measurement of Air Pollution from Satellites (MAPS) instrument on Space Shuttle orbiter flights for three 10-day missions in 1984 and 1994 (Connors et al., 1994, 193755) and by the Measurement of Pollution in the Troposphere (MOPITT) on the Terra satellite since 2000 (Emmons et al., 2004, 193756). Surface spatial coverage with both space-based instruments was limited by the common problems of cloud cover, high surface albedo and emissivities, and image swath pattern and timing, with the result that much of the CONUS, for example, was missed some of the time. In addition, all of these satellite measurements were limited though somewhat differently in the vertical resolution of their total column CO concentration values.

For a determination of a PRB-equivalent background concentration for 2008, the MAPS data would be of no use, except for comparisons on temporal trends, and even that is limited by the very few observations from MAPS. MOPITT data might seem more useful were it not for MOPITT's very low precision and accuracy in the lowest few kilometers above the Earth's surface of its integrated total column CO measurement by thermal infrared radiances (Shindell et al., 2005, 193746). MOPITT CO profile sensitivities are so low at the surface that retrievals at the 850 hPa level, the lowest reported, do not capture the surface concentration accurately but actually represent a broad and deep vertical slice of the lower troposphere with an integral concentration that often peaks well above 850 hPa (Shindell et al., 2006, 091028). Error analysis by Emmons et al. (2004, 193756), reported in Shindell et al. (2006, 091028) revealed that MOPITT concentration error in the lower troposphere was 7% and had greater bias over cleaner sites, which are of most interest when estimating a CONUS PRB.

Since the integrated total column measurements of CO from space-borne instruments are dominated by CO in the mid- and upper troposphere, comparisons to surface measurements are subject to appreciable error. Using a subset of seven to nine of the ESRL GMD network stations in North America, for example, to compare to the MAPS and MOPITT data, Shindell et al. (2005, 193746) found that the satellite data showed an increase of between 3 and 13 ppb CO while the surface data at these locations showed a decrease of 20 ppb in the years 2000-2002 relative to 1994. Mean global concentrations of CO were apparently decreasing before 2000, but that trend has now mostly ended (Duncan and Logan, 2008, 194042), so that the integrated column CO total measured from space may have indicated a false trend.

CO concentrations can also be predicted with numerical CTMs on regional, continental, and global scales. Hence it would, in principle, be possible to predict CO PRB concentrations for the CONUS. The chief limitation to this method comes from the highly uncertain emissions of CO worldwide needed to drive the global CTMs, which in turn set the boundary conditions and chemical flow fields for the finer-scale models that might be used to compute PRB. Interannual variability in CO emissions from global biomass burning is very high, and the emissions source strength of this signal is a very strong component of the CONUS PRB given the CO τ of ~57 d. The long τ means that PRB monitoring sites are subject to contamination by regional pollution. Estimates of total global CO emissions used in recent forward and inverse model experiments range from <1,100 MT/yr to >3,300 MT/yr (Shindell et al., 2005, 193746).

A comprehensive evaluation of 26 state-of-the-science atmospheric chemistry models exercised for present-day and future CO simulations was performed and reported by Shindell et al. (2006, 091028). They found substantial under-prediction of CO in the extra-tropical Northern Hemisphere compared to satellite and local surface observations and large variability among the models as well, even when using identical CH_4 abundances and CO emissions. In North America, for example, the multimodel average underestimated the observations of lower troposphere CO by 60 ppb or more, or by ~50% or more of the measured background concentration at many of the ESRL GMD sites. The Pearson r values for the multimodel average against MOPITT data globally for 2000-2001 was 0.84 ± 0.08 for April at 850 hPa (as near to the surface as tested) but only 0.55 ± 0.11 in October (Shindell et al., 2006, 091028). Shindell et al. (2006, 091028) proposed several reasons why this could contribute to pervasive underprediction: (1) the models do not adequately simulate CO build-up during the wintertime periods of lower OH flux; (2) the models have no seasonal CH_4 cycle with build-up in the Northern Hemisphere winter; and (3) variability in the models' OH concentrations, which accounted for ~80% of the CO intermodel variance (Shindell et al., 2006, 091028).

All of the above methods have their own advantages and disadvantages. The levels determined by the ESRL/GMD network show the temporal and spatial variability of CO levels. Although these sites are subject to North American pollution sources to varying degrees, these data could be used provided this caveat is borne in mind. Resulting errors in estimating excess risks will be very small because the concentrations are only a small fraction of the CO NAAQS.

3.6. Issues in Exposure Assessment

3.6.1. Summary of Findings from 2000 CO AQCD

The 2000 CO AQCD (U.S. EPA, 2000, 000907) describes the results of studies completed prior to 1999 on personal exposures and microenvironmental concentrations of CO. Although these studies may no longer be representative of current exposure levels due to declining ambient CO concentrations, the personal-microenvironmental-ambient relationships are still instructive. Time spent commuting, particularly in cars, was a major contributor to personal CO exposures. Many studies measured in-vehicle concentrations of CO and found elevated concentrations compared to fixed-site monitors. Roadside CO monitors were elevated compared to ambient levels and equal to or lower than in-vehicle levels (Ott et al., 1994, 076546; Rodes et al., 1998, 010611). A small portion of the CO concentrations inside a vehicle cabin comes from the vehicle itself, while a substantial fraction comes from roadway mobile source emissions entering the cabin via air exchange. Studies summarized in the 2000 CO AQCD found that in-vehicle CO concentrations were generally two to five times higher than ambient CO concentrations obtained at fixed-site monitors within the cities studied. High-traffic volumes contributed to increased in-vehicle concentrations.

Prior to the 2000 CO AQCD, it was well known that CO levels in residences may be elevated above ambient due to nonambient indoor sources, such as cooking, space heating, and smoking. Separation of indoor CO into ambient and nonambient components was found to be important for determining the effect of ambient CO concentrations, although this had not been done successfully in studies conducted to date. Two large studies performed in Denver, CO, and Washington, DC, in the early 1980s found that fixed-site monitor concentrations were higher than personal exposures for those with low-level exposures, while fixed-site monitor concentrations were lower than exposures for those with high-level exposures (Akland et al., 1985, 011618; Johnson, 1984, 024652). Nonambient sources contributing to high-total exposures likely obscured this relationship. In Denver, gas stove operation, passive smoking, and attached garages increased residential indoor exposure by 2.6, 1.6, and 0.4 ppm, respectively, compared to individuals without those sources present. Categorical analyses found significantly higher personal exposures on high-ambient concentration days than on low-ambient concentration days, suggesting that personal exposures are related to ambient levels. Nonambient exposures tend to obscure the relationship between ambient CO concentrations, as measured at ambient monitors, and total personal CO exposure.

3.6.2. General Exposure Concepts

A theoretical model of personal exposure is presented to highlight measurable quantities and the uncertainties that exist in this framework. An individual's time-integrated total exposure to CO can be described based on a compartmentalization of the person's activities throughout a given time period:

$$E_T = \int C_j dt$$

Equation 3-2

where E_T = total (T) exposure over a time-period of interest, C_j = airborne CO concentration at microenvironment *j*, and *dt* = portion of the time-period spent in microenvironment *j*. Equation 3-2 can be decomposed into a model that accounts for exposure to CO of ambient (E_a) and nonambient (E_{na}) origin of the form:

$$E_T = E_a + E_{na}$$

Equation 3-3

Examples of ambient CO sources include industrial and mobile source emissions, biomass combustion, and agricultural processes. Examples of nonambient sources include environmental tobacco smoke (ETS), cooking, and home heating. CO concentrations generated by ambient and

nonambient sources are subject to spatial and temporal variability that can affect estimates of exposure and resulting health effects. Exposure factors affecting interpretation of epidemiologic studies are discussed in detail in Section 3.6.8.

This assessment focuses on the ambient component of exposure because this is more relevant to the NAAQS review. E_a can be expressed in terms of the fraction of time spent in various outdoor and indoor microenvironments (Wallace et al., 2006, 089190; Wilson et al., 2000, 010288):

$$E_a = \sum f_o C_o + \sum f_i F_{\text{inf},i} C_{o,i}$$

Equation 3-4

where f = fraction of the relevant time period (equivalent to dt in Equation 3-2), subscript o = index of outdoor microenvironments, subscript i = index of indoor microenvironments, subscript o,i = index of outdoor microenvironments adjacent to a given indoor microenvironment i, and $F_{\text{inf}}i$ = infiltration factor for indoor microenvironment i. Equation 3-4 is subject to the constraint $\Sigma f_o + \Sigma f_i = 1$ to reflect the total exposure over a specified time period, and each term on the right hand side of the equation has a summation because it reflects various microenvironmental exposures. Here, "indoors" refers to being inside any aspect of the built environment, e.g., home, office buildings, enclosed vehicles (automobiles, trains, buses), and/or recreational facilities (movies, restaurants, bars). "Outdoor" exposure can occur in parks or yards, on sidewalks, and on bicycles or motorcycles. F_{inf} is a function of the building air exchange characteristics. Assuming steady state ventilation conditions, the infiltration factor is a function of the penetration (P) of CO, the air exchange rate (a) of the microenvironment, and the rate of CO loss (k) in the microenvironment; $F_{\text{inf}} = Pa/(a+k)$. Given that $k \rightarrow 0$ for CO, F_{inf} reduces to P. Studies of CO infiltration are reviewed in Section 3.6.5.1. In epidemiologic studies, C_a is often used in lieu of outdoor microenvironmental data to represent these exposures based on the availability of data. Thus it is often assumed that $C_o = C_a$ and that the fraction of time spent outdoors can be expressed cumulatively as f_o; the indoor terms still retain a summation because infiltration differs among different microenvironments. If an epidemiologic study employs only C_a, then the assumed model of an individual's exposure to ambient CO, first given in Equation 3-4, is re-expressed solely as a function of C_a:

$$E_a = \left(f_o + \sum f_i P\right) C_a$$

Equation 3-5

Meteorology, strength of CO sources, spatial variability of CO concentration, proximity of the study population to sources of CO, design of the epidemiologic study, and other factors determine whether or not Equation 3-5 is a reasonable approximation for Equation 3-4. Errors and uncertainties inherent in use of Equation 3-5 in lieu of Equation 3-4 are described in Section 3.6.8 with respect to implications for interpreting epidemiologic studies. Epidemiologic studies often use concentration measured at a central site monitor to represent ambient concentration; thus α, the ratio between personal exposure to ambient CO and the ambient concentration of CO, is defined as:

$$\alpha = \frac{E_a}{C_a}$$

Equation 3-6

Combination of Equation 3-5 and Equation 3-6 yield:

$$\alpha = f_o + \sum f_i P$$

Equation 3-7

α varies between 0 and 1. If a person's exposure occurs in a single microenvironment, the ambient component of a microenvironmental CO concentration can be represented as the product of the ambient concentration and P. Wallace et al. (2006, 089190) note that time-activity data and corresponding estimates of P for each microenvironmental exposure are needed to compute an individual's α with accuracy. If local sources and sinks exist and are significant but not captured by central site monitors, then the ambient component of the local outdoor concentration may be

estimated using dispersion models, land use regression models, receptor models, fine scale CTMs or some combination of these techniques. These techniques are described in Section 3.6.3.

3.6.3. Exposure Modeling

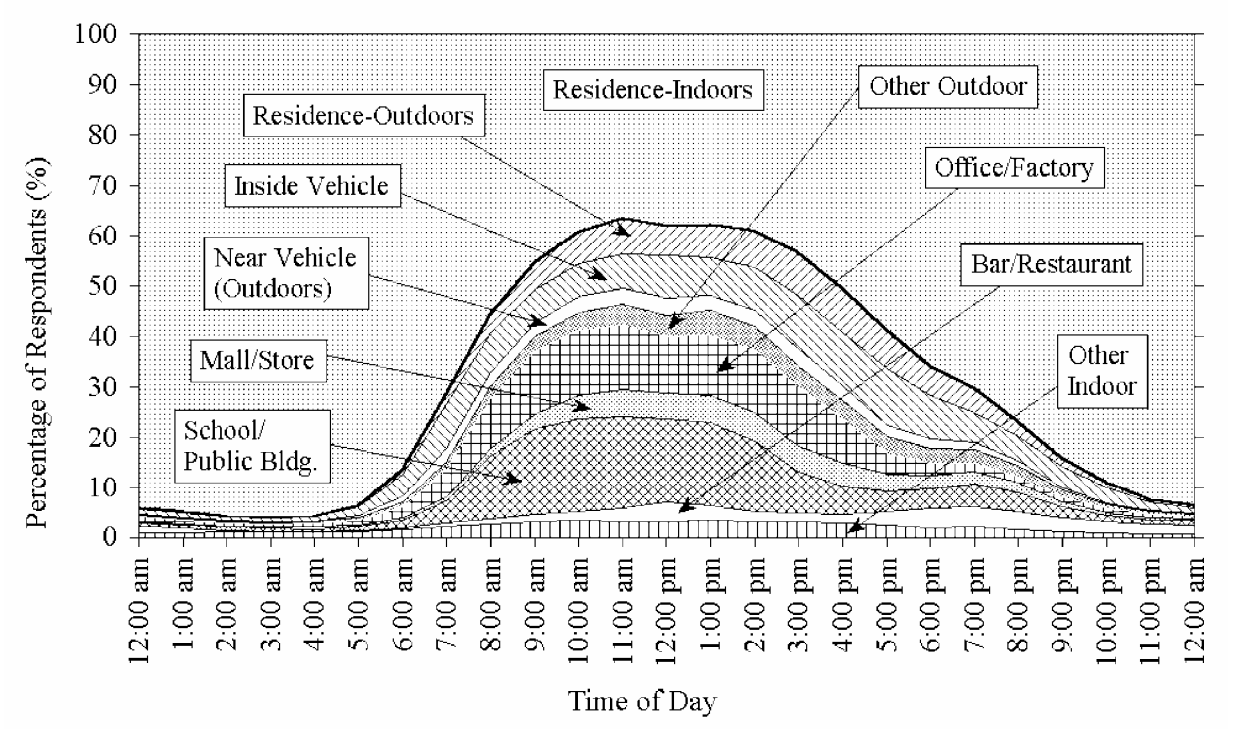
3.6.3.1. Stochastic Population-Based Time-Weighted Microenvironmental Exposure Models

Population-based methods, such as the Air Pollution Exposure (APEX) and Stochastic Human Exposure and Dose Simulation (SHEDS) models, involve stochastic treatment of the model inputs (Burke et al., 2001, 014050; U.S. EPA, 2009, 194009). These are described in detail in the 2008 NO_X ISA (U.S. EPA, 2008, 157073), in Annex AX 3.6.1. Stochastic models utilize distributions of pollutant-related and individual-level variables, such as ambient and local CO concentration source contributions and breathing rate respectively, to compute the distribution of individual exposures across the modeled population. The models also have the capability to estimate received dose through a dosimetry model. Using distributions of input parameters in the model framework rather than point estimates allows the models to incorporate uncertainty and variability explicitly into exposure estimates (Zidek et al., 2007, 190076). These models estimate time-weighted exposure for modeled individuals by summing exposure in each microenvironment visited during the exposure period. For example, Bruinen de Bruin et al. (2004, 190943) utilized the EXPOLIS (exposure in polis, or cities) model to predict CO population exposures in Milan, Italy, based on subjects' time-activity data broken into 15-min intervals. The simulation results showed that the U.S. 8-h NAAQS level was exceeded in 1 case out of 1,000. The model also showed that exposures exceeded 20 ppm in 1 case out of 100,000. The results were not shown to be very sensitive to the number of microenvironments (e.g., outdoors, indoors, in-vehicle) included in the model.

The initial set of input data for population exposure models is ambient air quality data, which may come from a monitoring network or model estimates. Estimates of concentrations in a set of microenvironments are generated either by mass balance methods or microenvironmental factors. Microenvironments modeled include indoor residences; other indoor locations, such as schools, offices, and public buildings; and vehicles. The sequence of microenvironments and exertion levels during the exposure period is determined from characteristics of each modeled individual. The APEX model does this by generating a profile for each simulated individual by sampling from distributions of demographic variables such as age, gender, and employment; physiological variables such as height and weight; and situational variables such as living in a house with a gas stove or air conditioning. Activity patterns from a database such as Consolidated Human Activity Database (CHAD) are assigned to the simulated individual using age, gender, and biometric characteristics (U.S. EPA, 2009, 194010). Breathing rates are calculated for each activity based on exertion level, and the corresponding received dose is then computed. For APEX, the CO dosimetry algorithm calculates venous COHb levels using the nonlinear CFK model, as described in Chapter 4. (U.S. EPA, 2008, 191775). Summaries of individual- and population-level metrics are produced, such as maximum exposure or dose, number of individuals exceeding a specified exposure/dose threshold, and number of person-days at or above benchmark exposure levels. The models also consider the nonambient contribution to total exposure. Nonambient source terms are added to the infiltration of ambient pollutants to calculate the total concentration in the microenvironment. Output from model runs with and without nonambient sources can be compared to estimate the ambient contribution to total exposure and dose.

Recent larger-scale human activity databases, such as those developed for the CHAD or the National Human Activity Pattern Survey (NHAPS), have been designed to characterize exposure patterns among much larger population subsets than can be examined during individual panel studies (Klepeis et al., 2001, 002437; McCurdy et al., 2000, 000782). CHAD consists of a consolidation of human activity data obtained during several panel studies in which diary or retrospective activity data were obtained, while NHAPS acquired sample population time-activity data through surveys about human activity (Klepeis et al., 2001, 002437). The complex human activity patterns across the population (all ages) are illustrated in Figure 3-44 (Klepeis et al., 2001, 002437), which is presented to illustrate the diversity of daily activities among the entire population as well as the proportion of time spent in each microenvironment. Different patterns would be anticipated when breaking down

activity patterns only for subgroups such as children or the elderly. Population exposures can be estimated using CO concentration data in each microenvironment.



Source: Reprinted with Permission of Nature from Klepeis et al. (2001, 002437).

Figure 3-44. Distribution of time that the sample population spends in various environments, from the NHAPS.

Compartmental models, such as the Indoor Air Model (INDAIR), can be used to assess exposure to infiltrated ambient air pollutants in a deterministic or probabilistic framework (Dimitroulopoulou et al., 2001, 014737). To examine indoor concentrations of ambient CO, Dimitroulopoulou et al. (2006, 090302) used the probabilistic formulation of the INDAIR model to examine indoor exposure to ambient CO, along with NO_X and PM for a given distribution of background CO levels, meteorology, residential air exchange rate, and residential room dimensions. They found that 24-h avg CO concentration increased from 1.86 ppm outdoors to 1.90-1.93 ppm indoors in the absence of nonambient sources, and that indoor 24-h avg CO concentration could increase to 1.93-2.00 ppm in the presence of smoking and to 1.98-2.32 ppm in the presence of gas cooking. Similarity between the outdoor and nonsource indoor concentrations was attributed to the lack of CO loss mechanisms. In the Reducing Urban Pollution Exposure from Road Transport (RUPERT) study, Bell et al. (2004, 192376) presented methodology to use the probabilistic form of INDAIR for development of personal exposure frequency distributions of CO, NO_X, and PM, based on time spent in residential, transportation, school, office, and recreational environments, with inputs from transportation source categories (Chen et al., 2008, 193986).

3.6.3.2. Using Spatial Models to Estimate Exposure

Another set of approaches to improve exposure estimates in urban areas involves construction of a concentration surface over a geographic area, with concentration between monitors estimated using a model to compensate for missing data. The calculated CO concentration surface can then be used to estimate exposures outside residences, schools, workplaces, roadways, or other locations of

interest. This technique does not estimate exposure directly because it does not account for activity patterns or concentrations in different microenvironments. There are two main types of approaches: spatial interpolation of measured concentrations, and regression models using land use, roadway characteristics, and other variables to predict concentrations at receptors in the domain. Rigorous first-principle models, such as dispersion models and CTMs, can also be used for this type of application, but are less suitable because they have intensive resource requirements and are typically applied over larger domains.

The STEMS model provides an example of an integrated-exposure modeling approach using a range of spatial inputs. STEMS maps exposures based on inputs for traffic levels, atmospheric dispersion, background concentrations, and geography. Gulliver and Briggs (2005, 191079) tested the STEMS model for CO and observed some correlation between modeled and measured CO concentrations ($R^2 = 0.41$), which was consistent with results for PM_{10} and NO_X. Exposures were estimated from the predicted ambient CO concentration using a term similar to α that varied depending on whether the individual was walking or in a vehicle. Gulliver and Briggs (2005, 191079) noted that a limitation to modeling CO is the scarcity of background CO data obtained at rural sites. For this reason, they assumed a constant value obtained from estimates made over the North Atlantic Ocean. Although the authors only presented detailed results for a model of PM_{10} based on traffic and meteorology in Northampton, U.K., they found that the majority of variation on a given day in modeled exposure among school children was due to differences in travel routes. Variation across days was also influenced by background and meteorological conditions. Similar results can be expected for CO based on the tendency for variation of the CO concentration profile on the neighborhood and microscales (Jerrett et al., 2005, 092864). Flachsbart (1999, 015857) tested numerous meteorological, traffic, and background CO input variables in a regression approach to predicting CO exposure among individuals while traveling in a vehicle. This work showed travel time and average speed of on-road vehicles to be important determinants of CO exposure in a vehicle. Results from individual models of this nature can be pooled to develop a distribution for examination of population effects or for comparison with population exposure models.

Dispersion Models

Dispersion models have been used both for direct estimation of exposure and as inputs for stochastic modeling systems, as described above. Location-based exposures have been predicted using a model such as California Line Source Dispersion Model (CALINE), the American Meteorological Society/Environmental Protection Agency Regulatory Model (AERMOD), CALPUFF (long-range plume transport model created by the California Air Resources Board), or the Operational Street Pollution Model (OSPM) for estimation of street-level ambient CO exposure (e.g., Abdul-Wahab, 2004, 194011; Delfino et al., 2009, 190254; Zhou and Levy, 2008, 190091). CALINE, CALPUFF, and AERMOD utilize Gaussian dispersion models to describe pollutant transport, while OSPM is a semi-empirical model of airflow and pollutant transport within an infinite street canyon. Delfino et al. (2009, 190254) used CALINE (version 4) to model exposure in the near-road environment for estimation of relative risks of asthma hospitalizations as a function of increases in ambient CO and NO_X concentrations. The concentration at each subject's home was computed with the dispersion model, and then the data were aggregated to estimate a population risk. Zhou and Levy (2008, 190091) used results from an OSPM simulation to compute intake fraction, defined as the fraction of emissions that are inhaled or ingested, for ambient CO and other copollutants. Daytime activity patterns were modeled using both CHAD and the American Community Survey (http://www.census.gov/acs/www) to model commuting behaviors that would affect both mobile-source emissions and population-based exposures. With an individualized exposure approach, the model is deterministic. However, population exposures were estimated by performing repeated simulations using various housing characteristics and then computing the probability distribution function for exposure. When comparing street-canyon exposure computed by OSPM with near-road exposure computed simply with a Gaussian dispersion model, Zhou and Levy (2008, 190091) estimated that the street-canyon exposures would be three times greater than those in the general community. Isakov et al. (2009, 191192) developed a methodology to link a chemical transport model, used to compute regional scale spatiotemporally-varying concentration in an urban area, with stochastic population-exposure models to predict annual and seasonal variation in population exposure within urban microenvironments. Although this approach was demonstrated for $PM_{2.5}$, it is

similar to the one used by Zhou and Levy (2008, 190091) for linking ambient CO concentrations with population activity pattern data to associate the spatial-concentration field with personal exposure to ambient CO.

Land Use Regression Models

Land use regression (LUR) models have also been developed to estimate pollution levels as a function of several land use factors, such as land use designation, traffic counts, home heating usage, point source strength, and population density (Briggs et al., 1997, 025950; Gilliland et al., 2005, 098820; Ryan and LeMasters, 2007, 156063). LUR is a regression derived from monitored concentration values as a function of data from a combination of the land use factors. The regression is then used for predicting concentration at multiple locations based on the independent variables at those particular locations without monitors. At the census-tract level, a LUR is a multivariate description of pollution as a function of traffic, land use, and topographic variables (Briggs et al., 1997, 025950). Like deterministic-dispersion models, LUR can be performed over wide areas to develop a probability density function of exposure at the urban scale. However, Hoek et al. (2008, 195851) warn of several limitations of LUR, including distinguishing real associations between pollutants and covariates from those of correlated copollutants, limitations in spatial resolution from monitor data, applicability of the LUR model under changing temporal conditions, and introduction of confounding factors when LUR is used in epidemiologic studies.

A GIS platform is typically used to organize the independent variable data and map the results from an LUR simulation. The GIS software creates numerous lattice points for the regression of concentration as a function of the covariates. For instance, Krewski et al. (2009, 191193) computed $PM_{2.5}$ concentrations for the New York City and Los Angeles metropolitan areas. For the Los Angeles analysis, the LUR was estimated at 23 monitors and then applied to simulate $PM_{2.5}$ concentration at 18,000 points in the simulation domain, and an inverse distance weighting (IDW) kriging method was applied to interpolate the predicted concentration. In New York City, the LUR was estimated at 49 monitors for a 3-yr model and at 36 monitors for a model of winter 2000 and then applied to simulate $PM_{2.5}$ concentration at 5,600 locations in the 28-county domain; kriging was employed only for the purpose of visualizing the concentration between monitors. The models explained 69% and 66% of the variation in $PM_{2.5}$ in Los Angeles and New York City, respectively.

GIS-based spatial-smoothing models can be used to estimate concentrations where monitors are not located. Yanosky et al. (2008, 099467) described an approach to estimate PM concentrations, using a combination of reported AQS data and GIS-based and meteorological covariates. Temporally stationary covariates included distance to nearest road for different PM size fractions, urban land use, population density, point-source emissions within 1 and 10 km buffers, and elevation above sea level. Time-varying covariates included area-source emissions, precipitation, and wind speed. In this analysis, the GIS-based covariates were temporally stationary, while the meteorological and PM monitored concentration inputs were time varying. This approach was applied to estimate $PM_{2.5}$, $PM_{10\text{-}2.5}$, and PM_{10} exposures for the Nurse's Health Study and provided estimates of concentration at approximately 70,000 nodes with $PM_{2.5}$ and/or PM_{10} data input from more than 900 AQS sites, with good validation of the $PM_{2.5}$ and PM_{10} models (Paciorek et al., 2009, 190090; Yanosky et al., 2008, 099467; Yanosky et al., 2009, 190114).

Marshall et al. (2008, 193983) compared four spatial interpolation techniques for estimation of CO concentrations in Vancouver, BC. The investigators assigned a daily average CO concentration to each of the 51,560 postal-code centroids using one of the following techniques: (1) the concentration from the nearest monitor within 10 km; (2) the average of all monitors within 10 km; (3) the IDW average of all monitors in the area; and (4) the IDW average of the three closest monitors within 50 km. Method 1 (the nearest-monitor approach) and Method 4 (IDW-50 km) had similar mean and median estimated annual average concentrations, although the 10th-90th percentile range was smaller for IDW-50. This is consistent with the averaging of extreme values inherent in IDW methods. The Pearson correlation coefficient between the two methods was 0.88. Methods 2 and 3 were considered sub-optimal and were excluded from further analysis. In the case of Method 2, a single downtown high-concentration monitor skewed the results in the vicinity, partially as a result of the asymmetric layout of the coastal city of Vancouver. Method 3 was too spatially homogenous because it assigned most locations a concentration near the regional average, except for locations immediately adjacent to a monitoring site. LUR results were also reported in this study for

NO and NO_2 and indicated that LUR's higher spatial precision reflects neighborhood-scale effects from nearby land use but may not account for urban-scale variation. Brauer et al. (2008, 156292) also evaluated LUR and IDW-based spatial-interpolation models and suggested that LUR is appropriate for directly-emitted pollutants with high spatial variability; Brauer et al. (2008, 156292) used NO and BC as examples, but CO emitted from mobile sources would also fall in that category. These results highlight the variation in local concentration estimates with choice of estimation technique.

Originally, LUR was used to model NO_2 dispersion. It has been adapted for modeling exposures to other pollutants, although application of LUR to CO exposures has been performed in only a few studies. Findings related to other pollutants are provided because they are instructive in how LUR can be used to predict CO concentrations. Carslaw et al. (2007, 148210) used multiple-regression modeling to examine the effects of traffic volumes, wind components, temperature, and time on concentrations of CO, NO_X, NO_2 (O_3 was also a predictive variable for NO_2), benzene, and butadiene at a single site. These results were used for forecasting concentrations at that site, but the study lacked the spatial resolution to predict concentrations at alternate sites. Cassidy et al. (2007, 199975) applied LUR to analyze the effect of wind, temperature, traffic volume, roadway size, number of stories of surrounding buildings, other sources of pollution, terrain, and time of day on concentrations of CO, $PM_{2.5}$, and PM_{10} at 30 street-level sites within Baguio City, Philippines. In this work, they found traffic volume was the only significant predictor of CO during rush-hour periods, while winds significantly predicted early morning concentrations of CO, $PM_{2.5}$, and PM_{10}. The model was not used for spatial interpolation in this case. Brauer et al. (2003, 155702) used LUR to analyze $PM_{2.5}$ exposure at 40-42 sites each within Stockholm, Sweden, Munich, Germany, and throughout The Netherlands. This study found a measure of traffic density to be the most significant variable predicting $PM_{2.5}$ exposure and used GIS to apply the model at home addresses of asthmatic subjects to estimate exposures. Ryan et al. (2008, 156064) reported on an LUR model developed from monitor and land-use data and then applied at the locations of children to assess their exposure to traffic-derived EC for the Cincinnati Allergy and Air Pollution Study. Ryan et al. (2008, 156064) found traffic to be the most important determinant of diesel exhaust particle exposure. In this case, wind direction was also factored into the model as a determinant of EC mixing. Although these studies differed in the number of sites and in the pollutants of focus, they are instructive in considering how LUR can be employed for estimating CO exposure.

3.6.4. Personal Exposure Monitors for CO

Portable monitors for measuring personal CO exposure include the Langan and Draeger monitors, both of which use electrochemical oxidation-reduction techniques (Langan, 1992, 046120). These monitors continuously log CO concentrations, making them suitable for use in personal monitoring studies. Electrochemical CO sensors typically have an LOD of 1 ppm and a 90% sensor response time (or the time required for the sensor to register 90% of a step change in CO concentration) of 20-60 s. The 2000 CO AQCD (U.S. EPA, 2000, 000907) provided detail on design updates of electrochemical CO sensors made during the 1990s. Commercially available personal CO exposure monitors are not designed to detect concentrations below 1 ppm. Electrochemical personal CO monitors are also typically sensitive to temperature changes, so that data correction is normally required.

3.6.5. Indoor Exposure to CO

3.6.5.1. Infiltration of Ambient CO

CO is a relatively inert gas, making the indoor decay rate negligible compared to typical air exchange rates (~1/h). In the absence of indoor sources, this would lead to an indoor-outdoor concentration ratio (I/O) of approximately 1. For this reason, few studies have calculated I/O for CO. Polidori et al. (2007, 156877) calculated I/O of 0.94-1.21 for two retirement communities in the Los Angeles area. The authors suggested that similarity between I/O for CO and NO_X can be attributed to lack of indoor sources of either gas. Chaloulakou and Mavroidis (2002, 026050) reported I/O using CO measurements in the absence of indoor sources in a school building in Athens, Greece, and

found that I/O varied with season. During the summer, median I/O was reported to be 0.57 on weekdays, 0.91 on Saturdays, and 0.81 on Sundays. In winter, median I/O was reported to be 0.82 during weekdays, 0.90 on Saturdays, and 0.74 on Sundays. In a related study, Chaloulakou et al. (2003, 190945) reported the median I/O over all days as 0.8 for the same school and 0.9 for an Athens office building with no ETS (the presence of other sources was not clearly stated but assumed zero). However, observed indoor values are often greater than outdoor concentrations in the presence of indoor sources. A recent study in the U.K. reported I/O of 3.9-4.3 in homes with gas cookers (Dimitroulopoulou et al., 2006, 090302), which is consistent with previous studies. A multipollutant study conducted in 2000-2001 attempted to measure I/O for CO and calculated residential infiltration factors, but low CO concentrations resulted in a large number of measurements below the LOD (Williams et al., 2003, 053335). Ni Riain et al. (2003, 053792) examined the effects of mechanical ventilation and wind speed on I/O. In this study, the authors measured indoor and outdoor concentrations at two buildings located on a six-lane highway in central London with natural and mechanical ventilation. Ni Riain et al. (2003, 053792) found that outdoor concentrations for each building and ventilation condition ranged from 1.5 ± 0.1 ppm to 1.9 ± 0.1 ppm. Ni Riain et al. (2003, 053792) reported cumulative I/O approaching 0.9 within 30 min of sampling for the mechanical ventilation case and cumulative I/O varying between 0.65 and 0.8 for more than 70 h of sampling for the natural ventilation case. Ni Riain et al. (2003, 053792) found that wind speed and direction influenced the variation in I/O.

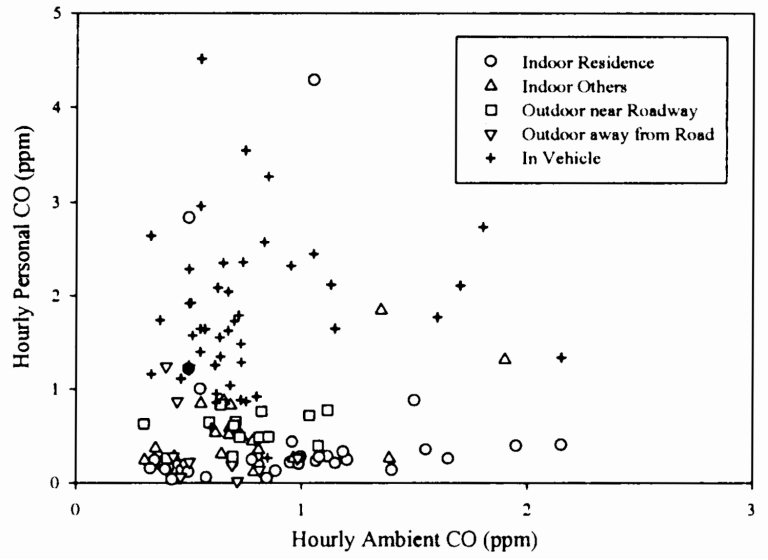
Indoor air flow may affect CO exposure in the absence of indoor sources. Milner et al. (2006, 123100) compared hourly CO concentration time series from different parts of a building (with a mix of natural and mechanical ventilation) located near a busy road and intersection in central London, U.K. They found that, within a given floor, CO concentration is greater in rooms that are closer to busy roads or an intersection. They noted that the correlation coefficient between indoor and outdoor CO concentrations also decreased within the building with distance from the road; the correlation coefficients were reported to be 0.80 for two time series obtained in rooms near the road, while they were reported to range between 0.46 and 0.55 on the sides of the building furthest from the road. The magnitude of the difference between CO concentrations in different rooms located nearer or further from the roads also depended on wind direction. Milner et al. (2006, 123100) noted that I/O tended to decrease with increasing wind speed, but Chaloulakou et al. (2003, 190945) also noted that indoor CO concentration varied inversely with wind speed. Chaloulakou et al. (2003, 190945) attributed their observation to reduced concentrations related to dilution effects. Milner et al. (2006, 123100) stated that this relationship could be due to dilution of CO or to the tendency of people to keep windows closed on windy days. Additionally, CO concentrations were higher on lower floors of the building and varied over a given day throughout the building. These findings suggest that differences in exposure can occur within the same building as a result of differences in air exchange related to access to windows, mechanical ventilation, and outdoor meteorological conditions.

3.6.5.2. Exposure to Nonambient CO

Several papers have investigated the microenvironmental sources of total personal CO exposure. The CDC conducted a survey of ED visits for nonfatal CO poisoning, CO exposure, or potential CO exposure, and found that home heating was the largest known source of CO exposure, prompting 16.4% of CO-related ED visits, followed by motor vehicle exhaust exposure accounting for 8.1% of ED visits (Annest et al., 2008, 190236). Alm et al. (2000, 192374; 2001, 020237) studied factors that contributed to elevated CO exposures among preschool children and found that presence of a gas stove at home, ETS, natural ventilation, and living in a high-rise building all contributed to increased CO exposures. Time-activity diaries were linked to personal CO exposures in the EXPOLIS study. Here, Georgoulis et al. (2002, 025563) observed that geometric mean exposure among smokers ranged from 0.33 ppm in Helsinki, Finland, to 3.2 ppm in Athens, Greece, while among nonsmokers it ranged from 0.36 ppm in Helsinki to 1.7 ppm in Milan and ambient CO concentration ranged from 0.42 ppm in Helsinki to 3.2 ppm in Athens. Bruinen de Bruin (2004, 190943) found, for a panel of 46 subjects in Milan, that indoor CO concentrations were 3.4 ppm in the presence of gas cooking and ETS, compared with 2.9 ppm in the presence of ETS only, 2.4 ppm in the presence of gas cooking only, and 1.8 ppm in the absence of indoor CO sources. Scotto di Marco et al. (2005, 144054) reported that average indoor CO increased in the presence of ETS from 0.96-1.2 ppm for the home indoor environment and from 1.0-1.4 ppm for the work indoor

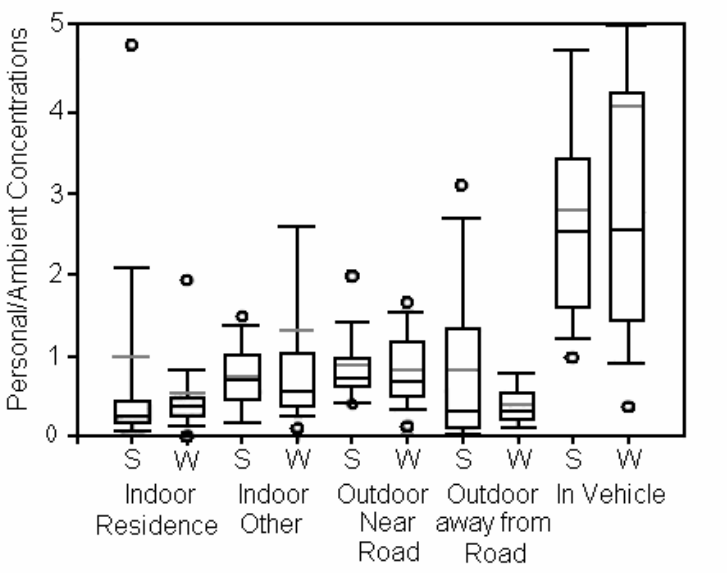
environment. CO concentrations were measured to decrease from 1.5 to 1.3 ppm in other (not home or work) indoor environments, but those locations included garages, restaurants, and bars and could have been differently influenced by CO from cooking, indoor automobiles, or other sources.

Personal CO concentrations can also be much more variable than ambient measurements. Figure 3-45 shows hourly versus personal CO concentration data obtained by Chang et al. (2000, 001276) for a 1998-1999 multipollutant sampling campaign in Baltimore, MD. Personal exposures were obtained in five separate microenvironments in this study. A high degree of scatter is evident in this figure, which suggests that these personal exposures are influenced by both ambient and nonambient sources of CO. Figure 3-46 is a box plot of the personal-to-ambient CO concentration ratio for the same five microenvironments. Wide variability is seen in these plots, particularly during the summer. Much of that variability could be due to the influence of nonambient sources, which would then result in poor correlation between total personal exposure and ambient concentration.



Source: Reprinted with Permission of the Air and Waste Management Association from Chang et al. (2000, 001276)

Figure 3-45. Hourly personal versus ambient CO concentrations obtained in Baltimore, MD, during summer of 1998 in five settings: indoor residence, indoor other, outdoor near road, outdoor away from road, and in vehicle.



Source: Adapted with Permission of the Air and Waste Management Association from Chang et al. (2000, 001276)

Figure 3-46. Box plots of the ratio of personal to ambient concentrations obtained in Baltimore, MD, during summer of 1998 and winter of 1999 in five settings: indoor residence, indoor other, outdoor near road, outdoor away from road, and in vehicle. The grey line shows the mean, and the black mid-line shows the median. S = summer; W = winter.

Vehicle self-pollution, defined by Behrentz et al. (2004, 155682) as the fraction of a vehicle's own exhaust entering the vehicle microenvironment, is another potential nonambient source of CO exposure. This has been studied using inert tracer gases to evaluate exposures of children riding school buses. Behrentz et al. (2004, 155682) used sulfur hexafluoride (SF_6) tracer gas emitted from school bus engines to determine the proportion of in-vehicle pollution related to self-pollution. Based on the SF_6 concentration, they calculated that 0.04-0.29% of the bus cabin air contained exhaust for high-emitting diesel engines, 0.01-0.03% for "regular" diesel buses, 0.02-0.04% for buses fitted with a particle trap, and 0.03-0.04% for buses running on compressed natural gas. SF_6 concentrations were higher when bus windows were closed.

3.6.6. Exposure Assessment Studies at Different Spatial Scales

3.6.6.1. Neighborhood to Urban Scale Studies of Ambient CO Exposure

Although several multipollutant exposure studies have been conducted recently in the U.S., (e.g., Sarnat et al., 2006, 089784), most have not included CO in the suite of pollutants, possibly due to high detection limits in personal monitors. A few studies conducted in Europe and Canada measured personal-ambient relationships for CO. This section summarizes CO exposure assessment studies that compare personal exposure measurements with ambient concentration measurements for the purpose of examining how well these measures correspond.

The EXPOLIS study (Georgoulis et al., 2002, 025563) found that 48-h personal exposures were significantly correlated with ambient concentrations in each of five European cities (Athens, Basel, Helsinki, Milan, and Prague). Controlling for source terms, including ETS, traffic, and natural gas appliances, regression coefficients between personal exposure and ambient concentration ranged from 0.28 in Milan to 1.99 in Helsinki and were all statistically significant ($p \leq 0.01$ for all cities except Prague, where $p = 0.05$). The regression coefficient for Helsinki (>1) likely reflects nonambient sources that were not controlled in the study. The ambient concentration was the only variable that was statistically significantly associated with 48-h personal exposure for all five cities

in this study, with correlations between personal CO exposure and ambient CO concentration ranging from 0.33 to 0.77. Georgoulis et al. (2002, 025563) reported that CO exposure in traffic ranged from 0.99 ppm in Helsinki to 4.2 ppm in Athens, while ambient CO concentration ranged from 0.42 ppm in Helsinki to 3.2 ppm in Athens. As part of this study, personal CO exposure was measured for a panel of 50 office workers in Milan (Bruinen de Bruin et al., 2004, 190943). Average measured 1-h personal exposures were 7.3 ppm in comparison with 5.0 ppm for fixed site 1-h measurements. Average 8-h (3.3 ppm) and 24-h (2.1 ppm) CO concentrations were the same for personal and fixed-site measurements. Percentage of time exposed, exposures, and percentage of exposure from the Bruinen de Bruin et al. (2004, 190943) study, in the absence of nonambient CO from ETS and gas cooking, are shown in Table 3-13. The largest percentage of time-weighted CO exposure was attributed to home indoor exposure in the absence of indoor sources, while the highest exposure levels were observed during transit; Scotto di Marco et al. (2005, 144054) found similar results. Bruinen de Bruin et al. (2004, 190943) and Scotto di Marco et al. (2005, 144054) found that mobile source emissions were important contributors to personal exposure, as described in Section 3.6.6.2.

Table 3-13. Percentage of time exposed to ambient CO (adjusted to reflect the absence of nonambient CO from ETS and gas cooking), average CO exposures, and percentage of exposure estimated for the population.

	Percent of time exposed (%)	Exposure (ppm)	Percent of exposure (%)
INDOORS	89.6		81.1
Home	56.5	1.8	49.4
Work	29.1	1.9	26.8
Other	4.1	2.5	4.9
OUTDOORS	1.8		2.1
Home	0.2	2.3	0.2
Work	0.6	2.1	0.6
Other	1.0	2.6	1.2
IN-TRANSIT	8.5		16.8
Walking	3.0	3.0	4.4
Train/metro	0.7	3.0	1.0
Bus/tram	2.0	3.8	3.7
Motorbike	0.2	4.5	0.4
Car/taxi	2.6	5.7	7.2

Source: Reprinted with Permission of Nature from Bruinen de Bruin et al. (2004, 190943)

EXPOLIS also looked at the special case of children's exposure to CO because children generally do not produce CO in their daily activities and have no occupational exposures. Alm et al. (2000, 192374; 2001, 020237) reported higher personal exposures than ambient concentrations for children aged 3-6 yr in Helsinki. Their mean 1-h daily max exposure was 5.2 ppm, compared to 1.4 ppm measured at a fixed-site monitor. For the average of 8-h and 24-h daily max concentrations, the corresponding values were 2.9 ppm and 2.1 ppm for personal exposure and 0.8 and 0.6 ppm, respectively, for fixed site measurements. The Spearman rank correlation, although statistically significant, was relatively low ($r = 0.15$) between individual 24-h avg exposure and the ambient monitor. The correlation improved when the average exposure of children measured on the same day ($r = 0.33$, 3-6 children) or the same week ($r = 0.55$, 10-23 children) was compared to the monitor data. A regression model using questionnaire data found that parental smoking status, parental education, and presence of a gas stove explained only 12% of the variability in the 8-h max

exposures, indicating that other factors, such as time spent outdoors and proximity to roadways, are likely to be important in determining personal exposure.

Kim et al. (2006, 089820) reported mean CO concentrations of 1.4 ppm for a panel of 28 cardiac-compromised individuals in Toronto, Canada. Corresponding fixed-site monitor mean concentrations ranged from 0.5 to 1.4 ppm, with an overall mean of 1.0 ppm. The observed higher personal exposures may have been due to both indoor sources and proximity to roadways when outdoors. Personal-ambient Spearman correlations ranged from -0.65 to 0.93, with a median of $r = 0.31$, indicating that while moderate correlations are observed overall, inter-individual differences based on time spent in different microenvironments have a strong influence on the observed correlation. Lai et al. (2004, 056811) measured relationships between personal CO exposure and microenvironmental (home indoor, home outdoor, and work indoor) concentrations in Oxford, U.K. The highest personal exposures were associated with smoking, cooking, and transportation, while low correlations were observed between personal and indoor residential concentrations, further indicating the importance of indoor sources and the need to separate ambient contributions to personal exposure from total personal exposure.

The studies presented above present mixed results regarding the association between ambient CO concentration measurements and personal CO exposures. Some personal CO measurements have been reported to be higher than ambient concentrations, while others are similar. Additionally, correlation between ambient CO concentration and personal exposure has varied in the literature. Nonambient (described in Section 3.6.5) and in-transit sources (described in Section 3.6.6.2) have been identified as important contributors to personal exposure. These observations raise questions about where and when ambient CO concentration can be used as a surrogate for personal CO exposure; these concepts are explored further in Section 3.6.8.

3.6.6.2. Microscale Studies of Ambient CO Exposure: Near-Road and On-Road Exposures

The 2007 American Housing Survey (AHS) (U.S. Census Bureau, 2008, 194013) reports that 17.9 million occupied homes nationwide (16.1%) are within ~90 m (300 ft) of a "4-or-more-lane highway, railroad, or airport" and so are exposed to the near-road environment. Within city centers, 6.2 million occupied homes (19.7% of those living in city centers) are within approximately 90 m of a highway, railroad, or airport; whereas in rural areas outside designated Metropolitan Statistical Areas (MSA), 1.4 million occupied homes (9.2% of those in rural areas outside MSAs) are near a highway, railroad, or airport. Those data can be put into context for exposure assessment in the near-road environment; Section 3.5.1.3 describes near-road studies in which ambient CO was measured within the vicinity of a road and microscale AQS data obtained in the near-road environment. The AQS data suggest some spatial variability (20-40% difference between microscale and middle scale monitors, with the hourly microscale concentration having a median of 0.5 ppm and a 99th percentile value of 2.2 ppm), which was much lower than that reported by Zhu et al. (2002, 041553) for the near-road environment, in which the average concentration at 17 m from the road was 2.3 ppm (range 1.9-2.6 ppm) and a factor of about 12.5 lower for the monitoring site located 300 m from the road. The larger discrepancy observed between the Zhu et al. (2002, 041553) data and the AQS data might be attributed to the fact that the sampling equipment used by Zhu et al. (2002, 041553) were downwind of the freeway for the entire sampling period, while the hourly AQS data represents a range of wind speeds and directions that vary across different monitoring sites. For those living in the 16.1% of occupied homes situated in the near-road environment (within ~90 m), median hourly CO concentrations are typically higher than those further from the road, but the magnitude of the outdoor concentration is still in most circumstances measured to be below 2.2 ppm.

Kaur and Nieuwenhuijsen (2009, 194014) and Carslaw et al. (2007, 148210) suggest that CO exposures are related to traffic volume and fleet mix in the street-canyon environment. In this research, Kaur and Nieuwenhuijsen (2009, 194014) developed a multiple linear regression of CO as a function of mode of traffic, broken down by vehicle type, wind speed, temperature, and traffic count for data obtained in central London as part of the DAPPLE study of traffic-related pollution. They added each variable successively and found traffic count, temperature, wind speed, and walking to be significant parameters in the model, with traffic count being the strongest determinant. Analysis of variance showed variability in traffic count to explain 78% of the variability in CO levels for these data, and variability in mode of transport explained 6% of the variability. Likewise, Carslaw et al. (2007, 148210) used a generalized additive model to determine how CO concentration

(log-transformed) varies as a function of year, the along-street and cross-street components of wind, temperature, Julian day, light and heavy traffic counts, and temperature for data obtained in central London. Light-duty vehicle count was a more important determinant of CO concentration than was heavy-duty (i.e., diesel) vehicle count in this study, which is not surprising because gasoline-powered vehicles are known to emit more CO than diesel engines. They found that the CO concentration declined steadily with year and that wind was the most significant covariate. The decline in CO concentration with year, adjusted for all other covariates, was usually significantly different than the simple relationship between concentration and year, but the adjusted and unadjusted trends were similar. In addition to showing meteorology to be an important determinant of concentration, these modeling exercises also suggest a linear or log-linear relationship between concentration and traffic count.

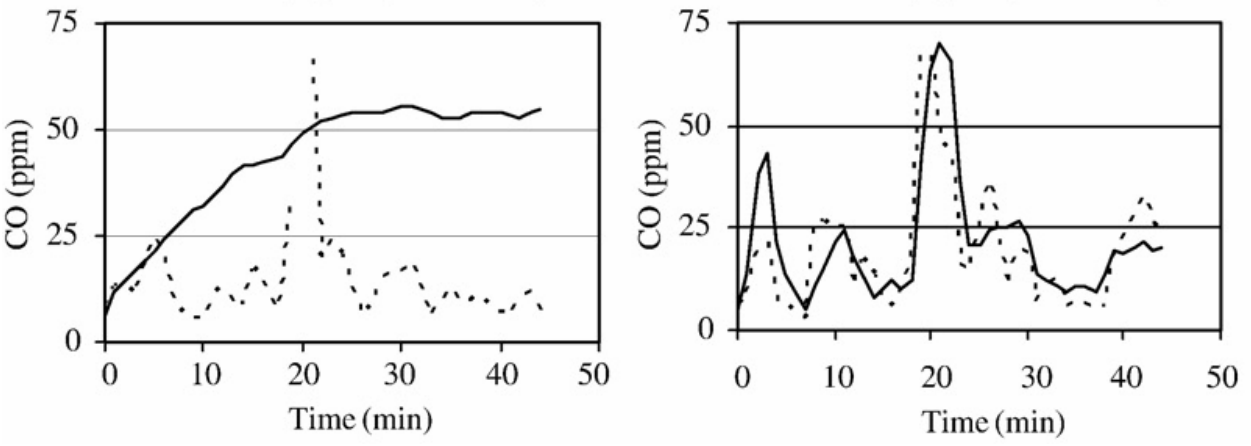
Findings regarding meteorology are consistent with in-vehicle CO concentration studies. Gómez-Perales et al. (2007, 138816) also noted that meteorology can impact in-vehicle exposures, with evening increases in wind speed causing a 50% reduction in CO exposures among bus and minibus commuters. Alm et al. (1999, 047196) made a similar observation in a study of urban commuters' exposure within a vehicle. These observations are sensible given the influence of meteorology on near-road concentrations shown by Baldauf et al. (2008, 190239) and Gokhale and Khare et al (2007, 194015).

A number of studies have focused on transit-time CO exposure, which can occur while in a vehicle or cycling (on-road) or while walking (near-road). Chang et al. (2000, 001276) showed that personal exposures in vehicles were on average 2.8 times higher than ambient concentrations during the summer and 4.1 times higher than ambient concentrations in the winter (Figure 3-46). For the other four microenvironments tested, the average ratio of personal exposure to ambient concentration was ~1. Kaur et al. (2005, 086504) found that transit time exposures in London, U.K., were significantly higher than measurements made at a fixed-site background monitor away from traffic (0.3 ± 0.1 ppm) for car riders (1.3 ± 0.2 ppm), taxi riders (1.1 ± 0.1 ppm), bicyclers (1.1 ± 0.2 ppm), walkers (0.9 ± 0.2 ppm), and bus riders (0.8 ± 0.1 ppm). Curbside measurements (1.5 ± 0.7 ppm) in this study were slightly higher than car riders' exposures. Duci et al. (2003, 044199) found that average in-transit exposures in Athens, Greece, were highest for cars (winter: 21.4 ± 4 ppm), followed by pedestrians (winter: 11.5 ± 2.6 ppm; summer: 10.1 ± 1.7 ppm), buses (winter: 10.4 ± 2.9 ppm; summer: 9.4 ± 3.6 ppm), trolleys (winter: 9.6 ± 1.9 ppm; summer: 8.2 ± 3 ppm), and rail transit (winter: 4 ± 0.6 ppm; summer: 3.4 ± 0.7 ppm). Duci et al. (2003, 044199) did not provide fixed-site CO concentrations but stated that in-transit exposures were higher in each case. Gómez-Perales et al. (2004, 054418) measured CO exposures on buses, minibuses, and metro cars in Mexico City, Mexico, to be 12 ppm, 15 ppm, and 7 ppm, respectively. These values are much higher than CONUS measurements and those presented by Kaur et al. (2005, 086504), but the relative difference between the minibus and bus exposures in the Gómez-Perales et al. study are similar to those seen for the taxi-to-bus or car-to-bus comparisons in Kaur et al. (2005, 086504). These studies indicate that on-road exposures might be influenced by vehicle type, but that city-to-city differences are likely larger than differences between different modes of transport.

Additional analyses from the EXPOLIS study indicated that on-road mobile source emissions were the most important source of CO exposure for non-ETS-exposed subjects (Bruinen de Bruin et al., 2004, 190943; Scotto Di Marco et al., 2005, 144054). Scotto di Marco et al. (2005, 144054) found that, for a panel of 201 adult Helsinki, Finland, residents (aged 25-55 yr), subjects spent 8.1% (1.9 h) of their time in transit, which accounted for 12.6% of their total exposure (range of means = 0.96 ppm on a train – 2.8 ppm in a car). Similarly, in a panel study of 50 office workers, Bruinen de Bruin et al. (2004, 190943) found that, in the absence of nonambient sources, the subjects spent 8.5% (2 h) of their time in transit, which accounted for 16.8% of their total exposure, with 2.6% of time spent in a car or taxi accounting for 7.2% of exposure (mean = 5.7 ppm). Commuting time was an important predictor of exposure, such that subjects living in low CO concentration suburban areas and commuting to work experienced higher exposures than urban residents with short commute times. According to the 2007 AHS (U.S. Census Bureau, 2008, 194013), 110.1 million U.S. workers (87.8% of those working) commute to work in automobiles. 32.8% of U.S. workers work at home or commute less than 15 min to work, 32.1% commute 15-29 min to work, 15.1% commute 30-44 min to work, 5.7% commute 45-59 min to work, and 5.0% commute 1 h or longer to work.

Vehicle ventilation can be an important determinant of in-vehicle concentrations. A study from Abi Esber and El Fadel (2008, 190939) in Beirut, Lebanon, is presented because the authors observed in-vehicle CO concentration time series under a range of ventilation conditions, although

the in-vehicle CO concentrations measured are substantially higher than those typically observed in the U.S. Abi Esber and El Fadel (2008, 190939) reported results from CO concentration measurements taken directly outside and within an automobile in Beirut, Lebanon, during the morning commute period of 7:30-9:30 a.m under three different ventilation conditions. Figure 3-47 shows that the time series for the cabin and outdoor CO samples are very similar for the fresh air scenario. However, for the recirculating air ventilation scenario, the in-vehicle concentration increases and then reaches a plateau at a higher level. Abi Esber et al. (2007, 190941) stated that unaccounted sources of CO cause the build-up of in-cabin CO concentrations when the ventilation is set to recirculation mode. The correspondence between in-vehicle and outside-vehicle concentrations for the fresh air ventilation experiments, and lack thereof for the recirculation mode ventilation experiments, observed by Abi Esber and El Fadel (2008, 190939) suggests that in-vehicle concentrations of ambient CO are affected by mode of ventilation.



Source: Reprinted with Permission of Elsevier Ltd. from Abi Esber and El Fadel (2008, 190939)

Figure 3-47. Comparison of in-vehicle (solid line) and outside-the-vehicle (dotted line) results for (left) driving with windows closed and air conditioner in recirculating air mode, and (right) driving with windows closed and air conditioner in fresh air mode.

Substantial variability can occur over time within a vehicle. Riediker et al. (2003, 043761) measured CO concentrations inside highway patrol cars during shifts. Troopers recorded in a time-activity diary the ventilation settings of their cars and exit/entry from the vehicle, and the air conditioning was typically set to recirculation mode during the shifts. Riediker et al. (2003, 043761) found that CO concentrations (mean ± SD: 2.6 ± 1.1 ppm) were higher than ambient monitor concentrations (0.8 ± 0.3 ppm). They were also higher than roadside CO concentrations (1.1 ± 0.3 ppm), indicating that either the vehicle itself contributes to in-cabin CO or on-road concentrations are higher than roadside concentrations or both. Riediker et al. (2003, 043761) noted that within-shift variability was higher than between-shift variability, which underscores the variability in police officers' activities during a given shift. Data were not segregated by ventilation settings, although the police officers typically operated the air conditioning continually because the study was performed during the summer. Alm et al. (1999, 047196) reported in-vehicle CO concentrations of 5.7 ppm in the morning and 3.1 ppm in the afternoon commute for Kuopio, Finland. These data indicate that within-shift variability observed by Riediker et al. (2003, 043761) might be related to time of day. Likewise, Rodes et al. (1998, 010611) reported CO concentrations in vehicles in Sacramento and Los Angeles under different driving conditions (arterial, freeway, high-occupancy-vehicle freeway lane, and "maximum" conditions at rush-hour and nonrush-hour times). They measured peak in-vehicle concentrations spanning 7-67 ppm on a freeway during rush hour, although the mean for each scenario was <6 ppm. In comparison, the peak roadside concentration ranged from 3 to 11 ppm and the peak ambient CO concentration was 1.3 ppm at the time of the measurements. The Rodes et al. (1998, 010611) data agree with results from the Riediker et al.

(2003, 043761) and Alm et al. (1999, 047196) studies showing that substantial variability in CO concentration inside the cabin of a vehicle can occur during the course of a commute.

In their review of roadway exposures to CO and PM, Kaur et al. (2007, 190070) listed a number of factors that may influence near-road or on-road exposure. Vertical CO concentration gradients have been documented in which concentrations decreased with height; lower breathing zone height among children may make them more likely to be exposed to higher CO tailpipe emissions. With respect to transportation, Kaur et al. (2007, 190070) suggested that vehicle ventilation, speed, position in traffic, and start/stop activity influence in-vehicle exposures. Abi Esber and El Fadel (2008, 190939) and Riediker et al. (2003, 043761) illustrated the effect of vehicle ventilation on in-vehicle concentrations. The influence of vehicle speed and start/stop activity is consistent with the turbulence research of Khare et al. (2005, 194016) and Gokhale and Khare (2007, 194015) that suggested an increase in traffic volume and vehicle movement acts to dilute the on-road concentration of CO discussed in Section 3.5.1.3.

3.6.7. Association between Personal CO Exposure and Copollutants

Since incomplete combustion is the primary source of ambient CO in urban areas, exposure to ambient CO is accompanied by exposure to other combustion-related pollutants, such as NO_X, PM, and VOCs. Thus, ambient CO is often considered a surrogate for exposure to traffic-generated pollutants. However, the specific mix of CO with NO_X and PM depends on the source; for example, the mixture generated by gasoline engines differs from that produced by natural gas combustion. Correlations between ambient CO and ambient $PM_{2.5}$, PM_{10}, NO_2, SO_2, and O_3 from AQS data and the peer-reviewed literature were presented in Section 3.5.3. Nationwide, ambient CO was most highly correlated with ambient NO_2, followed by $PM_{2.5}$ and PM_{10}. Correlations between CO and $PM_{2.5}$ were not consistently positive on a national basis; correlations spanned from negative to positive for ambient CO with ambient SO_2 and ambient PM_{10}, and ambient CO was negatively correlated with ambient O_3. The correlation between ambient CO and specific ambient VOCs depends on parameters such as ambient temperature and the volatility of a specific compound.

Relationships between personal CO exposures and copollutants were reported less frequently in the literature, but results from these studies were consistent with the findings cited above. In a study of personal exposures to CO, $PM_{2.5}$, and ultrafine PM in a street canyon, Kaur et al. (2005, 086504) found low Pearson's correlation of total personal CO exposure with personal $PM_{2.5}$ exposure ($r = 0.23$). Personal CO exposure had much better correlation with personal ultrafine particle (UFP) exposure ($r = 0.68$). Chang et al. (2000, 001276) reported correlations of personal CO exposure with personal $PM_{2.5}$, personal toluene, and personal benzene exposures in Baltimore, MD, at five locations, labeled indoor residential, indoor nonresidential, outdoors near roadway, outdoors away from road, and in vehicle. Much variability was observed in the correlations for different locations and seasons (winter versus summer). In general, the correlations of personal CO with personal VOCs tended to be stronger in the winter. Chang et al. (2000, 001276) suggested that lower wintertime indoor air exchange rates could increase exposure to nonambient CO and VOC sources, such as ETS, and hence increase correlations between personal exposure of CO to VOCs. Significant associations of CO with benzene and toluene were also observed in vehicle microenvironments.

3.6.8. Implications for Epidemiology

Exposure error can be an important contributor to variability in epidemiologic study results. Community time-series studies may involve thousands or millions of people whose exposure and health status is estimated over the course of a few years using a short monitoring interval (hours to days). Community-averaged concentration is typically used as a surrogate for ambient exposure in community time-series studies. Exposures and health effects are spatially aggregated over the time intervals of interest because community time-series studies are designed to examine health effects and their potential causes at the community level (e.g., Bell et al., 2009, 194033). A longitudinal cohort epidemiology study typically involves hundreds or thousands of subjects followed over several years or decades. Concentrations are generally aggregated over time and by community to estimate exposures (e.g., Rosenlund et al., 2006, 089796). In addition, panel studies, which consist of a relatively small sample (typically tens) of study participants followed over a period of days to months, have been used to examine the health effects associated with exposure to ambient

concentrations of air pollutants. Panel studies include time-activity diary studies (Akland et al., 1985, 011618; Bruinen de Bruin et al., 2004, 190942; Scotto Di Marco et al., 2005, 144054). These studies may apply a microenvironmental model to represent exposure to an air pollutant.

The importance of exposure misclassification varies with study design and is dependent on the spatial and temporal aspects of the design. For example, the use of a community-averaged CO concentration in a community time-series epidemiologic study may not allow for adequate examination of the role of spatial variability. Other factors that could influence exposure estimates include spatial and temporal variability related to source strength, topography of the natural and built environment, and meteorology; measurement errors; use of ambient CO concentration as a surrogate for ambient CO exposure; and the presence of CO in a mixture of combustion-related pollutants. The following sections will consider various sources of error and how they affect the interpretation of results from epidemiologic studies of different designs.

3.6.8.1. Measurement Error

Measurement Error at Community-Based Ambient Monitors and Exposure Assessment

Because CO concentrations measured with community-based ambient monitors are often used as surrogates for ambient CO exposure in epidemiology studies, the limitations of the instrumentation are important to consider. As stated in Section 3.4.2, among the 291 monitors meeting completeness criteria for 2005-2007, only 8 were monitors with LOD = 0.04 ppm; the other monitors had LOD of 0.5 ppm. Among the nationwide AQS data for 2005-2007 from these 291 monitors, more than 50% of the hourly CO concentration data were below the LOD of the instrumentation. Data below the LOD adds uncertainty to the association between CO exposure and health effects estimates. Additionally, many of the monitors are not sited for a specific measurement scale, and a given scale classification can represent a range of CO source conditions, as described in Section 3.5.1.3. These factors also contribute uncertainty in interpretation of measurements.

Instrumental measurement error, other than that related to high LOD, is not expected to bias health effect estimates substantially in most circumstances. Because there will be some random component to instrumental measurement error, the correlation of the measured CO concentration with the true CO concentration will likely be <1. When analyzing the effect of instrument error for measuring nonreactive ambient pollutants, Zeger et al. (2000, 001949) stated that the instrument error for ambient measurements "is close to the Berkson type." In the Berkson error model, the measured-exposure estimate is used instead of the true exposure, based on the assumption that the average measurement is the average of the true exposure. It is generally expected that the health effects estimate will not be biased by using measured values with error but may have more uncertainty than would an estimate based on the true-average exposure. In order for instrument error to cause substantial bias in health effects estimates, the error term (the difference between the true concentrations and the measured concentrations) must be strongly correlated with the measured concentrations.

Measurement Error for Personal Exposure Monitors

Personal electrochemical CO monitors are subject to interference and drift and have a relatively high LOD (~1 ppm) relative to current ambient concentrations. Previous studies in the 1980s and 1990s, when ambient levels were higher, involved successful deployment of these monitors, but more recent exposure studies have avoided personal CO measurements because there are now a high percentage of nondetects. The lack of a suitable personal monitor for measuring low-level exposures (<1 ppm) has hampered field studies assessing personal exposure to ambient CO. Chang et al. (2001, 019216) evaluated the Langan CO monitor as part of an air quality sampling manifold. At relatively high (0.4-3.0 ppm) CO concentrations, the instrument correlated well (R^2 = 0.93) with a reference NDIR CO monitor, with the Langan underestimating the CO concentration by 41%. When ambient levels fell consistently below that level, coefficient of determination (R^2) between the Langan and reference monitor fell to R^2 = 0.40 in summer and R^2 = 0.59 in winter, with

the arithmetic average concentration underestimated by 47% in summer and by 63% in winter. Chang et al. (2001, 019216) pointed out the need for frequent instrument zeroing to minimize instrument drift. Abi Esber and El Fadel (2007, 190940) evaluated a similar personal electrochemical CO sensor, the GEM™ 2000, by comparing measured concentrations with those obtained through co-located grab-bag sampling in a vehicle cabin. Differences between the GEM™ 2000 and the reference samples were fairly low during weekday driving (differences = 2.1-10.6%). Differences on Sundays, when traffic was significantly lower than during weekdays, were dependent on vehicle ventilation conditions, with better agreement when vehicle ventilation allowed for higher cabin CO concentrations (differences = 3.4-5.6%). But the electrochemical sensor did not compare well with reference values when concentrations were low (differences = 20-71%). In general, it is difficult to separate the large instrumental measurement error seen at concentrations below instrument LOD from variation related to nonambient CO sources. This large variation in personal measurements can result in high levels of classical measurement error (Sheppard et al., 2005, 079176).

3.6.8.2. Exposure Issues Related to Nonambient CO

The focus of the ISA is on ambient CO because that is relevant to the NAAQS. Uncertainty related to nonambient CO exposure may make it difficult to distinguish the effect of ambient CO on health effects. Wallace and Ziegenfus (1985, 011656) used NHANES II (1976-1980) data to evaluate the relationship between COHb levels and ambient CO concentration in 20 U.S. cities. They found a significant slope of 0.066% per 1 ppm increase of CO concentration. However, there was much scatter in the data, and variability in ambient CO concentration only accounted for 3% of the variation in COHb. The authors attributed this scatter to variability in nonambient sources such as gas cooking and ETS. This finding illustrates the importance of considering the relative role of ambient and nonambient CO in total personal exposure.

Ambient and nonambient CO are chemically identical and so exert the same health effects. At the same time, ambient and nonambient sources are distinct and not correlated with each other (Wilson and Suh, 1997, 077408) and so would not confound the association between ambient CO exposure and the health effect (see also Sheppard et al., 2005, 079176). Zeger and Diggle (2001, 026017) noted that, because ambient and nonambient CO exposures are uncorrelated, in a health effects model the regression coefficient of ambient concentration should be equal to the product of α (the ratio of ambient exposure to ambient concentration) and the regression coefficient obtained when average personal exposure is used. The confidence intervals around the estimate obtained using total personal exposure would be wider because nonambient CO concentrations add variability. This is true even for the case when the chemical compound is the same for the ambient and nonambient pollutants, as in the case of CO. Likewise, Sheppard et al. (2005, 079176) simulated ambient and nonambient exposures to a nonreactive pollutant and observed that nonambient exposure has no effect on the association between ambient exposure and health outcomes for the case where ambient and nonambient concentrations were independent. Hence, the bias that will be introduced to epidemiologic models by using ambient CO concentration instead of personal exposure to ambient CO is given by the average α. Random variations in daily values of α would not change the health effects estimate but would also widen the confidence intervals around the health effect estimate.

3.6.8.3. Spatial Variability

CO concentration is known to be spatially heterogeneous, as evidenced by the near-road and in-vehicle studies cited in Sections 3.5.1.3 and 3.6.6.2, as well as the intraurban correlations provided in Section 3.5.1.2 and Tables A-9 through A-16 of Annex A. Results from Zhu et al. (2002, 041553), which showed a large CO concentration gradient in the near-road environment, support the contention that CO exposures for those living in the near-road environment but far from a monitor might be underestimated. Conversely, exposures for those living away from roads might be overestimated by near-road CO concentration measurements. Exposure error may occur if the ambient CO concentration measured at the central site monitor is used as an ambient exposure surrogate and differs from the actual ambient CO concentration outside a subject's residence and/or worksite (in the absence of indoor CO sources). Averaging data from a large number of samplers will dampen intersampler variability, and use of multiple monitors over smaller land areas may allow for

more variability to be incorporated into an epidemiologic analysis. This is consistent with conclusions presented in the 2000 AQCD (U.S. EPA, 2000, 000907).

Community exposure may not be well represented when monitors cover large areas with several subcommunities having different sources and topographies. The intersampler correlations of AQS data from monitors, presented in Section 3.5.1.2, reflect how well the time series of concentration data correspond across metropolitan areas. Overall, the data show moderate site-to-site correlation; for example, in the Los Angeles CSA the mean of the correlation was 0.50, and within one standard deviation of the mean, the range of correlations was 0.36-0.65. Bell et al. (2009, 194033) tested the association between monitor density and 1-h max CO effect estimates for CVD hospitalizations for 126 U.S. counties and found an 8% increase in effect estimate size (95% CI: -7% to - 24%) with an IQR decrease in area covered by the monitor. This difference was not statistically significant but suggested that the magnitude of the effect estimate might be related to monitor coverage. Sarnat et al. (2009, 180084) studied the spatial variability of CO, along with NO_2, O_3, and $PM_{2.5}$, in the Atlanta, GA, metropolitan area and how spatial variability affects interpretation of epidemiologic results, using time-series data for circulatory disease ED visits. Sensitivity to spatial variability was examined at slightly greater than neighborhood scale (8 km) in this study. Interestingly, Sarnat et al. (2009, 180084) found that relative risk varied with distance between the monitor and study population when comparing urban to rural locations, but distance of the study population to the monitor was not an important factor when comparing urban population groups. This suggests that, even for spatially heterogeneous CO, urban scale measures may produce results comparable to neighborhood-scale exposures in some circumstances. This may be due to comparability of sites throughout a city, for example, as a result of similar traffic patterns. However, Sarnat et al. (2009, 180084) caution that, because their study was limited to 8 km radii, it is not possible to interpret this work with respect to near-road and on-road microscale exposures.

3.6.8.4. Temporal Variability

Temporal Correlation

Within a city, lack of correlation of relevant time series at various sites results in smoothing the exposure/surrogate concentration function over time and resulting loss of peak structure from the data series. At the same time if monitors are well correlated across a metropolitan area, even if the magnitude of concentration varies over space, time series analyses should provide comparable results across larger spatial areas. Such temporal correlation resulted in the small variation in relative risk estimates within the metropolitan region in Sarnat et al. (2009, 180084), where peak rush-hour times were similar throughout the city, in comparison with the rural area where temporal driving patterns were different. Burnett and Goldberg (2003, 042798) found that community time-series epidemiologic study results reflect actual population dynamics only when five conditions are met: environmental covariates are fixed spatially but vary temporally; the probability of the health effect estimate is small at any given time; each member of the population has the same probability of the health effect estimate at any given time after adjusting for risk factors; each member of the population is equally affected by environmental covariates; and, if risk factors are averaged across members of the population, they will exhibit smooth temporal variation. Note that for this study, Burnett and Goldberg (2003, 042798) analyzed mortality related to PM exposure, but the results are not specific to a given pollutant or health effect and thus are generalized here for time-series analysis. Dominici et al. (2000, 005828) noted that ensuring correlation between ambient and community average exposure time-series air pollutant data is made difficult by limitations in availability and duration of detailed ambient concentration and exposure time-series data, resulting in a source of uncertainty. If sufficient data are available and the time series of concentration data adequately represent population dynamics, then high temporal correlation between sampling sites should limit bias in health effects estimates, even if the magnitude of the concentrations differ.

Seasonality

Community time-series epidemiologic studies can be designed to investigate seasonal effects by incorporating seasonal interaction terms for the exposure surrogate and/or meteorology (e.g., Dominici et al., 2000, 005828). Sheppard et al. (2005, 079176) examined the role of seasonality on epidemiologic models. They found that α for the population will vary seasonally. This makes sense because α is a function of the amount of time spent indoors and outdoors and of indoor ventilation. Given that use of ambient CO concentration instead of ambient CO exposure biases the coefficient used in epidemiologic models by α, Sheppard et al. (2005, 079176) found that seasonal trends causing a change in α would contribute additional positive or negative bias, depending on the season and region of the country. However, several studies discussed in Chapter 5 investigated seasonal effects. No consistent seasonal pattern across health outcomes was observed in these studies.

3.6.8.5. CO Exposure in Copollutant Mixtures

Because CO exposures most often occur together with exposure to other combustion-related pollutants, especially in traffic, interpretation of health studies using ambient CO data can be a challenge, as discussed further in Chapter 5. Ambient CO concentrations from AQS data (Section 3.5.3) have been shown to be correlated with ambient concentrations of NO_2 and VOCs, and personal CO exposures have been correlated with personal PM and VOC exposures (Section 3.6.7). Correlation between factors is one condition for confounding, so it is possible that coexistence of CO with NO_2 or VOCs could confound estimates of the health effects of ambient CO concentrations, and CO concentration could potentially confound estimates of the health effects of NO_2 or VOCs. For this to be true, both CO and the copollutant would have to be correlated with the health outcome of interest. The moderately high correlations between ambient CO and copollutants make it difficult to discern the extent to which CO and other compounds are associated with a given health effect.

It is also possible that the factor of interest may be the multipollutant mixture emitted from on-road or other combustion processes. The HEI Report on Traffic Related Pollutants (HEI, 2009, 191009) suggests that ambient CO, NO_2, and benzene could all be considered as surrogates for mobile source-related pollution, but none are ideal surrogates for mobile-source pollution because ambient CO concentration tends to decrease rapidly with distance from the source (e.g., Baldauf et al., 2008, 190239; Zhu et al., 2002, 041553), NO_2 is reactive and benzene is volatile. Additionally, PM components of mobile source emissions change rapidly in size and composition from secondary formation and other atmospheric processing. Given that the mixture of mobile source-related emissions changes rapidly as a result of these factors, the ratio of CO to other components of mobile-source emissions also changes. Hence, even if CO is itself stable within the mixture of copollutants, the dynamic evolution of the mixture may change the representativeness of CO as an indicator of that mixture over time. Additionally, reductions in CO emissions over the past 30 yr have brought ambient CO concentrations down substantially, with more than half of hourly measurements below the LOD for most instruments (Section 3.5.1.1). Furthermore, CO and other copollutants found in mobile-source emissions have multiple anthropogenic and biogenic sources and, as a result, are difficult to attribute solely to mobile source pollution (Section 3.2). For all of these reasons, the representativeness of CO as an indicator of the multipollutant mixture of mobile-source emissions has not been clearly determined.

3.6.8.6. Conclusions

This section presents considerations for exposure assessment and the exposure errors and uncertainties that can potentially affect health effects estimates. These issues can be categorized into the following areas: measurement, nonambient sources, spatial variability, temporal variability, and CO in copollutant mixtures. Potential influences of each of these sources on health effect estimates derived from panel, time-series, and longitudinal epidemiologic studies are described above. Additionally, error sources have the potential to interact with each other. For example, CO concentrations have been shown to decrease rapidly with distance from a highway, and so spatial variability is an important issue in assessing CO exposure. Exposure error may occur if the ambient CO concentration measured at the central site monitor is used as an ambient exposure surrogate and differs from the actual ambient CO concentration outside a subject's residence and/or worksite.

However in time-series epidemiologic studies, spatial variability will only be an important source of error if the time series of CO concentration at different locations are not well correlated in time. The spatial variability of CO, in mixture with the dynamically changing group of mobile source pollutants, adds to the difficulty of quantifying the health effects related specifically to CO compared with those related to other combustion-related copollutants. In most circumstances, exposure error tends to bias a health effect estimate downward (Sheppard et al., 2005, 079176; Zeger et al., 2000, 001949). Insufficient spatial or temporal resolution to capture true variability and correlation of CO with copollutants are examples of sources of uncertainty that could widen confidence intervals and so reduce the statistical significance of health effects estimates.

3.7. Summary and Conclusions

3.7.1. CO Sources, Emissions, and Chemistry

In the U.S., on-road mobile sources constituted more than half, or ~61 MT out of ~117 MT, of total CO emissions in the 2002 NEI and BEIS, which are the most recent publicly available CO emission datasets meeting EPA's data quality assurance objectives. In metropolitan areas in the U.S., for example, as much as 75% of all CO emissions can come from on-road vehicle exhaust (U.S. EPA, 2006, 157070). The majority of these on-road CO emissions derive from gasoline-powered vehicles since the O_2 content, pressure, and temperature required for diesel fuel ignition do not produce large quantities of CO. Anthropogenic CO emissions are estimated to have decreased 35% between 1990 and 2002. On-road vehicle sector emissions controls have produced nearly all these national-level CO reductions. Nationally, biogenic emissions, excluding fires, were estimated to contribute ~5%, or ~5.8 MT, of total CO emissions from all sources in 2002, and fires in 2002 added another 16%, or ~18.5 MT, to the national CO emissions total. Although these estimates are generated using well-established approaches, uncertainties inherent in the emission factors and models used to represent sources for which emissions have not been directly measured and vary by source category, season, and region.

In addition to being emitted directly by incomplete combustion, CO is produced by photooxidation of CH_4 and other VOCs in the atmosphere, including NMHCs. Estimating the CO yield from oxidation of HCs larger than CH_4 requires computing the yields of several intermediate products and reactants from oxidation of the parent molecules. The major pathway for removal of CO from the atmosphere is reaction with OH to produce CO_2 and HO_2. The mean photochemical lifetime (τ) of CO in the northern hemisphere is ~57 days. During winter at high latitudes, CO has nearly no photochemical reactivity on urban and regional scales.

3.7.2. Climate Forcing Effects Related to CO

Recent data do not alter the current well-established understanding of the role of urban and regional CO in continental- and global-scale chemistry outlined in the 2000 CO AQCD (U.S. EPA, 2000, 000907) and subsequently confirmed in the recent global assessments of climate change by the Intergovernmental Panel on Climate Change (IPCC, 2001, 156587; IPCC, 2007, 092765). CO is a weak direct contributor to RF and greenhouse warming. Sinha and Toumi (1996, 193747) estimated the direct RF of CO computed for all-sky conditions at the tropopause to be 0.024 W/m^2 based on an assumed change in CO mean global concentrations from 25 to 100 ppb since preindustrial times. The direct RF attributed to CO over this time-frame is ~1.5% of the direct RF for CO_2 estimated by the IPCC (Forster et al., 2007, 092936).

More importantly, CO can indirectly cause increased RF because it reacts with tropospheric OH and thus can increase the lifetime of trace gases in the atmosphere including the GHGs CH_4 and O_3. Additionally, the major pathway for removal of CO from the atmosphere is reaction with OH to produce CO_2. CH_4, O_3, and CO_2 absorb infrared radiation from the Earth's surface and contribute to the greenhouse effect. Indirect RF attributed to 1750-2005 emissions of CO through changes in concentration of the GHGs O_3, CH_4, and CO_2 was estimated by Forster et al. (2007, 092936) to be ~0.2 W/m^2 or ~12% of the direct RF of CO_2 (Figure 3-7). The future direct and indirect integrated

RF for year 2000 emissions of CO was estimated to be ~0.2 $W/m^2 \cdot yr$ with ~50% uncertainty over both 20-yr and 100-yr time horizons (Figure 3-8). The RF related to short-lived CO is ~25% of that for CO_2 for a 20-yr time horizon, but only ~7% of that for longer-lived CO_2 over a 100-yr time horizon. Overall, the evidence reviewed in this assessment is sufficient to conclude that **a causal relationship exists between current atmospheric concentrations of CO and effects on climate**.

3.7.3. Ambient CO Measurements

As of August 2009, 24 automated FRMs and no FEMs had been approved for monitoring CO. All EPA FRMs for CO operate on the principle of nondispersive infrared (NDIR) detection and can include gas filter correlation (GFC). Current specifications for CO monitoring are designed to help states demonstrate whether they have met compliance criteria, with requirements for an LOD of 1 ppm. The reported LOD for 20 of the 24 FRMs is 0.5 ppm, and four models of FRMs are in operation with an LOD of 0.04 ppm. FRMs with higher LOD also are limited to a precision of 0.1 ppm and are more subject to drift compared with newer monitors with automatic drift correction options.

For 2005-2007, there were 291 CO monitors meeting the 75% completeness requirements and reporting values year-round to the AQS in the 50 states, plus the District of Columbia, Puerto Rico, and the Virgin Islands. 57 monitors across the U.S. have been sited at microscale to capture near-road concentrations, 31 have been sited at middle scale, and 119 are sited for neighborhood scale monitoring; among the remaining 84 monitors, states did not declare the spatial scale of monitoring for 71 monitors, and 13 are sited for monitoring urban or regional scale. For CO, traffic is the major source in an urban setting and therefore microscale data are sited "to represent distributions within street canyons, over sidewalks, and near major roadways" while middle scale monitors are sited to represent "air quality along a commercially developed street or shopping plaza, freeway corridors, parking lots and feeder streets" (40 CFR Part 58 Appendix D). At middle and neighborhood scales, required minimum monitor distance from a road is directly related to the road's average daily traffic count to capture community averages. Ambient monitors for CO and other criteria pollutants are located to monitor compliance rather than population exposures. However, AQS monitors are often used for exposure assessment. When comparing CO monitor location with population density, it was observed that population coverage varies both within and between cities.

3.7.4. Environmental CO Concentrations

CO concentration data for 1-h and 8-h intervals were available for 243 counties and autonomous cities or municipalities that maintained active CO monitoring stations meeting the 75% completeness criteria for the years 2005-2007. There were no violations of the 1-h or 8-h NAAQS in those years. The nationwide mean, median, and interquartile range for 1-h measurements reported between 2005 and 2007 were 0.5, 0.4, and 0.4 ppm, respectively, and these statistics did not change by more than 0.1 ppm for each year of the 3-yr period. More than 50% of the data nationwide were below the LOD for the majority of monitors in use. The nationwide mean, median, and interquartile range for 8-h daily max concentrations, reported between 2005 and 2007, were 0.7, 0.5, and 0.5 ppm, respectively. Half of the 8-h daily max concentrations fell below the LOD for the majority of CO monitors in the field. The 2006 annual second highest 8-h CO concentration, averaged across 144 monitoring sites nationwide, was 75% below that for 1980 and is the lowest concentration recorded during the past 27 yr. The mean annual second highest 8-h ambient CO concentration has been below 5 ppm since 2004. The downward trend in CO concentrations in the 1990s parallels the downward trend observed in CO emissions and can be attributed largely to decreased mobile source emissions.

The correlation structures for measurements at the monitors in each of the 11 CSAs/CBSAs examined for this assessment reveal a wide range of responses between monitors in each city and among the cities. While this wide range is produced by the interactions of many physical and chemical elements, the location of each monitor and the uniqueness of its immediate surroundings can often explain much of the agreement or lack thereof. CO concentrations can be elevated near roadways and decrease with increasing distance from the road. Anchorage, AK, had concentrations roughly twice those of the other metropolitan areas. Most of the CSAs/CBSAs examined here had

diel concentration curves with pronounced morning and evening rush hour peak CO levels, although diel CO concentrations had less variability for New York City, Atlanta, and Seattle than for the other eight cities. For most metropolitan areas examined here, concentrations were generally highest in the winter (December-February) and fall (September-November) and decreased, on average, during the spring (March-May) and summer (June-August). Measurements near or below the 0.5 ppm LOD for most instruments, coupled with the coarsely reported measurement resolution of 0.1 ppm, can artificially influence the comparison statistics shown in the tables and result in apparent heterogeneity in the box plots (Figure 3-19 and Figure 3-22).

CO measurements obtained at different monitoring scales were compared to assess spatial variability of CO concentration. The median hourly CO concentration across the U.S. obtained at microscale monitors was 25% higher than at middle scale and 67% higher than at neighborhood scale. The microscale and middle scale CO data reported here are consistent with hourly concentrations reported in the literature for the near-road environment within the United States, with CO concentration decaying with downwind distance from the road. Determinants of spatial variability of ambient CO concentration within the near-road environment include roadway density, traffic counts, meteorology, and natural and urban topography.

In all cases, a wide range of correlations existed between CO and copollutants computed from AQS data. The mean and median correlations between CO and copollutants were positive for NO_2, PM_{10}, and $PM_{2.5}$; near zero for SO_2; and negative for O_3. These findings might reflect common combustion sources for CO, NO_2, and PM. Among those copollutants with positive associations, NO_2 had the highest mean and median correlations, followed by $PM_{2.5}$ and PM_{10}. Within and between individual metropolitan areas, the distribution of copollutant correlations varied substantially. Studies in the literature also found fairly high correlations of CO with EC and certain VOCs.

This assessment has used data from 2005-2007 at 12 remote sites as part of the international CCGG CASN in the CONUS, Alaska, and Hawaii to determine PRB. All sites demonstrate the well-known seasonality in background CO, with minima in the summer and fall and maxima in the winter and spring. The 3-yr avg CO PRB in Alaska was 130 ppb; in Hawaii it was 99 ppb; and over the CONUS it was 132 ppb.

3.7.5. Exposure Assessment and Implications for Epidemiology

Very few recent exposure assessment studies involve ambient CO concentration data. The studies of personal exposure to ambient CO presented here generally found that the largest percentage of time in which an individual is exposed to ambient CO occurs indoors, but the highest ambient CO exposure levels occur in transit. In-vehicle CO concentrations are typically reported to be between 2 and 5 times higher than ambient concentrations, although peak in-vehicle concentrations more than an order of magnitude higher than corresponding ambient monitor concentrations have also been reported. Among commuters, exposures were higher for those traveling in automobiles in comparison with those traveling on buses and motorbikes and with those cycling or walking. Ambient CO exposure in automobiles has been demonstrated to vary with vehicle ventilation settings, and a very small portion of that exposure is thought to come from the vehicle in which the exposed person travels. High near-road CO concentrations can be important for those living in the near-road environment because virtually all of ambient CO infiltrates indoors. Hence, indoor exposure to ambient CO is determined by the CO concentration outside the building. Residents of the 17.9 million occupied homes located within approximately 90 m of a highway, railroad, or airport may be exposed to elevated ambient CO levels. However, CO concentration in the near-road environment has been shown to decrease sharply with downwind distance from a highway, wind direction, emission source strength (e.g., number of vehicles on a highway). Natural and urban topography also influence localized ambient CO levels.

Recent exposure assessment studies support one of the main conclusions of the 2000 CO AQCD, that central-site ambient CO monitors may overestimate or underestimate individuals' personal exposure to ambient CO because ambient CO concentration is spatially variable, particularly when analyzing exposures in the near-road environment. Exposure error may occur if the ambient CO concentration measured at the central-site monitor is used as an ambient exposure surrogate and differs from the actual ambient CO concentration outside a subject's residence and/or worksite. For example, measurement at a "hot spot" could skew community exposure estimates upwards, and likewise measurement at a location with few nearby CO sources could skew exposure

estimates downwards. Correlations across CO monitors can vary widely from within and between cities across the U.S. as a function of natural and urban topography, meteorology, and strength and proximity to sources. Typically, intersampler correlation ranges from 0.35 to 0.65 for monitors sited at different scales within a metropolitan area, although it can be greater than 0.8 in some areas. Health effects estimates from time-series epidemiologic studies are not biased by spatial variability in CO concentrations if concentrations at different locations are correlated in time. Additionally, exposure assessment is complicated by the existence of CO in multipollutant mixtures emitted by combustion processes. Because ambient CO exists in a mixture with volatile and reactive pollutants, the correlation between exposure to ambient CO and copollutants can vary substantially over time and across locations. For this reason, it is difficult to quantify the effects related specifically to CO exposure compared with those related to another combustion-related pollutant or mix of pollutants. In most circumstances, exposure error tends to bias a health effect estimate downward. Spatial and temporal variability not fully captured by ambient monitors and correlation of CO with copollutants are examples of sources of uncertainty that could widen confidence intervals of health effects estimates.

References

Abdul-Wahab SA (2004). An application and evaluation of the CAL3QHC model for predicting carbon monoxide concentrations from motor vehicles near a roadway intersection in Muscat, Oman. Environ Manage, 34: 372-382. 194011

Abi-Esber L; El-Fadel M (2008). In-vehicle CO ingression: Validation through field measurements and mass balance simulations. Sci Total Environ, 394: 75-89. 190939

Abi-Esber L; El-Fadel M; Nuwayhid I; Saliba N (2007). The effect of different ventilation modes on in-vehicle carbon monoxide exposure. Atmos Environ, 41: 3644-3657. 190941

Abi-Esber L; El-Fadel M; Shihadeh A (2007). Comparison of trip average in-vehicle and exterior CO determinations by continuous and grab sampling using an electrochemical sensing method. Atmos Environ, 41: 6087-6094. 190940

Akland GG; Hartwell TD; Johnson TR; Whitmore RW (1985). Measuring human exposure to carbon monoxide in Washington, DC, and Denver, Colorado, during the winter of 1982-1983. Environ Sci Technol, 19: 911-918. 011618

Alm S; Jantunen MJ; Vartiainen M (1999). Urban commuter exposure to particle matter and carbon monoxide inside an automobile. J Expo Sci Environ Epidemiol, 9: 237-244. 047196

Alm S; Mukala K; Jantunen MJ (2000). Personal carbon monoxide exposures of preschool children in Helsinki, Finland: Levels and determinants. Atmos Environ, 34: 277-285. 192374

Alm S; Mukala K; Tiittanen P; Jantunen MJ (2001). Personal carbon monoxide exposures of preschool children in Helsinki, Finland-comparison to ambient air concentrations. Atmos Environ, 35: 6259-6266. 020237

Altshuller AP (1991). Estimating product yields of carbon-containing products from the atmospheric photooxidation of ambient air alkenes. J Atmos Chem, 13: 131-154. 192375

Andreae MO (1991). Biomass burning: its history, use, and distribution and its impact on environmental quality and global climate. In Levine JS (Ed.),Global Biomass Burning: Atmospheric, Climatic, and Biospheric Implications (pp. 1-21). Cambridge, MA: MIT Press. 078147

Annest JH; Clower J; Yip F; Stock A; Lucas M; Iqbal S (2008). Nonfatal, unintentional, non-fire-related carbon monoxide exposures-United States, 2004-2006. JAMA, 57: 896-9. 190236

Baldauf R; Thoma E; Hays M; Shores R; Kinsey J; Gullett B; Kimbrough S; Isakov V; Long T; Snow R; Khlystov A; Weinstein J; Chen FL; Seila R; Olson D; Gilmour I; Cho SH; Watkins N; Rowley P; Bang J (2008). Traffic and meteorological impacts on near-road air quality: Summary of methods and trends from the Raleigh near-road study. J Air Waste Manag Assoc, 58: 865-878. 190239

Baldauf R; Thoma E; Khlystov A; Isakov V; Bowker G; Long T; Snow R (2008). Impacts of noise barriers on near-road air quality. Atmos Environ, 42: 7502-7507. 191017

Behrentz E; Fitz DR; Pankratz DV; Sabin LD; Colome SD; Fruin SA; Winer AM (2004). Measuring self-pollution in school buses using a tracer gas technique. Atmos Environ, 38: 3735-3746. 155682

Bell M; Namdeo A; Chen H; Ashmore M; Terry A; Dimitroulopoulou S (2004). Reducing Urban Pollution Exposure from Road Transport (RUPERT). In Urban Transport (pp. 829-838). Southampton, UK: WIT Press. 192376

Bell ML; Peng RD; Dominici F; Samet JM (2009). Emergency hospital admissions for cardiovascular diseases and ambient levels of carbon monoxide: results for 126 U.S. urban counties, 1999-2005. Circulation, 120: 949-955. 194033

Bergamaschi P; Hein R; Heimann M; Crutzen PJ (2000). Inverse modeling of the global CO cycle 1. Inversion of CO mixing ratios. J Geophys Res, 105: 1909-1927. 192377

Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at http://epa.gov/hero. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISAs) and the Integrated Risk Information System (IRIS)

Berntsen T; Fuglestvedt JS; Joshi M; Shine KP; Stuber N; Sausen R; Li L; Hauglustaine DA; Ponater M (2005). Response of climate to regional emissions of ozone precursors: Sensitivities and warming potentials. Tellus B Chem Phys Meteorol, 57: 283-304. 193241

Berntsen T; Fuglestvedt JS; Myhre G; Stordal F; Berglen TF (2006). Abatement of greenhouse gases: Does location matter? Clim Change, 74: 377-411. 193244

Bey I; Jacob DJ; Yantosca RM; Logan JA; Field B; Fiore AM; Li Q; Liu H; Mickley LJ; Schultz MG (2001). Global modeling of tropospheric chemistry with assimilated meteorology: model description and evaluation. J Geophys Res, 106: 23073-23095. 051218

Bishop GA; Stedman DH (2008). A decade of on-road emissions measurements. Environ Sci Tech, 42: 1651-1656. 194670

Bogo H; Gomez DR; Reich SL; Negri RM; Roman ES (2001). Traffic pollution in a downtown site of Buenos Aires City. Atmos Environ, 35: 1717-1727. 192378

Borrego C; Tchepel O; Costa AM; Martins H; Ferreira J; Miranda AI (2006). Traffic-related particulate air pollution exposure in urban areas. Atmos Environ, 40: 7205-7214. 155697

Bowker GE; Baldauf R; Isakov V; Khlystov A; Petersen W (2007). The effects of roadside structures on the transport and dispersion of ultrafine particles from highways. Atmos Environ, 41: 8128-8139. 149997

Brauer M; Hoek G; van Vliet P; Meliefste K; Fischer P; Gehring U; Heinrich J; Cyrys J; Bellander T; Lewne M; Brunekreef B (2003). Estimating long-term average particulate air pollution concentrations: application of traffic indicators and geographic information systems. Epidemiology, 14: 228-239. 155702

Brauer M; Lencar C; Tamburic L; Koehoorn M; Demers P; Karr C (2008). A cohort study of traffic-related air pollution impacts on birth outcomes. Environ Health Perspect, 116: 680-686. 156292

Brewer DA; Ogliaruso MA; Augustsson TR; Levine JS (1984). The oxidation of isoprene in the troposphere: Mechanism and model calculations. Atmos Environ, 18: 2723-2744 . 194402

Briggs DJ; Collins S; Elliott P; Fischer P; Kingham S; Lebret E; Pryl K; Van Reeuwijk H; Smallbone K; Van Der Veen A (1997). Mapping urban air pollution using GIS: a regression-based approach. Int J Geogr Inform Sci, 11: 699-718. 025950

Britter RE; Hanna SR (2003). Flow and dispersion in urban areas. Annu Rev Fluid Mech, 35: 469-496. 090295

Bruinen de Bruin Y; Carrer P; Jantunen M; Hänninen O; Scotto di Marco G; Kephalopoulos S; Cavallo D; Maroni M (2004). Personal carbon monoxide exposure levels: Contribution of local sources to exposures and microenvironment concentrations in Milan. J Expo Anal Environ Epidemiol, 14: 312-322. 190943

Bruinen de Bruin Y; Hanninen O; Carrer P; Maroni M; Kephalopoulos S; Scotto di Marco G; Jantunen M (2004). Simulation of working population exposures to carbon monoxide using EXPOLIS-Milan microenvironment concentration and time-activity data. J Expo Anal Environ Epidemiol, 14: 154-163. 190942

Burgard DA; Bishop GA; Stedman DH; Gessner VH; Daeschlein C (2006). Remote sensing of in-use heavy-duty diesel trucks. Environ Sci Technol, 40: 6938-6942. 193222

Burke JM; Zufall MJ; Ozkaynak H (2001). A population exposure model for particulate matter: case study results for PM2.5 in Philadelphia, PA. J Expo Sci Environ Epidemiol, 11: 470-489. 014050

Burnett RT; Goldberg MS (2003). Size-fractionated particulate mass and daily mortality in eight Canadian cities. Health Effects Institute. Boston, MA. 042798

CalTrans (2009). CalTrans. Retrieved 02-AUG-09, from http://traffic-counts.dot.ca.gov/. 194036

Carslaw DC; Beevers SD; Tate JE (2007). Modelling and assessing trends in traffic-related emissions using a generalised additive modelling approach. Atmos Environ, 41: 5289-5299. 148210

Carter WPL (1998). Updated maximum incremental reactivity scale for regulatory applications. Air Pollution Research Center and College of Engineering, Center for Environmental Research and Technology. University of California, Riverside CA. 192380

Cassidy BE, Alabanza-Akers MA, Akers TA, Hall DB, Ryan PB, Bayer CW, Naeher LP (2007). Particulate matter and carbon monoxide multiple regression models using environmental characteristics in a high diesel-use area of Baguio City, Philippines. Sci Total Environ, 381: 47-58. 199975

Chaloulakou A; Mavroidis I (2002). Comparison of indoor and outdoor concentrations of CO at a public school: Evaluation of an indoor air quality model. Atmos Environ, 36: 1769-1781. 026050

Chaloulakou A; Mavroidis I; Duci A (2003). Indoor and outdoor carbon monoxide concentration relationships at different microenvironments in the Athens area. Chemosphere, 52: 1007-1019. 190945

Chang C-H; Meroney RN (2003). Concentration and flow distributions in urban street canyons: wind tunnel and computational data. J Wind Eng Ind Aerod, 91: 1141-1154. 090298

Chang L-T; Koutrakis P; Catalano PJ; Suh HH (2000). Hourly personal exposures to fine particles and gaseous pollutants--results from Baltimore, Maryland. J Air Waste Manag Assoc, 50: 1223-1235. 001276

Chang L-T; Suh HH; Wolfson JM; Misra K; Allen GA; Catalano PJ; Koutrakis P (2001). Laboratory and field evaluation of measurement methods for one-hour exposures to O3, PM25, and CO. J Air Waste Manag Assoc, 51: 1414-1422. 019216

Chen H; Namdeo A; Bell M (2008). Classification of road traffic and roadside pollution concentrations for assessment of personal exposure. Environ Modell Softw, 23: 282-287. 193986

Collins WJ; Derwent RG; Johnson CE; Stevenson DS (2002). The oxidation of organic compounds in the troposphere and their global warming potentials. Clim Change, 52: 453-479. 044156

Connors VS; Gormsen BB; Nolf S; Reichle HG (1994). Space-borne observations of the global distribution of carbon monoxide in the middle troposphere during April and October 1994. J Geophys Res, 104: 21455-21470. 193755

Conrad R; Seiler W (1985). Influence of temperature, moisture, and organic carbon on the flux of H2 and CO between soil and atmosphere: field studies in subtropical regions. J Geophys Res, 90: 5699-5709. 029520

Croxford B; Penn A (1998). Siting considerations for urban pollution monitors. Atmos Environ, 32: 1049-1057. 087176

Crutzen PJ (1987). Role of the tropics in atmospheric chemistry. In Dickinson RE (Ed.),Geophysiology of Amazonia: Vegetation and climate interactions (pp. -). New York, NY: John Wiley and Sons. 002848

Crutzen PJ; Delany AC; Greenberg J; Haagenson P; Heidt L; Lueb R; Pollock W; Seiler W; Wartburg A; Zimmerman P (1985). Tropospheric chemical composition measurements in Brazil during the dry season. J Atmos Chem, 2: 233-256. 194403

Daniel JS; Solomon S (1998). On the climate forcing of carbon monoxide. J Geophys Res, 103: 13249-13260. 193235

Delfino RJ; Chang J; Wu J; Ren C; Tjoa T; Nickerson B; Cooper D; Gillen DL (2009). Repeated hospital encounters for asthma in children and exposure to traffic-related air pollution near the home. Ann Allergy Asthma Immunol, 102: 138-44. 190254

Derwent RG; Collins WJ; Johnson CE; Stevenson DS (2001). Transient behaviour of tropospheric ozone precursors in a global 3-D CTM and their indirect greenhouse effects. Clim Change, 49: 463-487. 047912

Dimitroulopoulou C; Ashmore MR; Byrne MA; Kinnersley RP (2001). Modelling of indoor exposure to nitrogen dioxide in the UK. Atmos Environ, 35: 269-279. 014737

Dimitroulopoulou C; Ashmore MR; Hill MTR; Byrne MA; Kinnersley R (2006). INDAIR: a probabilistic model of indoor air pollution in UK homes. Atmos Environ, 40: 6362-6379. 090302

Dominici F; Zeger SL; Samet JM (2000). A measurement error model for time-series studies of air pollution and mortality. Biostatistics, 1: 157-175. 005828

Doran JC; Berkowitz CM; Coulter RL; Shaw WJ; Spicer CW (2003). The 2001 Phoenix Sunrise experiment: vertical mixing and chemistry during the morning transition in Phoenix. Atmos Environ, 37: 2365-2377. 143352

Duci A; Chaloulakou A; Spyrellis N (2003). Exposure to carbon monoxide in the Athens urban area during commuting. Sci Total Environ, 309: 47-58. 044199

Duncan BN; Logan JA (2008). Model analysis of the factors regulating the trends and variability of carbon monoxide between 1988 and 1997. Atmos Chem Phys, 8: 7389-7403. 194042

Edwards DP; Emmons LK; Hauglustaine DA; Chu DA; Gille JC; Kaufman YJ; Petron G; Yurganov LN; Giglio L; Deeter MN; Yudin V; Ziskin DC; Warner J; Lamarque J-F; Francis GL; Ho SP; Mao D; Chen J; Grechko EI; Drummond JR (2004). Observations of carbon monoxide and aerosols from the Terra satellite: Northern Hemisphere variability. J Geophys Res, 109: D24202. 199889

Emmons LK; Deeter MN; Gille JC; Edwards DP; Attie JL; Warner J; Ziskin D; Francis G; Khattatov B; Yudin V; Lamarque JF; Ho SP; Mao D; Chen JS; Drummond J; Novelli P; Sachse G; Coffey MT; Hannigan JW; Gerbig C; Kawakami S; Kondo Y; Takegawa N; Schlager H; Baehr J; Ziereis H (2004). Validation of Measurements of Pollution In The Troposphere (MOPITT) CO retrievals with aircraft in situ profiles. J Geophys Res, 109: D03309. 193756

Fehsenfeld FC; Ancellet G; Bates TS; Goldstein AH; Hardesty RM; Honrath R; Law KS; Lewis AC; Leaitch R; McKeen S; Meagher J; Parrish DD; Pszenny AAP; Russell PB; Schlager H; Seinfeld J; Talbot R; Zbinden R (2006). International consortium for atmospheric research on transport and transformation (ICARTT): North America to Europe -overview of the 2004 summer field study . J Geophys Res, 111: D23S01.1-D23S01.36. 190531

Finlayson-Pitts BJ; Pitts JN Jr (2000). Chemistry of the upper and lower atmosphere: theory, experiments and applications. San Diego, CA: Academic Press. 055565

Fiore AM; Jacob DJ; Field BD; Streets DG; Fernandes SD; Jang C (2002). Linking ozone pollution and climate change: the case for controlling methane. Geophys Res Lett, 2919: 1919. 051221

Fiore AM; West JJ; Horowitz LW; Naik V; Schwartzkopf MD (2008). Characterizing the tropospheric ozone response to methane emission controls and the benefits to climate and air quality. J Geophys Res, 113: D08307. 193749

Fishman J; Bowman KW; Burrows JP; Richter A; Chance KV; Edwards DP; Martin RV; Morris GA; Pierce RB; Ziemke JR; Al-Saadi JA; Creilson JK; Schaack TK; Thompson AM (2008). Remote sensing of tropospheric pollution from space. Bull Am Meteorol Soc, 89: 805-821. 193927

Flachsbart PG (1999). Models of exposure to carbon monoxide inside a vehicle on a Honolulu highway. J Expo Sci Environ Epidemiol, 9: 245-260. 015857

Forster P; Ramaswamy V; Artaxo P; Berntsen T; Betts R; Fahey DW; Haywood J; Lean J; Lowe DC; Myhre G; Nganga J; Prinn R; Raga G; Schultz M; Van Dorland R (2007). Changes in atmospheric constituents and in radiative forcing, Chapter 2. In Solomon S, Qin D; Manning M; Chen Z; Marquis M; Averyt KB; Tignor M; Miller HL (Ed.),IPCC Fourth Assessment Report (AR4): Climate Change 2007: Working Group I Report: The Physical Science Basis. (pp. 129-234). Cambridge, U.K. and New York, NY: Intergovernmental Panel on Climate Change; Cambridge University Press. 092936

Fuglestvedt J; Berntsen T; Myhre G; Rypdal K; Skeie RB (2008). Climate forcing from the transport sectors. PNAS, 105: 454-458. 193242

Fuglestvedt JS; Berntsen TK; Isaksen ISA; Mao H; Liang X-Z; Wang W-C (1999). Climatic forcing of nitrogen oxides through changes in tropospheric ozone and methane; global 3D model studies. Atmos Environ, 33: 961-978. 047431

Gentner DR; Harley RA; Miller AM; Goldstein AH (2009). Diurnal and seasonal variability of gasoline-related volatile organic compound emissions in Riverside, California. Environ Sci Technol, 43: 4247-4252. 194034

Georgoulis LB; Hanninen O; Samoli E; Katsouyanni K; Kunzli N; Polanska L; De Bruin YB; Alm S; Jantunen M (2002). Personal carbon monoxide exposure in five European cities and its determinants. Atmos Environ, 36: 963-974. 025563

Gilliland F; Avol E; Kinney P; Jerrett M; Dvonch T; Lurmann F; Buckley T; Breysse P; Keeler G; de Villiers T; McConnell R (2005). Air pollution exposure assessment for epidemiologic studies of pregnant women and children: lessons learned from the Centers for Children's Environmental Health and Disease Prevention Research. Environ Health Perspect, 113: 1447-54. 098820

Gokhale S; Khare M (2007). Statistical behavior of carbon monoxide from vehicular exhausts in urban environments. Environ Modell Softw, 22: 526-535. 194015

Goldstein A; Galbally I (2007). Known and unexplored organic constituents in the earth’s atmosphere. Environ Sci Technol, 41: 1514–1521. 193247

Gómez-Perales JE; Colvile RN; Fernández-Bremauntz AA; Gutiérrez-Avedoy V; Páramo-Figueroa VH; Blanco-Jiménez S; Bueno-López E; Bernabé-Cabanillas R; Mandujano F; Hidalgo-Navarro M; Nieuwenhuijsen MJ (2007). Bus, minibus, metro inter-comparison of commuters' exposure to air pollution in Mexico City. Atmos Environ, 41: 890-901. 138816

Gómez-Perales JE; Colvile RN; Nieuwenhuijsen MJ; Fernández-Bremauntz A; Gutiérrez-Avedoy VJ; Páramo-Figueroa VH; Blanco-Jiménez S; Bueno-López E; Mandujano F; Bernabé-Cabanillas R (2004). Commuters' exposure to PM2.5, CO, and benzene in public transport in the metropolitan area of Mexico City. Atmos Environ, 38: 1219-1229. 054418

Gulliver J; Briggs DJ (2005). Time-space modeling of journey-time exposure to traffic-related air pollution using GIS. Environ Res, 97: 10-25. 191079

Hanst PL; Spence JW; Edney EO (1980). Carbon monoxide production in photooxidation of organic molecules in the air. Atmos Environ, 14: 1077-1088. 011988

Harley RA; Marr LC; Lehner JK; Giddings SN (2005). Changes in motor vehicle emissions on diurnal to decadal time scales and effects on atmospheric composition. Environ Sci Technol, 39: 5356-5362. 088154

Harley RA; McKeen SA; Pearson J; Rodgers MO; Lonneman WA (2001). Analysis of motor vehicle emissions during the Nashville/Middle Tennessee Ozone Study. J Geophys Res, 106: 3559-3567. 193922

Hauglustaine DA; Hourdin F; Jourdain L; Filiberti MA; Walters S; Lamarque JF; Holland EA (2004). Interactive chemistry in the Laboratoire de Meteorologie Dynamique general circulation model: Description and background tropospheric chemistry evaluation. J Geophys Res, 109: D04314. 193191

HEI (2009). Traffic-related air pollution: A critical review of the literature on emissions, exposure, and health effects. Health Effects Institute. Boston. Special Report 17. 191009

Heist DK; Perry SG; Brixey LA (2009). A wind tunnel study of the effect of roadway configurations on the dispersion of traffic-related pollution. Atmos Environ, In Press: In Press. 194037

Hoek G; Beelen R; de Hoogh K; Vienneau D; Gulliver J; Fischer P; Briggs D (2008). A review of land-use regression models to assess spatial variation of outdoor air pollution. Atmos Environ, 42: 7561-7578. 195851

Horowitz LW; Walters S; Mauzerall DL; Emmons LK; Rasch PJ; Granier C; Tie X; Lamarque J-F; Schultz MG; Tyndall GS; Orlando JJ; Brasseur GP (2003). A global simulation of tropospheric ozone and related tracers: Description and evaluation of MOZART, version 2. J Geophys Res, 108: D24. 057770

Hudman RC; Jacob DJ; Turquety S; Leibensperger EM; Murray LT; Wu S; Gilliland AB; Avery M; Bertram TH; Brune W; Cohen RC; Dibb JE; Flocke FM; Fried A; Holloway J; Neuman JA; Orville R; Perring A; Ren X; Sachse GW; Singh HB; Swanson A; Wooldridge PJ (2007). Surface and lightning sources of nitrogen oxides over the United States: Magnitudes, chemical evolution, and outflow. J Geophys Res, 112: D12S05. 089474

Hudman RC; Murray LT; Jacob DJ; Millet DB; Turquety S; Wu S; Blake DR; Goldstein AH; Holloway J; Sachse GW (2008). Biogenic versus anthropogenic sources of CO in the United States. Geophys Res Lett, 35: L04801. 191253

Inman RE; Ingersoll RB; Levy EA (1971). Soil: a natural sink for carbon monoxide. Science, 172: 1229-1231. 010972

IPCC (2001). Climate Change 2001: The Scientific Basis. Contribution of Working Group I to the Third Assessment Report (TAR) of the Intergovernmental Panel on Climate Change [Houghton, J.T.,Y. Ding, D.J. Griggs, M. Noguer, P.J. van der Linden, X. Dai, K. Maskell, and C.A. Johnson (eds.)]. Cambridge, UK and New York, NY, USA: Intergovernmental Panel on Climate Change, Cambridge University Press. 156587

IPCC (2007). Climate Change 2007: The Physical Science Basis. Contribution of Working Group I to the Fourth Assessment Report (AR4) of the Intergovernmental Panel on Climate Change . Cambridge, UK and New York, NY: Intergovernmental Panel on Climate Change, Cambridge University Press. 092765

Isakov V; Touma JS; Burke J; Lobdell DT; Palma T; Rosenbaum A; Ozkaynak H (2009). Combining regional- and local-scale air quality models with exposure models for use in environmental health studies. J Air Waste Manag Assoc, 59: 461-472. 191192

Isaksen ISA; Hov O (1987). Calculation of trends in the tropospheric concentration of O3, OH, CO, CH4 and NOx. Tellus B Chem Phys Meteorol, 39: 271-285. 019490

Jacob DJ; Wofsy SC (1990). Budgets of reactive nitrogen, hydrocarbons, and ozone over the Amazon forest during the wet season. J Geophys Res, 95: 16,737-16,754. 029668

Jeffries HE (1995). Photochemical air pollution. In Singh, H. B. (Ed.),Composition, chemistry, and climate of the atmosphereNew York, NY: Van Nostrand Reinhold. 003055

Jerrett M; Arain A; Kanaroglou P; Beckerman B; Potoglou D; Sahsuvaroglu T; Morrison J; Giovis C (2005). A review and evaluation of intraurban air pollution exposure models. J Expo Sci Environ Epidemiol, 15: 185-204. 092864

Johnson CE; Derwent RG (1996). Relative radiative forcing consequences of global emissions of hydrocarbons, carbon monoxide, and NOX from human activities estimated with a zonally averaged two-dimensional model. Clim Change, 34: 439-462. 193192

Johnson TR (1984). A study of personal exposure to carbon monoxide in Denver, Colorado. U.S. Environmental Protection Agency. Research Triangle Park, NC. EPA-600/4-84-014. 024652

Joshi M; Shine KP; Ponater M; Stuber N; Sausen R; Li (2003). A comparison of climate response to different radiative forcings in three general circulation models: Towards an improved metric of climate change. Clim Dynam, 20: 843-854. 193752

Kanakidou M; Crutzen PJ (1999). The photochemical source of carbon monoxide: importance, uncertainties and feedbacks. Chemosphere Global Change Sci, 1: 91-109. 011760

Kanakidou M; Singh HB; Valentin KM; Crutzen PJ (1991). A two-dimensional study of ethane and propane oxidation in the troposphere. J Geophys Res, 96: 15,395-15,413. 029701

Kastner-Klein P; Fedorovich E; Ois Sini JF; Mestayer PG (2000). Experimental and numerical verification of similarity concept for dispersion of car exhaust gases in urban street canyons. Environ Monit Assess, 65: 353-361. 194035

Kastner-Klein P; Plate EJ (1999). Wind-tunnel study of concentration fields in street canyons. Atmos Environ, 33: 3973-3979. 001961

Kaur S; Nieuwenhuijsen M; Colvile R (2005). Personal exposure of street canyon intersection users to PM2.5, ultrafine particle counts and carbon monoxide in central London, UK. Atmos Environ, 39: 3629-3641. 086504

Kaur S; Nieuwenhuijsen MJ (2009). Determinants of personal exposure to PM2.5, ultrafine particle counts, and CO in a transport microenvironment. Environ Sci Technol, 43: 4737-4743. 194014

Kaur S; Nieuwenhuijsen MJ; Colvile RN (2007). Fine particulate matter and carbon monoxide exposure concentrations in urban street transport microenvironments. Atmos Environ, 41: 4781-4810. 190070

Khalil MAK; Rasmussen RA (1990). Atmospheric carbon monoxide: latitudinal distribution of sources. Geophys Res Lett, 17: 1913-1916. 012443

Khalil MAK; Rasmussen RA (1990). The global cycle of carbon monoxide: trends and mass balance. Chemosphere, 20: 227-242. 012352

Khare M; Chaudhry KK; Gowda RMM; Ahmad K (2005). Effects of the homogeneous traffic on vertical dispersion parameter in the near field of roadways – A wind tunnel study. Environ Monit Assess, 10: 55-62. 194016

Kim D; Sass-Kortsak A; Purdham JT; Dales RE; Brook JR (2006). Associations between personal exposures and fixed-site ambient measurements of fine particulate matter, nitrogen dioxide, and carbon monoxide in Toronto, Canada. J Expo Sci Environ Epidemiol, 16: 172-183. 089820

King GM (1999). Characteristics and significance of atmospheric carbon monoxide consumption by soils. Chemosphere, 1: 53-63. 002828

Kirchhoff VWJH; Marinho EVA (1990). Surface carbon monoxide measurements in Amazonia. J Geophys Res, 95: 16933-16943. 194406

Klepeis NE; Nelson WC; OttWR; Robinson JPTsang AM; Switzer P; Behar JV; Hern SC; Engelmann WH (2001). The National Human Activity Pattern Survey (NHAPS): a resource for assessing exposure to environmental pollutants. J Expo Sci Environ Epidemiol, 11: 231-252. 002437

Krewski D; Jerrett M; Burnett RT; Ma R; Hughes E; Shi Y; Turner MC; Pope AC III; Thurston G; Calle EE; Thun MJ (2009). Extended follow-up and spatial analysis of the American Cancer Society study linking particulate air pollution and mortality. Health Effects Institute. Cambridge, MA. Report Nr. 140. 191193

Kristjansson JE (2002). Studies of the aerosol indirect effect from sulfate and black carbon aerosols. J Geophys Res, 107: 4246. 045282

Lai HK; Kendall M; Ferrier H; Lindup I; Alm S; Hanninen O; Jantunen M; Mathys P; Colvile R; Ashmore MR; Cullinan P; Nieuwenhuijsen MJ (2004). Personal exposures and microenvironment concentrations of PM25, VOC, NO2 and CO in Oxford, UK. Atmos Environ, 38: 6399-6410. 056811

Langan L (1992). Portability in measuring exposure to carbon monoxide. Presented at In: Measuring, understanding, and predicting exposures in the 21st century: proceedings of the conference; November 1991; Atlanta, GA. J. Exposure Anal. Environ. Epidemiol. 1(suppl. 1): 223-239. 046120

Lelieveld J; Berresheim H; Borrmann S; Crutzen PJ; Dentener FJ; Fischer H; Feichter J; Flatau PJ; Heland J; Holzinger R; Korrmann R; Lawrence MG; Levin Z; Markowicz KM; Mihalopoulos N; Minikin A; Ramanathan V; De Reus M; Roelofs GJ; Scheeren HA; Sciare J; Schlager H; Schultz M; Siegmund P; Steil B; Stephanou EG; Stier P; Traub M; Warneke C; Williams J; Ziereis H (2002). Global air pollution crossroads over the Mediterranean. Science, 298: 794-799. 190361

Lobert JM; Scharffe DH; Hao WM; Kuhlbusch TA; Seuwen R; Warneck P; Crutzen PJ (1991). Experimental evaluation of biomass burning emissions: Nitrogen and carbon containing compounds. In Levine JS (Ed.),Global biomass burning: Atmospheric, climatic, and biospheric implications (pp. 289-304). Cambridge, MA: MIT Press. 029473

Manning MR; Brenninkmeijer CAM; Allan W (1997). Atmospheric carbon monoxide budget of the southern hemisphere: Implications of 13C/12C measurements. J Geophys Res, 102: 10673-10682 . 194401

Marshall JD; Nethery E; Brauer M (2008). Within-urban variability in ambient air pollution: comparison of estimation methods. Atmos Environ, 42: 1359-1369. 193983

McCurdy T; Glen G; Smith L; Lakkadi Y (2000). The National Exposure Research Laboratory's consolidated human activity database. J Expo Sci Environ Epidemiol, 10: 566-578. 000782

Menon S; Hansen J; Nazarenko L; Luo Y (2002). Climate effects of black carbon aerosols in China and India. Science, 297: 2250-2253. 155978

Michie RN; McElroy FF; Sokash JA; Thompson VL; Dayton DP; Sutcliffe CR (1983). Performance test results and comparative data for designated reference methods for carbon monoxide. U.S. Environmental Protection Agency. Research Triangle Park. EPA-600/S4-83-013. 194043

Millet DB; Jacob DJ; Turquety S; Hudman RC; Wu S; Fried A; Walega J; Heikes BG; Blake DR; Singh HB; Anderson BE; Clarke AD (2006). Formaldehyde distribution over North America: Implications for satellite retrievals of formaldehyde columns and isoprene emission. J Geophys Res, 111: D24S02. 195106

Milner JT; ApSimon HM; Croxford B (2006). Spatial variation of CO concentrations within an office building and outdoor influences. Atmos Environ, 40: 6338-6348. 123100

Mobley D; Deslauriers M; Rojas-Brachos L (2005). Improving emission inventories for effective air-quality management across North America: A NARSTO assessment. NARSTO. Pasco, WA . NARSTO-05-001. 194008

Murena F; Garofalo N; Favale F (2008). Monitoring CO concentration at leeward and windward sides in a deep street canyon. Atmos Environ, 42: 8204-8210. 194038

Naik V; Mauzerall D; Horowitz L; Schwarzkopf MD; Ramaswamy V; Oppenheimer M (2005). Net radiative forcing due to changes in regional emissions of tropospheric ozone precursors. J Geophys Res, 110: D24306. 193194

Ni Riain CM; Mark D; Davies M; Harrison RM; Byrne MA (2003). Averaging periods for indoor-outdoor ratios of pollution in naturally ventilated non-domestic buildings near a busy road. Atmos Environ, 37: 4121-4132. 053792

NRC (1999). Ozone-forming potential of reformulated gasoline. Washington, DC: National Research Council, National Academy of Sciences. 010614

Ott W; Switzer P; Willits N (1994). Carbon monoxide exposures inside an automobile traveling on an urban arterial highway. J Air Waste Manag Assoc, 44: 1010-1018. 076546

Paciorek CJ; Yanosky JD; Puett RC; Laden F; Suh HH (2009). Practical large-scale spatio-temporal modeling of particulate matter concentrations. Ann Appl Stat, 3: 370-397. 190090

Parrish DD (2006). Critical evaluation of US on-road vehicle emission inventories. Atmos Environ, 40: 2288-2300. 090352

Parrish DD; Trainer M; Hereid D; Williams EJ; Olszyna KJ; Harley RA; Meagher JF; Fehsenfeld FC (2002). Decadal change in carbon monoxide to nitrogen oxide ratio in US vehicular emissions. J Geophys Res, 107: 4140. 052472

Pfister G; Hess PG; Emmons LK; Lamarque JF; Wiedinmyer C; Edwards DP; Petron G; Gille JC; Sachese GW (2005). Quantifying CO emissions from the 2004 Alaskan wildfires using MOPITT CO data. Geophys Res Lett, 32: L11809. 093009

Pokharel SS; Bishop GA; Stedman DH (2002). An on-road motor vehicle emissions inventory for Denver: An efficient alternative to modeling. Atmos Environ, 36: 5177-5184. 052473

Pokharel SS; Bishop GA; Stedman DH (2003). Emissions reductions as a result of automobile improvement. Environ Sci Technol, 37: 5097-5101. 053740

Polidori A; Arhami M; Sioutas C; Delfino RJ; Allen R (2007). Indoor/outdoor relationships, trends, and carbonaceous content of fine particulate matter in retirement homes of the Los Angeles Basin. J Air Waste Manag Assoc, 57: 366-379. 156877

Pollack AK; Lindhjem C; Stoeckenius TE; Tran C; Mansell G; Jimenez M; Wilson G; Coulter-Burke S (2004). Final Report: Evaluation of the US EPA MOBILE6 highway vehicle emission factor model. ENVIRON International Corporation. Novato, CA. CRC Project E-64. 184461

Prather MJ (1996). Natural modes and timescales in atmospheric chemistry: Theory, GWPs for CH4 and CO, and runaway growth. Geophys Res Lett, 23: 2597-2600. 193195

Riediker M; Williams R; Devlin R; Griggs T; Bromberg P (2003). Exposure to particulate matter, volatile organic compounds, and other air pollutants inside patrol cars. Environ Sci Technol, 37: 2084-2093. 043761

Rind D; Lerner J (1996). Use of on-line tracers as a diagnostic tool in general circulation model development: 1. Horizontal and vertical transport in the troposphere. J Geophys Res, 101: 12667-12683. 193750

Rodes C; Sheldon L; Whitaker D; Clayton A; Fitzgerald K; Flanagan J; DiGenova F; Hering S; Frazier C (1998). Measuring concentrations of selected air pollutants inside California vehicles [final report]. California Environmental Protection Agency, Air Resources Board; South Coast Air Quality Management District. Sacramento, CA.http://www.arb.ca.gov/research/abstracts/95-339.htm. 010611

Rosenlund M; Berglind N; Pershagen G; Hallqvist J; Jonson T; Bellander T (2006). Long-term exposure to urban air pollution and myocardial infarction. Epidemiology, 17: 383-390. 089796

Rotstayn LD; Penner JE (2001). Indirect aerosol forcing, quasi-forcing, and climate response. J Clim, 14: 2960-2975. 193754

Ryan PH; LeMasters GK (2007). A review of land-use regression models for characterizing intraurban air pollution exposure. Inhal Toxicol, 19: 127. 156063

Ryan PH; LeMasters GK; Levin L; Burkle J; Biswas P; Hu S; Grinshpun S; Reponen T (2008). A land-use regression model for estimating microenvironmental diesel exposure given multiple addresses from birth through childhood. Sci Total Environ, 404: 139-147. 156064

Sarnat JA; Brown KW; Schwartz J; Coull BA; Koutrakis P (2005). Ambient gas concentrations and personal particulate matter exposures: implications for studying the health effects of particles. Epidemiology, 16: 385-395. 087531

Sarnat JA; Schwartz J; Catalano PJ; Suh HH (2001). Gaseous pollutants in particulate matter epidemiology: Confounders or surrogates? Environ Health Perspect, 109: 1053-1061. 019401

Sarnat SE; Coull BA; Schwartz J; Gold DR; Suh HH (2006). Factors affecting the association between ambient concentrations and personal exposures to particles and gases. Environ Health Perspect, 114: 649-654. 089784

Sarnat SE; Klein M; Sarnat JA; Flanders WD; Waller LA; Mulholland JA; Russell AG; Tolbert PE (2009). An examination of exposure measurement error from air pollutant spatial variability in time-series studies. J Expo Sci Environ Epidemiol, In Press: 1-12. 180084

Scotto Di Marco G; Kephalopoulos S; Ruuskanen J; Jantunen M (2005). Personal carbon monoxide exposure in Helsinki, Finland. Atmos Environ, 39: 2697-2707. 144054

Sheppard L; Slaughter JC; Schildcrout J; Liu L-JS; Lumley T (2005). Exposure and measurement contributions to estimates of acute air pollution effects. J Expo Sci Environ Epidemiol, 15: 366-376. 079176

Shindell DT; Faluvegi G; Bell N; Schmidt GA (2005). An emissions-based view of climate forcing by methane and tropospheric ozone. Geophys Res Lett, 32: L04803. 080129

Shindell DT; Faluvegi G; Emmons LK (2005). Inferring carbon monoxide pollution changes from space-based observations. J Geophys Res, 110: D23303. 193746

Shindell DT; Faluvegi G; Koch DM; Schmidt GA; Unger N; Bauer SE (2009). Improved attribution of climate forcing to emissions. Science, 326: 716-718. 201599

Shindell DT; Faluvegi G; Stevenson DS; Krol MC; Emmons LK; Lamarque J-F; Petron G; Dentener FJ; Ellingsen K; Schultz MG; Wild O; Amann M; Atherton CS; Bergmann DJ; Bey I; Butler T; Cofala J; Collins WJ (2006). Multimodel simulations of carbon monoxide: comparison with observations and projected near-future changes. J Geophys Res, 111: D19306. 091028

Shindell DT; Faluvegi G; Unger N; Aguilar E; Shmidt GA; Koch DM; Bauer SE; Miller RL (2006). Simulations of pre-industrial, present-day, and 2100 conditions in the NASA GISS composition and climate model G-PUCCINI. Atmos Chem Phys, 6: 4427-4459. 193751

Singh M; Phuleria HC; Bowers K; Sioutas C (2006). Seasonal and spatial trends in particle number concentrations and size distributions at the children's health study sites in Southern California. J Expo Sci Environ Epidemiol, 16: 3-18. 190136

Sinha A; Toumi R (1996). A comparison of climate forcings due to chloroflurocarbons and carbon monoxide. Geophys Res Lett, 23: 65-68. 193747

So ESP; Chan ATY; Wong AYT (2005). Large-eddy simulations of wind flow and pollutant dispersion in a street canyon. Atmos Environ, 39: 3573-3582. 110746

Thompson AM; Cicerone RJ (1986). Possible perturbations to atmospheric CO, CH4, and OH. J Geophys Res, 91: 10,853-10,864. 019374

Tolbert PE; Klein M; Peel JL; Sarnat SE; Sarnat JA (2007). Multipollutant modeling issues in a study of ambient air quality and emergency department visits in Atlanta. J Expo Sci Environ Epidemiol, 17: S29-S35. 090316

U.S. Census Bureau (2008). American Housing Survey for the United States: 2007. U.S. Government Printing Office. Washington, DC. 194013

U.S. EPA (2000). Air quality criteria for carbon monoxide. National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency. Research Triangle Park, NC. EPA 600/P-99/001F. 000907

U.S. EPA (2006). 2002 National Emissions Inventory Data and Documentation. Retrieved 02-DEC-09, from http://www.epa.gov/ttnchie1/net/2002inventory.html. 157070

U.S. EPA (2006). Air quality criteria for ozone and related photochemical oxidants. EPA. DC. 088089

U.S. EPA (2006). Cold temperature effects on vehicle HC emissions: draft report. U.S. Environmental Protection Agency. Washington, DC. EPA420-D-06-001. http://www.epa.gov/oms/regs/toxics/420d06001.pdf. 199897

U.S. EPA (2008). Integrated Science Assessment for Oxides of Nitrogen - Health Criteria. U.S. Environmental Protection Agency. Research Triangle Park, NC. EPA/600/R-08/071. 157073

U.S. EPA (2008). Inventory of U.S. greenhouse gas emissions and sinks: 1990 – 2006. US Environmental Protection Agency. Washington, DC. 184463

U.S. EPA (2008). Total Risk Integrated Methodology (TRIM) Air Pollutants Exposure Model Documentation (TRIM.Expo/APEX, Version 4.3). Volume 1: User's Guide. U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards. Research Triangle Park, NC. EPA-452/B-08-001b. 191775

U.S. EPA (2008). U.S. EPA's 2008 Report on the Environment (Final Report). U.S. Environmental Protection Agency. DC. 157076

U.S. EPA (2009). Consolidated Human Activity Database. Retrieved 27-AUG-09, from http://www.epa.gov/chadnet1/. 194010

U.S. EPA (2009). Human exposure modeling - Air pollutants exposure model (APEX/TRIM.Expo Inhalation). Retrieved 27-AUG-09, from http://www.epa.gov/ttn/fera/human_apex.html. 194009

Unger N; Shindell DT; Wang TS (2009). Climate forcing by the on-road transportation and power generation sectors. Atmos Environ, 43: 3077-3085. 193238

van der Werf GR; Randerson JT; Giglio L; Collatz GJ; Kasibhatla PS; Arellano Jr AF (2006). Interannual variability in global biomass burning emissions from 1997 to 2004. Atmos Chem Phys, 6: 3423–3441. 157084

Wallace L; Williams R; Suggs J; Jones P (2006). Estimating contributions of outdoor fine particles to indoor concentrations and personal exposures: effects of household characteristics and personal activities. U.S. Environmental Protection Agency; National Exposure Research Laboratory. Research Triangle Park, NC. EPA/600/R-06/023. 089190

Wallace LA; Ziegenfus RC (1985). Comparison of carboxyhemoglobin concentrations in adult nonsmokers with ambient carbon monoxide levels. J Air Waste Manag Assoc, 35: 944-949. 011656

Wang C; Prinn RG (1999). Impact of emissions, chemistry and climate on atmospheric carbon monoxide: 100-yr predictions from a global chemistry-climate model. Chemosphere Global Change Sci, 1: 73-81. 011758

Wigley TML; Smith SJ; Prather MJ (2002). Radiative forcing due to reactive gas emissions. J Clim, 15: 2690-2696. 047883

Wild O; Prather MJ (2000). Excitation of the primary tropospheric chemical mode in a global three-dimensional model. J Geophys Res, 105: 24,647-24,660. 052402

Wild O; Prather MJ; Akimoto H (2001). Indirect long-term global radiative cooling from NOX emissions. Geophys Res Lett, 28: 1719-1722. 193196

Williams R; Suggs J; Rea A; Leovic K; Vette A; Croghan C; Sheldon L; Rodes C; Thornburg J; Ejire A; Herbst M; Sanders W Jr (2003). The Research Triangle Park particulate matter panel study: PM mass concentration relationships. Atmos Environ, 37: 5349-5363. 053335

Wilson WE; Mage DT; Grant LD (2000). Estimating separately personal exposure to ambient and nonambient particulate matter for epidemiology and risk assessment: why and how. J Air Waste Manag Assoc, 50: 1167-1183. 010288

Wilson WE; Suh HH (1997). Fine particles and coarse particles: concentration relationships relevant to epidemiologic studies. J Air Waste Manag Assoc, 47: 1238-1249. 077408

Wuebbles DJ; Hayhoe K (2002). Atmospheric methane and global change. Earth Sci Rev, 57: 177-210. 044159

Xiaomin X; Zhen H; Jiasong W (2006). The impact of urban street layout on local atmospheric environment. Build Environ, 41: 1352-1363. 156165

Yanosky JD; Paciorek CJ; Schwartz J; Laden F; Puett R; Suh HH (2008). Spatio-temporal modeling of chronic PM10 exposure for the Nurses' Health Study. Atmos Environ, 42(18): 4047-4062. 099467

Yanosky JD; Paciorek CJ; Suh HH (2009). Predicting chronic fine and coarse particulate exposures using spatiotemporal models for the northeastern and midwestern United States. Environ Health Perspect, 117: 522-529. 190114

Zeger SL; Diggle PJ (2001). Correction: exposure measurement error in time-series air pollution studies. Environ Health Perspect, 109: A517. 026017

Zeger SL; Thomas D; Dominici F; Samet JM; Schwartz J; Dockery D; Cohen A (2000). Exposure measurement error in time-series studies of air pollution: concepts and consequences. Environ Health Perspect, 108: 419-426. 001949

Zhou Y; Levy JI (2008). The impact of urban street canyons on population exposure to traffic-related primary pollutants. Atmos Environ, 42: 3087-3098. 190091

Zhu Y; Hinds WC; Kim S; Shen S; Sioutas C (2002). Study of ultrafine particles near a major highway with heavy-duty diesel traffic. Atmos Environ, 36: 4323-4335. 041553

Zidek JV; Shaddick G; Meloche J; Chatfield C; White R (2007). A framework for predicting personal exposures to environmental hazards. Environ Ecol Stat, 14: 411-431. 190076

Zimmerman PR; Chatfield RB; Fishman J; Crutzen PJ; Hanst PL (1978). Estimates on the production of CO and H2 from the oxidation of hydrocarbon emissions from vegetation. Geophys Res Lett, 5: 679-682. 010758

Chapter 4. Dosimetry and Pharmacokinetics of Carbon Monoxide

4.1. Introduction

Inhaled ambient CO elicits various health effects by binding with and altering the function of a number of heme-containing molecules, mainly Hb. Traditional concepts for CO pathophysiology have been based on the high affinity of CO for hemoglobin, resulting in COHb formation and consequent reduction in O_2-carrying capacity of blood and impaired O_2 delivery to tissues. Research on CO pharmacokinetics dates back to the 1890s, but since the late 1970s has become limited. Current literature primarily focuses on endogenous CO produced by the metabolic degradation of heme by heme oxygenase (HO) and its role as a gaseous messenger. This chapter reviews the physiology and pharmacokinetics of CO. The chapter draws heavily from Chapter 5 of the previous AQCD (U.S. EPA, 2000, 000907). Relevant new data are included when available. Recent models of Hb binding are characterized, as well as measurements of tissue CO concentrations using new methods of extraction.

CO binds with a number of heme-containing molecules including Mb and cytochromes, but none have been studied as extensively as Hb. The primary focus of this chapter is placed on the models and kinetics of such binding and the factors influencing this event. The chapter discusses effects at ambient or near ambient levels of CO leading to low COHb levels (≤ 5%); however few studies are available at ambient CO concentrations. Both human and animal studies using higher CO exposure concentrations, resulting in moderate to high COHb levels (<20%), are discussed where needed to understand CO kinetics, pathophysiologic processes, and mechanisms of cytotoxicity. Where human studies could not experimentally test certain hypotheses or were unavailable, animal experiments were used as surrogates. CO uptake and elimination has been shown to be inversely proportional to body mass over environmentally relevant exposure levels, meaning the smaller the animal, the faster the rate of absorption and elimination (Klimisch et al., 1975, 010762; Tyuma et al., 1981, 011226). However, the basic mechanisms of CO toxicity between experimental animals and humans are similar and are thus extrapolated from animals to humans in this chapter, keeping in mind a number of interspecies differences.

4.2. Carboxyhemoglobin Modeling

4.2.1. The Coburn-Forster-Kane and Other Models

Investigators have modeled the effect of CO binding to Hb in a number of ways. Empirical and mechanistic models are two distinct approaches that have been taken to model in vivo COHb formation after CO exposure. First, empirical models were used to predict COHb by regressing concentration and duration of exogenous CO exposure with observed COHb, with or without the inclusion of physiological predictors such as initial COHb levels and alveolar ventilation (V_A). These methods were reviewed in depth in the previous AQCD (U.S. EPA, 2000, 000907). It is important to note that CO empirical regression models are limited to estimating COHb in the exact conditions on which the models were based. These simple models include those by Peterson and Stewart (1970,

Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at http://epa.gov/hero. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISAs) and the Integrated Risk Information System (IRIS).

012416) and Ott and Mage (1978, 011124), as well as various others (Chung, 1988, 012749; Forbes et al., 1945, 012850; Selvakumar et al., 1992, 013750; Sharan et al., 1990, 003798; Singh et al., 1991, 013583). Using a linear differential equation where ambient CO concentrations varied, it was shown that the presence of brief ambient CO concentration spikes averaged over hourly intervals may lead to underestimating the COHb concentration by as much as 21% of the true value. To avoid this problem, it was suggested that ambient CO measurements be monitored and averaged over 10- to 15-min periods (Ott and Mage, 1978, 011124). Other empirical models predict COHb as a function of exposure time (Sharan et al., 1990, 003798; Singh et al., 1991, 013583) or exposure time and altitude (Selvakumar et al., 1992, 013750). A comparison of empirical model predictions showed a wide disparity in predicted COHb values, highlighting the inaccuracy of these models outside of the conditions on which they were presented (Tikuisis, 1996, 080960).

Secondly, mechanistic models use physical and physiological processes and an understanding of biological processes to predict COHb production. The most commonly used mechanistic method for predicting levels of blood COHb after CO inhalation is the Coburn-Forster-Kane equation or CFK model developed in 1965 (Coburn et al., 1965, 011145). This differential equation was developed to examine endogenous CO production, using the major physiological and physical variables influencing this value. Since then, it has been shown to provide a good approximation to the COHb level at a steady level of inhaled exogenous CO (Peterson and Stewart, 1975, 010696; Stewart et al., 1973, 012428). The CFK model describes a four-element, physical system containing an exogenous CO source, a transfer interface, an endogenous CO source, and a storage compartment. The linear CFK model assumes O_2Hb concentration is constant and is as follows in Equation 4-1:

$$V_b \frac{d[COHb]_t}{dt} = \dot{V}_{CO} - \frac{[COHb]_0 P_{\bar{C}}O_2}{[O_2Hb]M}\left(\frac{1}{\frac{1}{D_LCO} + \frac{P_B - P_{H2O}}{\dot{V}_A}}\right) + \left(\frac{P_ICO}{\frac{1}{D_LCO} + \frac{P_B - P_{H2O}}{\dot{V}_A}}\right)$$

Equation 4-1

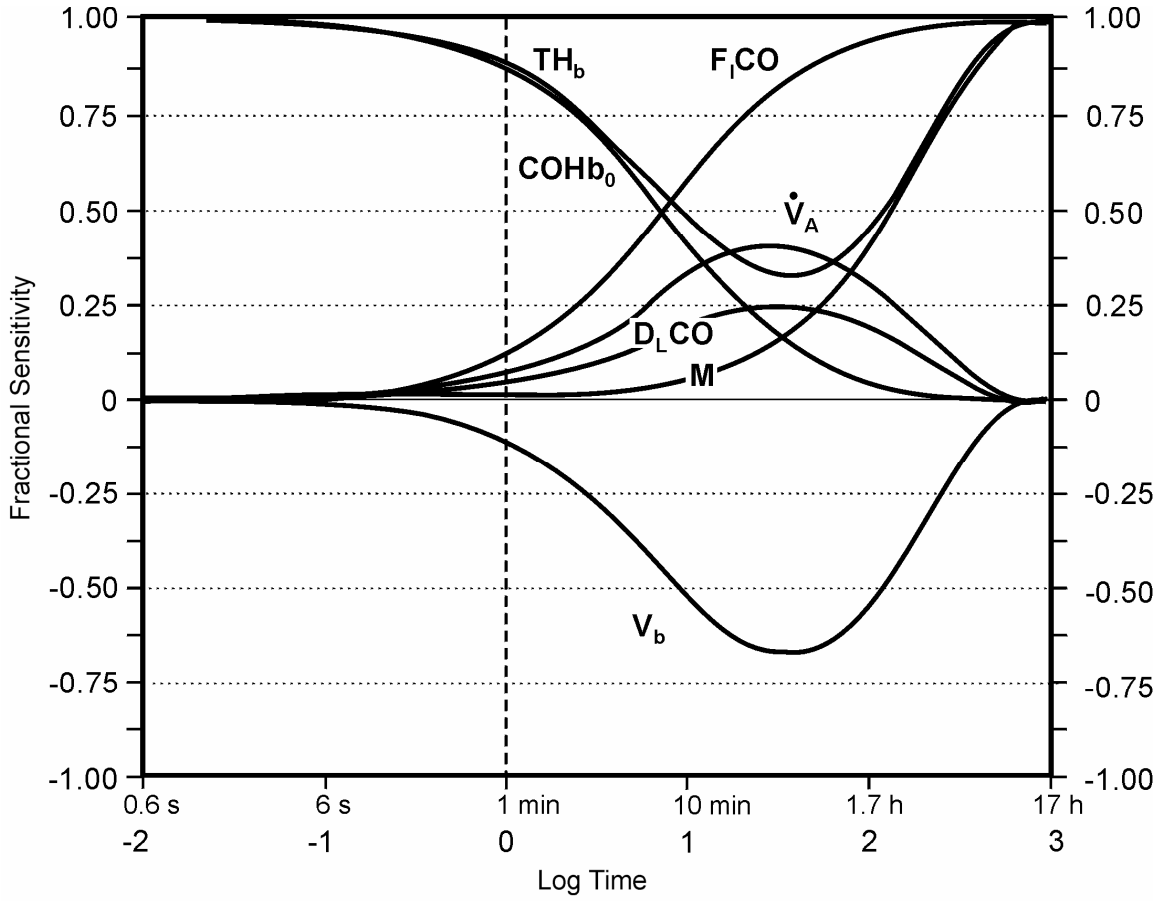
V_b	blood volume in milliliters (mL)
$[COHb]_t$	COHb concentration at time t in mL CO/mL blood, at standard temperature and pressure, dry (STPD)
V_{CO}	endogenous CO production rate in mL/min, STPD
$[COHb]_0$	COHb concentration at time zero in mL CO/mL blood, STPD
$[O_2Hb]$	O_2Hb concentration in mL O_2/mL blood, STPD
P_CO_2	average partial pressure of O_2 in lung capillaries in mmHg
M	Haldane coefficient representing the CO chemical affinity for Hb
D_LCO	lung diffusing capacity of CO in mL/min/mmHg, STPD
P_B	barometric pressure in mmHg
P_{H2O}	saturation pressure of water vapor at body temperature in mmHg (47 mmHg)
V_A	alveolar ventilation in mL/min, STPD
P_ICO	CO partial pressure in inhaled air in mmHg

The linear CFK model assumes instant equilibration of COHb concentration between venous and arterial blood, gases in the lung, and COHb concentrations between blood and extravascular tissues, which is not physiologically representative. The nonlinear CFK equation extends the linear CFK equation to incorporate the interdependence of COHb and O_2Hb levels since they are derived from the same pool of blood Hb. This interdependence can be modeled by substituting (1.38 Hb [COHb]) for O_2Hb, where TH_b refers to the number of grams of Hb per mililiter of blood (Peterson and Stewart, 1975, 010696). The nonlinear CFK differential equation is as follows in Equation 4-2:

$$V_b \frac{d[COHb]_t}{dt} = \dot{V}_{CO} - \frac{[COHb]_0 P_{\bar{C}}O_2}{(1.38[TH_b] - [COHb]_t)M} \left(\frac{1}{\frac{1}{D_L CO} + \frac{P_B - P_{H2O}}{\dot{V}_A}} \right) + \left(\frac{1}{\frac{1}{D_L CO} + \frac{P_B - P_{H2O}}{\dot{V}_A}} \right)$$

Equation 4-2

The nonlinear equation is more physiologically accurate; however the linear CFK equation gives a good approximation to the nonlinear solution over a large range of values during CO uptake and during low levels of CO elimination (Smith, 1990, 013164). The linear equation prediction of COHb concentration at or below 6% will deviate by no more than ± 0.5% COHb from the nonlinear equation prediction. Sensitivity analysis of the CFK equations has shown that alterations in each variable of the equation will affect the outcome variably at different times of exposure, so that the relative importance of the CFK variables will change with the experimental conditions (McCartney, 1990, 013162). Figure 4-1 illustrates the temporal changes in fractional sensitivities of the principal physiological determinants of CO uptake for the linear form of the CFK equation, where TH_b is the total blood concentration of Hb in g Hb/mL blood and F_ICO is the fractional concentration of CO in ambient air in ppm. The fractional sensitivity of unity means that, for example, a 5% error in the selected variable induces a 5% error in the predicted COHb value by the nonlinear model. As Figure 4-1 demonstrates, a constant or given percent error in one variable of the model does not generally produce the same error in the calculated blood COHb, and the error is time dependent. Thus, each variable influencing CO uptake and elimination will exert its maximal influence at different times of exposure. This analysis found that only F_ICO (shown in Figure 4-1) and V_{CO} will not affect the rate at which equilibrium is reached (McCartney, 1990, 013162).



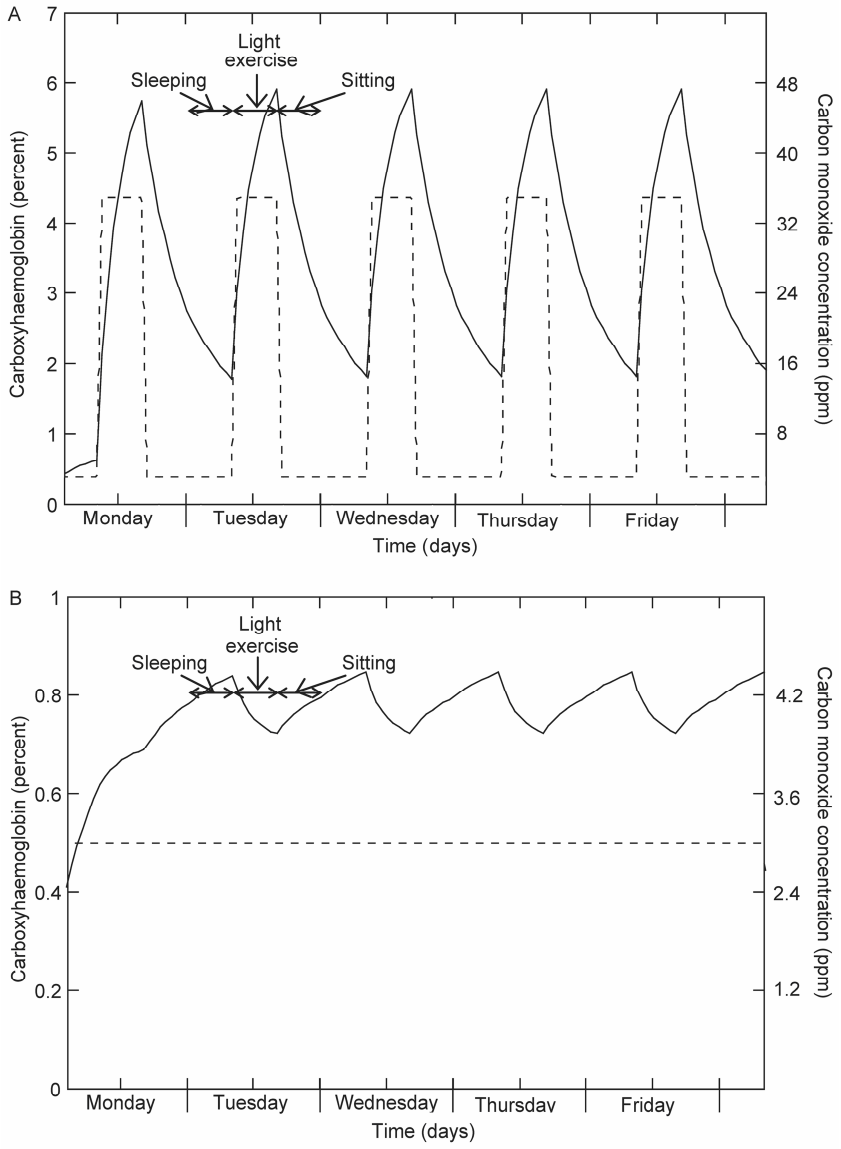
Source: Adapted with Permission of the American Industrial Hygiene Association from McCartney (1990, 013162)

Figure 4-1. Plot of fractional sensitivities of selected variables versus time of exposure.

The mechanistic CFK model contains a number of assumptions under which the model is solely applicable, including: (1) ventilation is a continuous process; (2) equilibrium between plasma CO concentration and COHb concentration is obtained in the pulmonary system; (3) percent COHb can exceed 100% saturation in the linear model; and (4) it does not account for the shape of the O_2 or CO saturation versus pO_2 or pCO relation (McCartney, 1990, 013162). Estimations outside of these assumptions have been attempted but with less predictive agreement. For example, transient exposures such as those that would simulate everyday conditions would violate the assumption of a single, well-mixed vascular compartment. COHb levels during exposure of subjects exposed to frequent but brief high CO exposures (667-7,500 ppm for 75 s to 5 min) were not accurately predicted by CFK modeling (Benignus et al., 1994, 013908; Tikuisis et al., 1987, 012219; Tikuisis et al., 1987, 012138). Consistently, the COHb value predicted by the nonlinear CFK overpredicted observed venous COHb (0.8-6%) and underpredicted arterial COHb (1.5-6.1%) and this disparity increased after exercise. Individual differences between arterial and venous COHb varied from 2.3-12.1% COHb (mean, 6.2 ± 2.7% COHb), where the observed steady state COHb averaged ~14% and the observed arterial peak COHb averaged ~17.5% (Smith et al., 1994, 076564)(Benignus et al., 1994, 013908). These inaccuracies between measured and predicted COHb values disappeared after simulated mixing of arterial and venous blood and thus are likely due to delays in mixing of arterial and venous blood and differences in cardiac output and lung wash-in. This discrepancy in predicted and observed COHb suggests that over a short period (<10 min) the arterial COHb levels that are delivered to tissues could be higher than what is predicted by the CFK equation. A modified CFK was created to adjust for these issues and produce a more accurate COHb prediction (Smith et al., 1994, 076564). This expanded CFK model used multiple compartments to model the lung, arm circulation, and the rest of the body (quickly and slowly perfused tissues). This model was more

accurate than the nonlinear CFK in predicting the individual peak or maximal values of arterial and venous COHb during CO uptake in the first 10 min after exposure. However, both the nonlinear CFK and this expansion produced accurate predictions several minutes after the 5-min exposure ended. The expanded model required the use of two parameters, V_A and V_b, that were not measured individually or derived from the literature, and instead were estimated by adjustments between the simulations and experimental subject data.

In addition to the limitations discussed above, the CFK model does not account for extravascular storage sites for CO, such as muscle Mb. CO will undergo reversible muscle Mb binding, similar to Hb, as well as uptake into other extravascular tissues (Vreman et al., 2006, 098272). The most recent adaptation to the CFK equation incorporates alveoli-blood and blood-tissue CO exchanges and mass conservation of CO at all times (Gosselin et al., 2009, 190946). This model has a single free parameter whose value is estimated from one data set; however, it better predicted COHb formation over a wide range of CO levels and several temporal scenarios (Stewart et al., 1970, 013972; Tikuisis et al., 1987, 012138; Tikuisis et al., 1987, 012219; Tikuisis et al., 1992, 013592) compared to the linear CFK model. Like the linear CFK model, this modified model assumes a constant level of oxyhemoglobin. Sensitivity analysis of the model showed that the most important parameter influencing the level of COHb in this model is M, followed by P_CO_2 and V_A. Ambient exposure scenarios were simulated with this model to determine the CO concentrations needed to reach certain COHb levels in humans from 3 months of age to 40-yr-old adults (Gosselin et al., 2009, 190946). The CO concentrations needed to achieve 2% COHb vary from 24.4-48.1 ppm for a 1-h exposure, from 11.1-13.1 ppm for an 8-h exposure, and from 9.8-10.1 ppm for a daily exposure. Infants (1 yr old) were most sensitive to CO concentrations, whereas newborns (3 mo old) required the highest CO concentration to reach 2% COHb. Newborns required a higher CO exposure partially because the values used in the model for the newborn blood Hb concentration (170 g_{Hb}/L_{blood}) is higher than at infancy (115 g_{Hb}/L_{blood}) or adulthood (150 g_{Hb}/L_{blood}). The model was also used to simulate time profiles of COHb formation for two work week exposure scenarios in a healthy 40-yr-old man. Figure 4-2A represents a high exposure scenario where the work period is spent at 35 ppm and the rest of the time at 3 ppm. Figure 4-2B represents a lower exposure scenario where there is a constant 3 ppm exposure. Both figures consist of 5 days where 24 h are broken up into 3 consecutive 8-h periods: sleeping from 12 a.m. to 8 a.m.; working with light exercise from 8 a.m. to 4 p.m.; and sitting from 4 p.m. to 12 a.m..



Source: Reprinted with Permission of Informa Healthcare from Gosselin et al. (2009, 190946)

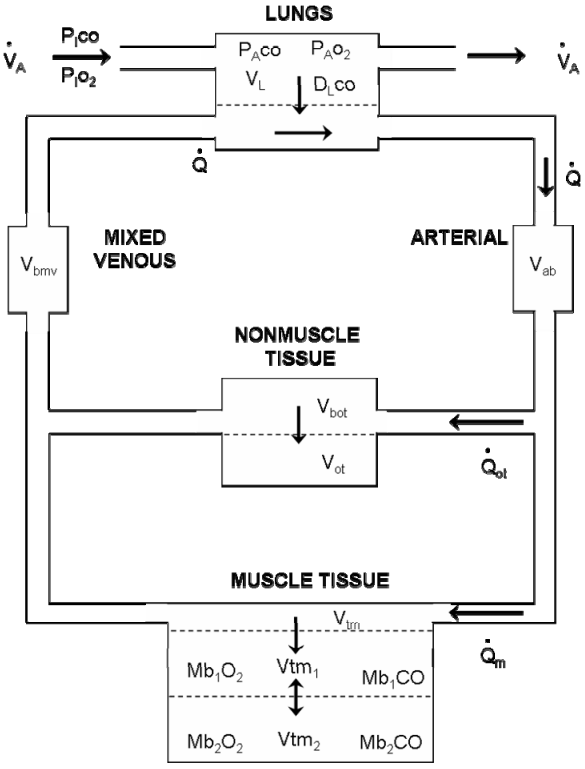
Figure 4-2. Simulated COHb formation for two 5-day workweeks. "The 24-h day consists of 3 consecutive 8-h periods: sleeping from 12 a.m. to 8 a.m.; working (light exercise) from 8 a.m. to 4 p.m.; and sitting from 4 p.m. to 12 a.m. (A) High exposure: work period at 35 ppm and the rest of the time at 3 ppm. (B) Low daily exposure at 3 ppm. The CO exposure periods are represented by dotted lines (----) and the COHb simulations by solid lines (—)."

4.2.2. Multicompartment Models

A third approach applied more recently to model COHb formation is the use of multicompartment or physiologically-based pharmacokinetic (PBPK) models. Cronenberger et al. (2008, 194085) described a two-compartment population-based model to describe and predict COHb pharmacokinetics from smoking. This model required a compartment for extravascular binding of

CO to accurately predict COHb formation during multiple short and rapid inhalations followed by a period of no exposure, as occurs in smoking.

A five-compartment PBPK model has been proposed to predict CO uptake and distribution from acute inhalation exposure and contains components for lung, arterial blood, venous blood, muscle tissue, and nonmuscle tissue (Bruce and Bruce, 2003, 193975; Bruce and Bruce, 2006, 193980; Bruce et al., 2008, 193977). This model structure is illustrated in Figure 4-3 and includes the dynamics of CO storage in the lung and its dependence on ventilation and CO pressure of mixed venous blood, relaxes the assumption that Hb is saturated by including the role of CO in altering the O_2 dissociation curve, includes a subcompartmentalized muscle tissue compartment, accounts for dissolved CO in blood and tissue, and predicts COHb based on age and body dimensions. This multicompartment model is limited by its exclusion of cellular metabolism or Mb diffusion, simplification of within tissue bed spatial variability, and assumption that ventilation and average partial pressure of alveolar O_2 (P_AO_2) are constant. Another limitation of this model is that some of the physiological parameters used in simulations are estimated through visual fits to the COHb profile and not from experimental or published data. This model better predicts COHb levels when inspired CO levels change rapidly or when incomplete blood mixing has occurred, and better predicts the CO washout time course compared to the CFK equation. Bruce and Bruce (2003, 193975) compared the two models and found similar results for long-duration exposure settings (1,000 min); however, the multicompartment model predicted somewhat lower COHb levels compared to the CFK model during transient CO uptake conditions when using data taken from Peterson and Stewart (1970, 012416).



Source: Adapted with Permission of Elsevier Science from Bruce and Bruce (2008, 193977)

Figure 4-3. Overall structure of the Bruce and Bruce (2008, 193977) multicompartment model of storage and transport of CO. Includes compartments for lung, arterial blood, venous blood, muscle tissue, and nonmuscle tissue. The muscle compartment is divided into two subcompartments for diffusion of gases within the tissue.

A multicompartment model of the human respiratory system was developed using characteristics of the tissue representation of Bruce and Bruce (2003, 193975), and the lung representation described in Selvakumar et al. (1992, 013750) and Sharan (1999, 194673), which considered the exchanges of CO, O_2, and CO_2 (Neto et al., 2008, 194672). The model contains six compartments including: alveolar, pulmonary capillaries, arterial, venous, tissue capillary, and tissues (muscular and non-muscular). The model was applied to four simulated physical activity levels, resting, sitting, standing, and walking, in a healthy subject exposed to the urban atmosphere of a metropolitan area of Brazil. The highest and lowest COHb levels were simulated in the walking individual, suggesting that greater variability in COHb occurs at higher physical activity levels.

4.2.3. Model Comparison

A number of models have been presented which predict COHb formation over numerous exposure scenarios. These models are often compared to the CFK equation to determine the most accurate predictive model under certain exposure conditions. As was mentioned in Section 4.2.1, Tikuisis (1996, 080960) conducted a comparison of empirical model predictions that showed a wide disparity in predicted COHb values, highlighting the inaccuracy of these models outside of the conditions on which they were presented. Smith et al. (1990, 013164) compared the linear and nonlinear CFK equations and concluded that the linear CFK equation gives a good approximation (within 1%) to the nonlinear solution over a large range of values during CO uptake and over a somewhat smaller range during CO elimination. The linear equation prediction of COHb concentration at or below 6% will only differ ± 0.5% COHb from the nonlinear equation prediction. Additionally, the most recently modified CFK model (Gosselin et al., 2009, 190946) better predicted COHb formation over a wide range of CO levels (50-4,000 ppm) and several temporal scenarios (Stewart et al., 1970, 013972; Tikuisis et al., 1987, 012138; Tikuisis et al., 1987, 012219; Tikuisis et al., 1992, 013592) compared to the linear CFK model. Linear regression slopes between the simulated COHb values from Gosselin et al. (2009, 190946) and the observed experimental values were closer to 1 in all experimental scenarios, indicating a better fit to the observed data. When evaluating all validation studies the modified model had an estimated slope of 0.996 (95% CI: 0.986-1.001) compared to 0.917 (95% CI: 0.906-0.927) using the linear CFK model. Bruce and Bruce (2003, 193975) compared their model to the CFK and found similar results for long-duration exposure settings (1,000 min [16.5 h]), however, their multicompartment model predicted somewhat lower COHb levels over transient CO uptake conditions when using data taken from Peterson and Stewart (1970, 012416). The Bruce and Bruce model better predicts However, there has not been a quantitative comparison of the recent multicompartment models (Bruce and Bruce, 2003, 193975; Neto et al., 2008, 194672) and the improved CFK equation models (Gosselin et al., 2009, 190946; Smith et al., 1994, 076564) to determine which is most accurate in predicting COHb levels under exposure scenarios that include occasional peak concentrations. The nonlinear and linear CFK equations remain the most extensively validated and applied models for COHb prediction. COHb levels when inspired CO levels change rapidly or when incomplete blood mixing has occurred, and better predicts the CO washout time course compared to the CFK equation. However, there has not been a quantitative comparison of the recent multicompartment models (Bruce and Bruce, 2003, 193975)(Neto et al., 2008, 194672) and the improved CFK equation models (Smith et al., 1994, 076564)(Gosselin et al., 2009, 190946) to determine which is most accurate in predicting COHb levels under exposure scenarios that include occasional peak concentrations. The nonlinear and linear CFK equations remain the most extensively validated and applied models for COHb prediction.

4.2.4. Mathematical Model Usage

As no new data have become available on the distribution of COHb levels in the U.S. population since large-scale nationwide surveys – e.g., National Health and Nutrition Examination Survey II (NCHS; et al., 1982, 011442) – and human exposure field studies – e.g., Denver, CO, and Washington, DC (Akland et al., 1985, 011618) – were conducted in the 1970s and 1980s, mathematical models are used to predict the resulting COHb levels from various CO exposure scenarios. Table 4-1 illustrates the predictions of venous COHb after 1, 8, or 24 h of CO exposure at a range of concentrations in a healthy adult human at rest (V_A = 6 L/min; D_LCO = 20

[mL/min]/mmHg), during light exercise (V_A = 15 L/min; D_LCO = 34 [mL/min]/mmHg), and during moderate exercise (V_A = 22 L/min; D_LCO = 43 [mL/min]/mmHg). The Quantitative Circulatory Physiology (QCP) model, which integrates human physiology using over 4,000 variables and equations based on published biological interactions, was used to predict these values (Abram et al., 2007, 193859; Benignus et al., 2006, 151344). This dynamic whole body model uses the nonlinear CFK equation with modifications presented in Smith et al. (1994, 076564). The contribution of alveolar ventilation and lung diffusion to the changes in COHb levels is discussed in Section 4.3.1.2. Increased ventilation leads to an increased rate of CO uptake, causing COHb levels to reach equilibrium earlier. Also, increased ventilation leads to a decrease in steady state COHb levels due to increased CO expiration. For example, 35 ppm CO exposure at moderate exercise (22 L/min) results in a lower 24-h COHb saturation (4.73%), compared to COHb saturation from 35 ppm CO at rest (5.03%) (Table 4-1). Whereas, after 1 h, COHb levels are still increasing following exposure at all levels of exercise and have not reached steady state, thus the greater uptake from increased ventilation leads to initially elevated COHb in higher ventilation situations.

Endogenous CO production varies as described in Section 4.5 but generally results in <1% COHb, with a QCP modeled value of 0.27% at time zero. The rate of endogenous CO production was set at 0.007 mL/min for this simulation, whereas both higher and lower values have been reported (Coburn et al., 1966, 010984) (Section 4.5). Table 4-1 illustrates that 35 ppm CO for 1-h results in between 0.9-1.9% COHb and 9 ppm CO for 8-h results in between 1.1-1.3% COHb, depending upon activity level. Also, this table shows that low concentration CO exposure over several hours can result in equivalent COHb levels compared to higher concentration, acute exposure. For example, in a resting condition without additional baseline COHb, COHb resulting from 35 ppm for 1 h (0.89%) is approximately equivalent to 6 ppm for 8 h (0.83%) or 4 ppm for 24 h (0.82%).

Table 4-1. Predicted COHb levels resulting from 1, 8, and 24 h CO exposures in a modeled human at rest (V_A = 6 L/min; D_LCO = 20 (mL/min)/mmHg; V_{CO} = 0.007 mL/min; initial COHb = 0.27%; Hb = 0.15 g/mL), during light exercise (V_A = 15 L/min; D_LCO = 34 (mL/min)/mmHg), and during moderate exercise (V_A = 22 L/min; D_LCO = 43 (mL/min)/mmHg). The QCP model used a dynamic nonlinear CFK with the Smith et al. (1994, 076564) COHb algorithm and affinity constant M = 218.

	1 h			8 h			24 h		
CO (ppm)	6 L/min	15 L/min	22 L/min	6 L/min	15 L/min	22 L/min	6 L/min	15 L/min	22 L/min
2	0.30	0.30	0.29	0.45	0.38	0.35	0.54	0.40	0.36
3	0.31	0.33	0.34	0.54	0.51	0.48	0.68	0.54	0.49
4	0.33	0.36	0.62	0.64	0.64	0.62	0.82	0.69	0.63
6	0.36	0.44	0.48	0.83	0.90	0.88	1.10	0.97	0.91
9	0.42	0.55	0.63	1.12	1.29	1.27	1.52	1.39	1.31
15	0.53	0.77	0.92	1.69	2.05	2.06	2.35	2.22	2.12
24	0.70	1.10	1.35	2.55	3.19	3.22	3.57	3.45	3.31
35	0.89	1.50	1.89	3.58	4.55	4.60	5.03	4.91	4.73

The QCP model incorporating the Smith et al. (1994, 076564) COHb algorithm was also used to simulate population exposure scenarios including various commuting concentrations (Figure 4-4) and endogenous production rates (Figure 4-5). Commuting concentrations were modeled since the highest ambient CO exposure levels are generally observed during transit (Section 3.6.6.2). Figure 4-4 presents simulated COHb levels in a healthy adult throughout the second of 5 modeled days containing a 60-min commute at various CO concentrations. The U.S. Census Bureau estimates that 5% of the population commutes in automobiles for 60 or more minutes to work daily (U.S. Census Bureau, 2008, 194013) and exposure studies have reported in-vehicle transit concentrations up to 50 ppm (Abi-Esber and El-Fadel, 2008, 190939; Duci et al., 2003, 044199). However, U.S. studies have reported in-vehicle concentrations of <6 ppm, although peak

concentrations in congested urban areas have been reported to be higher than 50 ppm (Rodes et al., 1998, 010611)(Riediker et al., 2003, 043761). CO concentrations during commuting lead to spikes in COHb in this model scenario with a 1% COHb increase over the initial COHb (0.3%) after 50 ppm exposure. Figure 4-4 also illustrates that the COHb saturation after CO exposure from commuting is not fully eliminated by the next commuting period. Modeling successive days results in the same pattern and degree of COHb formation, indicating no accumulation of COHb over time.

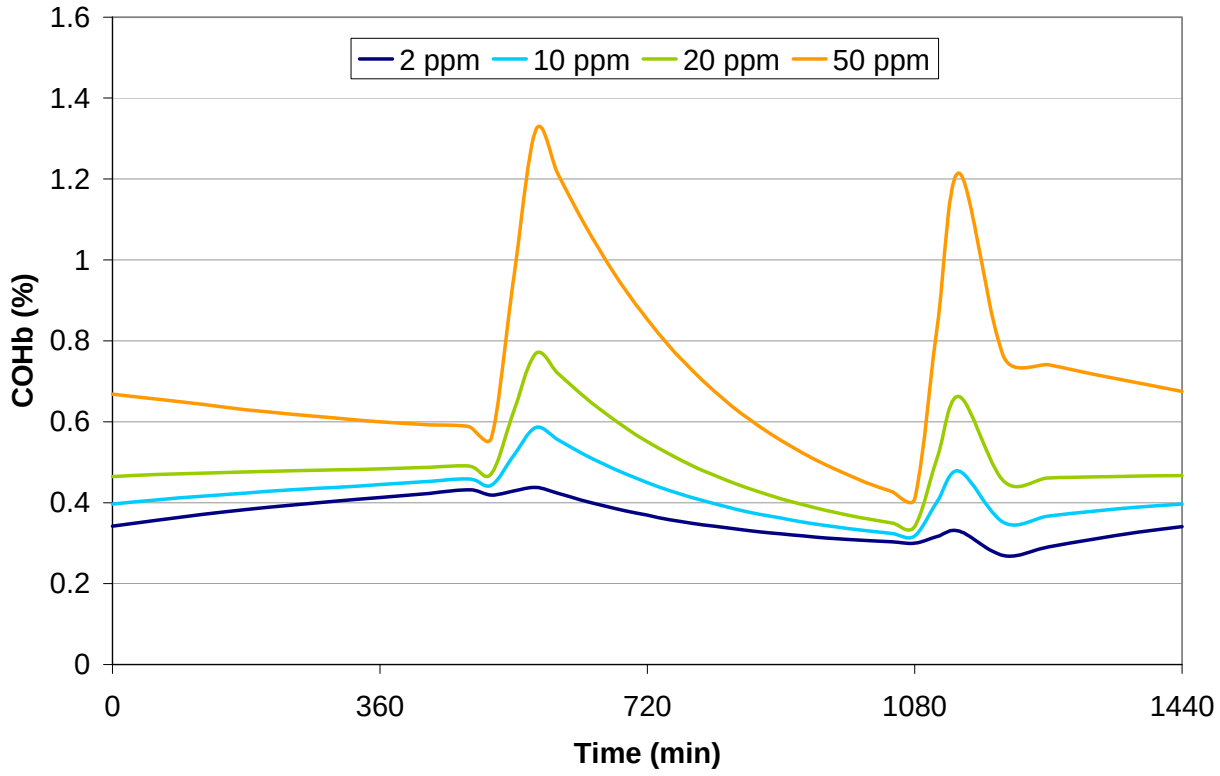


Figure 4-4. Predicted COHb levels in healthy commuters exposed to various CO concentrations over a 60-min commute twice a day. Ambient CO concentration not during commuting time was 1 ppm. The activity pattern simulated: (1) sleeping for 8 h; (2) standing and light exercise for 30 min; (3) sitting during a 60-min commute; (4) light exercise for 8.5 h; (5) sitting during a second 60-min commute; (6) moderate exercise for 60 min; and (7) sitting for 4 h. The graph illustrates the second day simulated under these conditions.[1]

Figure 4-5 presents simulated COHb levels in adults with various endogenous CO production rates throughout the second of 5 modeled days containing a 60-min commute at 20 ppm CO. The normal endogenous rate of CO production in young adult males with an average COHb of 0.88% averages 0.007 mL/min (18.7 ± 0.8 µmol/h) (Coburn et al., 1963, 013971). However, a number of diseases and conditions described in Section 4.5 can affect this production rate. Patients with

[1] Sleeping/lying human parameters: V_A- 3.8 L/min, V_T- 467 mL, V_D- 147 mL, V_{CO}- 0.007 mL/min, D_LCO- 17.9 mL/min/mmHg, M- 218, initial. COHb- 0.27%. Sitting human parameters: V_A- 5.2 L/min, V_T- 560 mL, V_D- 155 mL, V_{CO}- 0.007 mL/min, D_LCO- 18 mL/min/mmHg. Standing human parameters: V_A- 6.4 L/min, V_T- 636 mL, V_D- 161 mL, V_{CO}- 0.007 mL/min, D_LCO- 19.3 mL/min/mmHg. Light exercise (1 MPH, 32 W) human parameters: V_A- 13.4 L/min, V_T- 994 mL, V_D- 218 mL, V_{CO}- 0.007 mL/min, D_LCO- 30.4 mL/min/mmHg. Heavy exercise (3 MPH, 96 W) human parameters: V_A- 31.4 L/min, V_T- 1642 mL, V_D- 241 mL, V_{CO}- 0.007 mL/min, D_LCO- 49.6 mL/min/mmHg.

hemolytic anemia have endogenous CO production rates ranging from 0.012 to 0.053 mL/min (31-143 µmol/h) (Coburn et al., 1966, 010984). The venous COHb levels in these same patients ranged from 0.77 to 2.62%.

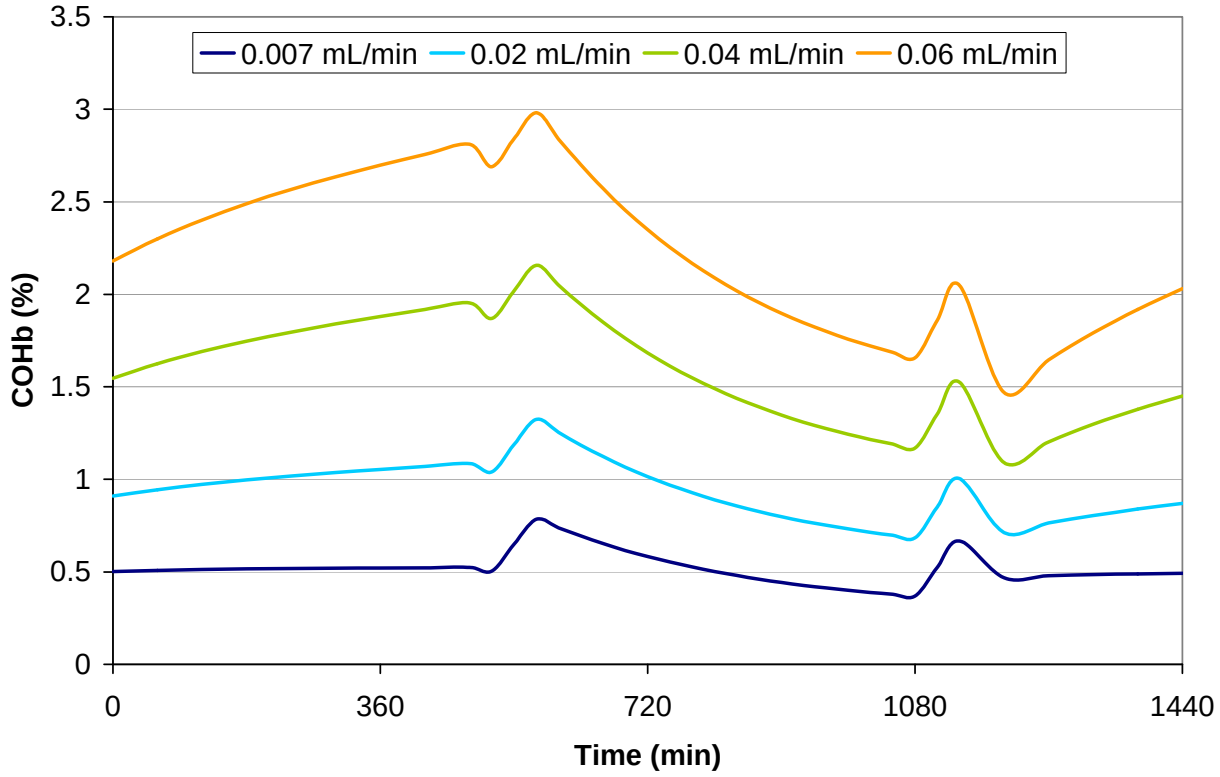


Figure 4-5. Predicted COHb levels due to various endogenous CO production rates. The activity pattern presented in Figure 4-4 was used. Ambient CO concentration not during commuting time was 1 ppm and commuting CO concentration was 20 ppm. The graph illustrates the second day simulated under these conditions.

4.3. Absorption, Distribution, and Elimination

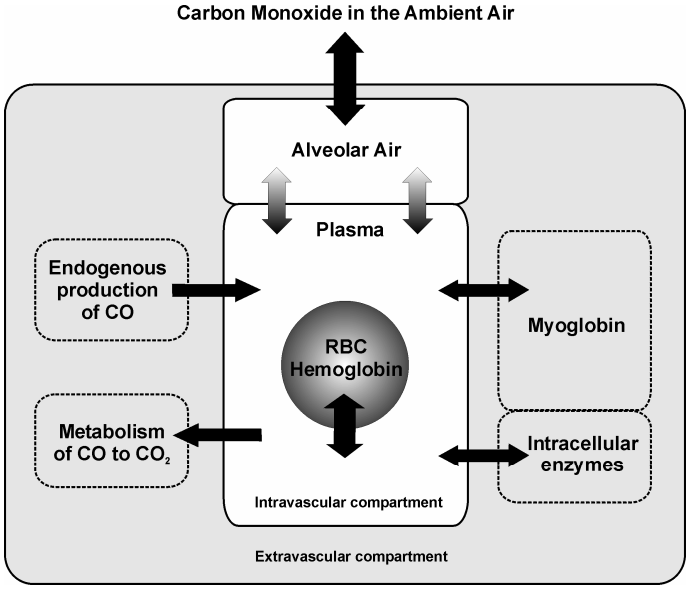
4.3.1. Pulmonary Absorption

Pulmonary uptake of CO accounts for all environmental CO absorption and occurs at the respiratory bronchioles and alveolar ducts and sacs. CO and O_2 share various physico-chemical properties, thus allowing for the extension of the knowledge about O_2 kinetics to those of CO despite the differences in the reactivity of the gases. The exchange of CO between the air and the body depends on a number of physical (e.g., mass transfer and diffusion), as well as physiological factors (e.g., alveolar ventilation and cardiac output), which are controlled by environmental conditions, physical exertion, and other processes discussed in Section 4.4. The ability of the lung to take up inhaled CO is measured by D_LCO, and CO uptake representing the product of D_LCO and the mean alveolar pressure (P_ACO). The importance of dead space volume, gas mixing and homogeneity, and

ventilation/perfusion matching were discussed in depth in the 2000 CO AQCD (U.S. EPA, 2000, 000907).

4.3.1.1. Mass Transfer of Carbon Monoxide

Mass transfer refers to the molecular and convective transport of CO molecules within the body stores, driven by random molecular motion from high to low concentrations. CO enters through the airway opening (mouth and nose) and transfers in a gas phase to the alveoli. CO transport is due to convective flow, the mechanical action of the respiratory system, and diffusion in the acinar zone of the lung (Engel et al., 1973, 014336). Then, CO diffuses across the air-blood interface into plasma and subsequently into red blood cells (RBC), binding RBC Hb. At environmental CO levels, CO uptake into RBC is limited by the reaction rate of binding of CO to O_2Hb forming COHb. Pulmonary capillary RBC CO diffusion is rapidly achieved (Chakraborty et al., 2004, 193759; Gibson and Roughton, 1955, 193941; Reeves and Park, 1992, 193847; Roughton and Forster, 1957, 193862). The formation rate and level of COHb depends upon pCO, pO_2 in the air, time of exposure, and the ventilation rate (Roughton and Forster, 1957, 193862). Most of the body CO is bound to Hb; however, 10-15% of the total body CO is located in extravascular tissues primarily bound to other heme proteins (Coburn, 1970, 013916). Considerable concentrations of CO have been measured in spleen, lung, kidney, liver, muscle, and heart (Vreman et al., 2005, 193786; Vreman et al., 2006, 098272), whereas less CO is localized to fatty tissues, such as adipose and brain. The transfer of CO occurs by a partitioning of CO between Hb and tissue. Less than 1% of the total body CO stores appear as dissolved in body fluids, due to the insolubility and small tissue partial pressure of CO (Coburn, 1970, 013916). Transport pathways and body stores of CO are shown in Figure 4-6.



Source: Adapted with Permission of Wiley-Blackwell from Coburn (1967, 011144)

Figure 4-6. Diagrammatic presentation of CO uptake and elimination pathways and CO body stores.

4.3.1.2. Lung Diffusion of Carbon Monoxide

Lung diffusion of CO is an entirely passive process of gas diffusion across the alveolo-capillary membrane, through the plasma, across the RBC membrane and into the RBC stroma, where

CO binding to Hb rapidly occurs. Membrane and blood phase transfer are governed by physico-chemical laws, including Fick's first law of diffusion. The diffusing capacity of the lung for CO, represented as D_LCO, is a measurement of the partial pressure difference between inspired and expired CO. Due to the rapid binding of CO to Hb, a high pressure differential between air and blood exists when CO air levels are increased. Inhalation of CO-free air reverses the pressure differential (higher CO pressure on the blood side than the alveolar side), and then CO is released into the alveolar air. Since CO is also produced endogenously, CO release will also be affected by this production pressure. However, the air-blood gradient for CO is usually higher than the blood-air gradient; therefore, CO uptake will be a proportionately faster process than CO elimination.

A number of factors have been found to affect D_LCO including Hb concentration, cardiac output (Q), erythrocyte flow, COHb concentration, P_ACO_2, body position, exercise, time of day, age, etc. (Forster, 1966, 180430; Hsia, 2002, 193857). D_LCO consistently decreases after intense bouts of exercise, likely due to the redistribution of blood volume to the periphery (Hanel et al., 1997, 193918; Manier et al., 1991, 193979). However, in going from rest to exercise, D_LCO can increase linearly from: lung expansion leading to unfolding and distension of alveolar septa, opening and/or distension of capillaries as Q increases, increased capillary hematocrit, and more homogeneous distribution of capillary erythrocytes (Hsia, 2002, 193857). D_LCO is less dependent upon lung volume at mid-range vital capacity, but at extreme volumes the diffusion rate is varied, higher than average at total lung capacity and lower at residual volume (McClean et al., 1981, 012411).

D_LCO is also altered by a number of diseases. Decreased D_LCO is evident in patients with restrictive lung disease (i.e., decreased lung volumes) since a loss of lung tissue leads to a loss of functional lung units. D_LCO also shows a good correlation with the severity of restrictive lung disease (Arora et al., 2001, 186713). Conditions affecting D_LCO vary and include chronic obstructive pulmonary disease (Terzano et al., 2009, 108046), ulcerative colitis (Marvisi et al., 2000, 186703; Marvisi et al., 2007, 186702), severe gastroesophageal reflux (Schachter et al., 2003, 186707), beta thalassemia (Arora et al., 2001, 186713), thoracic or abdominal aortic aneurysm (Sakamaki et al., 2002, 186706), pulmonary arterial hypertension (Proudman et al., 2007, 186705), and chemotherapy for breast cancer (Yerushalmi et al., 2009, 186711). Diseases affecting CO kinetics and D_LCO are also discussed in Section 4.4.4.

4.3.2. Tissue Uptake

4.3.2.1. Respiratory Tract

The upper respiratory tract contributes little to the overall CO uptake. The lung has nearly constant exposure to CO; however, relatively little CO diffuses into the tissue except at the alveolar region en route to the circulation. No detectable uptake of CO was observed in the human nasal cavity or upper airway (Guyatt et al., 1981, 011196) or in the monkey oronasal cavity after high CO exposure (Schoenfisch et al., 1980, 011404).

4.3.2.2. Blood

The blood is the largest reservoir for CO, where it reversibly binds to Hb. The chemical affinity of CO for adult human Hb is approximately 218 times greater than that of O_2, meaning one part CO and 218 (210-250) parts O_2 would form equal parts of O_2Hb and COHb (Engel et al., 1969, 193914; Rodkey et al., 1969, 008151; Roughton, 1970, 013931). This would happen when breathing air containing 21% O_2 and 960 ppm CO. This concept was presented by Haldane and Smith (1895, 010538) and later represented as the Haldane constant M (210-250) in the Haldane equation by Douglas, Haldane, and Haldane (1912, 013965). M is relatively unaffected by changes in physiological pH, CO_2, temperature, or 2,3-diphosphoglycerate:

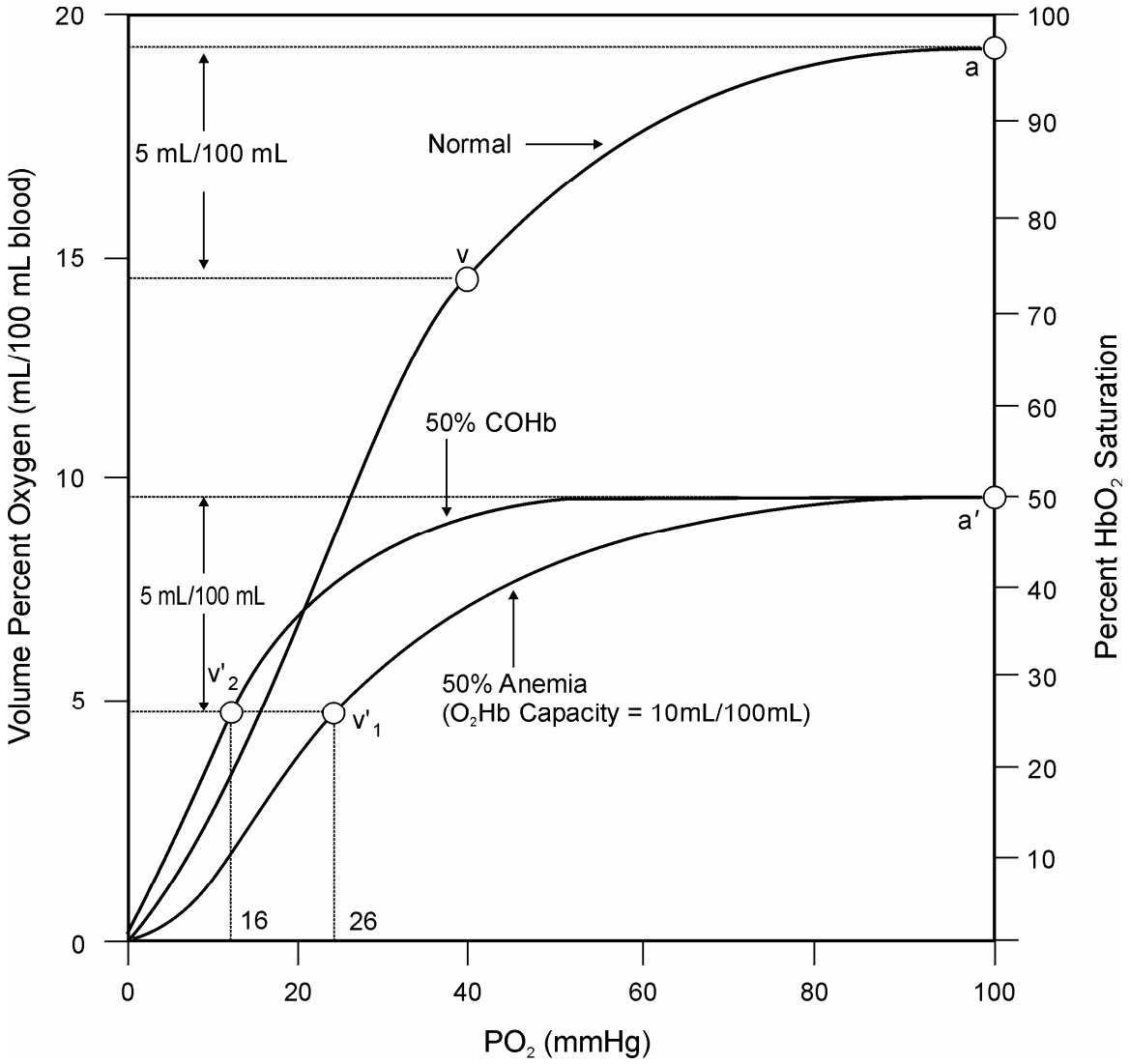
$$COHb \div O_2Hb = M \times (pCO \div pO_2)$$

Equation 4-3

The Hb association rate for CO is 10% slower than O_2 and occurs in a cooperative manner (Chakraborty et al., 2004, 193759; Sharma et al., 1976, 193766). Hb is composed of four globin

chains, each containing a heme group capable of binding CO or O_2. The associative reaction rates become faster with successive heme binding, attributed to interactions within the protein and to strains imposed on the heme and its ligands (Alcantara et al., 2007, 193867). More simply, the greater the number of heme sites bound to CO, the greater the affinity of free heme sites for O_2, thus causing Hb to bind and retain O_2 that would normally be released to tissues. Cooperativity is greatly reduced in CO dissociation, but the rate of dissociation of CO from Hb is orders of magnitude slower than O_2 ($k_{CO} = 4 \times 10\text{-}4\ k_{O2}$), which accounts for the high affinity values (Chakraborty et al., 2004, 193759). The half-time of dissociation reaction is about 11 s at 37°C (Holland, 1970, 193856). In general, CO uptake to COHb equilibrium is slower in humans and large animals, requiring 8-24 h, than in smaller species such as rats, which will equilibrate in 1-2 h (Penney, 1988, 012519). Also, COHb equilibrium within the blood stream is not instantaneous. Men exposed to brief (~5 min) high-dose CO had an initial delay of 1-2 min in the appearance of venous COHb after the start of CO inhalation (Benignus et al., 1994, 013908; Smith et al., 1994, 076564). Additionally, arterial COHb concentrations were considerably higher than venous concentrations during CO exposure; however, they converged within 2-10 min after the end of exposure, as venous and arterial blood mixed.

CO binding to Hb also has effects on the O_2 dissociation curve of the remaining Hb by shifting the curve progressively to the left and altering the normal S-shaped curve to become more hyperbolic due to increased cooperative O_2 binding (Roughton, 1970, 013931). This is referred to as the "Haldane effect" and causes tissues to have more trouble obtaining O_2 from the blood, even compared to the same extent of reduced Hb resulting from anemia. For example, Figure 4-7 (as explained in the 2000 CO AQCD) illustrates that in an acute anemia patient (50% of Hb) at a venous pO_2 of 26 mmHg (v'_1), 5 vol % of O_2 (50% saturation) was extracted from the blood. In contrast, for a CO poisoned person with 50% COHb, the venous pO_2 will have to drop to 16 mmHg (v'_2) to release the same 5 vol % O_2. This more severe effect on O_2 pressure may lead to brain O_2 depletion and loss of consciousness if any higher demand of O_2 is needed (e.g., exercise).



Source: U.S. EPA (1991, 017643)

Figure 4-7. O_2Hb dissociation curve of normal human blood, of blood containing 50% COHb, and of blood with only 50% Hb because of anemia.

4.3.2.3. Heart and Skeletal Muscle

Mb is a globular heme protein that facilitates O_2 diffusion from the muscle sarcoplasm to mitochondria, acting as an O_2 supply buffer to maintain adequate pO_2 for mitochondria when the O_2 supply changes, as in exercise. O_2 has a greater affinity for Mb than Hb, which allows small changes in tissue pO_2 to release large amounts of O_2 from O_2Mb (Wittenberg et al., 1975, 012436). Small reductions in O_2 storage capacity of Mb, due to CO binding, may have a profound effect on the supply of O_2 to the tissue.

Like Hb, Mb will undergo reversible CO binding, however the affinity constant is approximately eight-times lower than Hb (M = 20-40 versus 218, respectively) (Haab, 1990, 013359). The association rate constant of CO and Mb is approximately 27 times lower than O_2; however, the dissociation rate constant is approximately 630 times lower than O_2 (Gibson et al., 1986, 016289), causing CO to be retained and possibly stored in the muscle. CO levels have been measured in human muscle and heart tissues with <2% COHb concentrations at background levels

(15 and 31 picomole [pmol] CO/mg ww, respectively) (Vreman et al., 2006, 098272) (Table 4-2). Under conditions of CO asphyxiation, tissue concentrations increased 17-18 fold (265 and 527 pmol CO/mg ww muscle and heart tissue, respectively); however, heart tissue concentrations varied widely between individuals. Mouse muscle did not show this increase after exogenous CO exposure (Vreman et al., 2005, 193786). This may be due to the fact that human muscle has a 15-fold higher concentration of myoglobin protein than mouse muscle (Weller et al., 1986, 187298). The capacity for diffusion of CO into the muscle is represented by the coefficient D_mCO and is generally larger in males than in females, likely due to the differences in muscle mass and capillary density (Bruce and Bruce, 2003, 193975). COMb concentrations in the heart and skeletal muscle increase with work load, due to a higher relative rate of CO binding to Mb relative to Hb. This causes an increase in COMb/COHb that is not seen at rest (Sokal et al., 1984, 011591). Subjects with 2% COHb but not those with 20% COHb levels showed a significant uptake of CO from the blood to the muscle with increasing work intensity of the quadriceps muscle (Richardson et al., 2002, 037513).

Table 4-2. CO concentration in pmol/mg wet weight tissue and fold tissue CO concentration changes (normalized to background tissue concentrations) – human.

Exposure	Adipose	Brain	Muscle	Heart	Kidney	Lung	Spleen	Blood	% COHb
Background	3 ± 1	3 ± 3	15 ± 9	31 ± 23	23 ± 18	57 ± 59	79 ± 75	165 ± 143	1.5 ± 1.2
Fire	5 ± 4 [1.7]	7 ± 5 [2.3]	24 ± 16 [1.6]	54 ± 33 [1.7]	27 ± 11 [1.2]	131 ± 127 [2.3]	95 ± 69 [1.2]	286 ± 127 [1.7]	3.8 ± 3.2 [2.5]
Fire + CO	18 ± 29 [6.0]	17 ± 14 [5.7]	168 ± 172 [11.2]	128 ± 63 [4.1]	721 ± 427 [31.3]	1097 ± 697 [19.2]	2290 ± 1409 [29.0]	3623 ± 1975 [22.0]	40.7 ± 28.8 [27.1]
CO asphyxiation	25 ± 27 [8.3]	72 ± 38 [24.0]	265 ± 157 [17.7]	527 ± 249 [17.0]	885 ± 271 [38.5]	2694 ± 1730 [47.3]	3455 ± 1347 [43.7]	5196 ± 2625 [31.5]	56.4 ± 28.9 [37.6]

Source: Reprinted with Permission of Wiley-Blackwell from Vreman et al. (2006, 098272)

4.3.2.4. Other Tissues

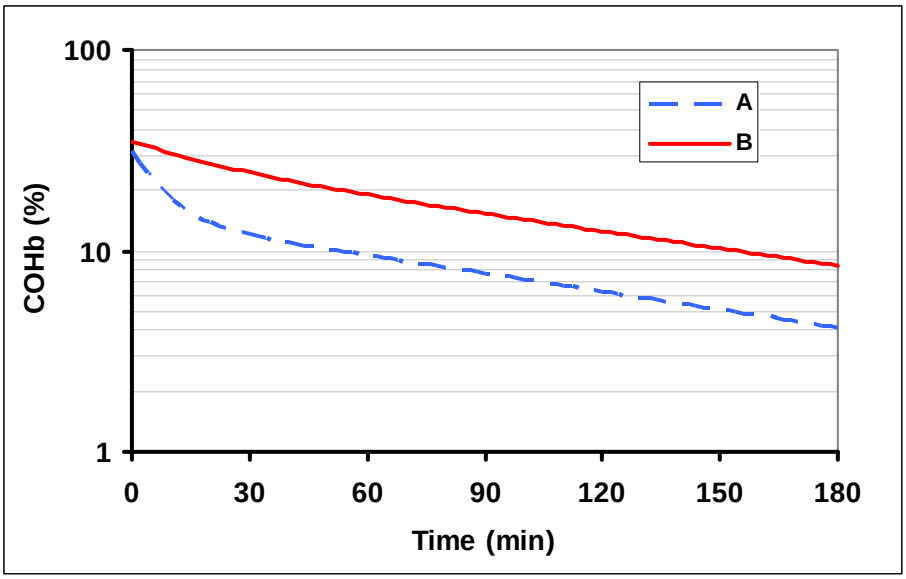
CO binds with other hemoproteins, such as cytochrome P450, cytochrome *c* oxidase, catalase, and peroxidase, but the possibility of this binding influencing CO-O_2 kinetics has not been established. CO transfers between COHb and tissue, the extent of which varies between organs. Blood-to-tissue flux causes less CO to be expired following CO exposure than what is lost from the blood in terms of COHb (Roughton and Root, 1945, 180418). This value is estimated to be 0.3-0.4% min^{-1} or 0.24 mL/min (Bruce and Bruce, 2003, 193975; Prommer and Schmidt, 2007, 180421). The equilibration rate from blood to tissue is uncertain. Newly modeled CO trafficking kinetics shows that CO continues to be taken up by the muscle and extravascular tissues well beyond the end of exposure because of a less than instant equilibration (Bruce and Bruce, 2006, 193980). Table 4-2 contains tissue CO concentrations from humans under different CO exposure conditions. The distribution of CO between the different human organs was shown to follow the same pattern versus percent of the blood CO concentration, irrespective of the level of blood CO (Vreman et al., 2006, 098272). Consistently, the spleen, lung, and kidney had the highest measured CO concentration and the most dramatic increases over basal levels; the brain and adipose had the lowest CO concentrations. In addition to these fatty tissues, the muscular tissues including the heart and skeletal muscle had similarly low increases over background CO levels. This pattern was also found in rodents exposed to exogenous CO; however, increased endogenous CO produced after heme administration did not follow this pattern of uptake (Vreman et al., 2005, 193786). Increased endogenous CO production led to moderately increased CO present in the lung, heart, liver, and spleen and no change in CO concentration in the testes, intestine, muscle, brain, and kidney. The spleen and liver have an abundance of HO-1 expression and are involved in the catabolism of heme, thus it is expected to have elevated CO concentrations in these organs after heme treatment. Also, elevated CO in the lung is not surprising since it is the site of CO excretion. The tissues analyzed in these studies were blanched before analysis; however, contamination of the tissue sonicates with blood from the vessels within each organ is a possible source of error. The measurements were presented by the authors as minimum tissue CO concentrations, due to the possibility of rapid loss of CO from blood and tissue exposed to the atmosphere, light, and elevated temperature (Chace et al., 1986, 012020; Ocak et al., 1985, 011641). These results are not consistent with older papers,

suggesting that negligible retention of CO occurs in the liver or brain (Sokal et al., 1984, 011591; Topping, 1975, 193784).

4.3.3. Pulmonary and Tissue Elimination

Blood COHb concentrations are generally considered to have a monotonically decreasing, second-order (logarithmic or exponential) elimination rate from equilibrium. However, more recent reports have presented evidence for a biphasic washout curve, especially after brief CO exposure (Figure 4-8) (Bruce and Bruce, 2006, 193980; Shimazu et al., 2000, 016420; Wagner et al., 1975, 010989). This event is modeled by a two-compartment system where the initial rapid decrease is the washout rate from the blood, followed by a slower phase due to CO flux from the muscle and extravascular compartments back to the blood. Tissue elimination rates have been reported as slower than those for blood (Landaw, 1973, 010803). The biphasic curve is more obvious after short-duration CO exposure (<1 h), whereas longer CO exposure (≥ 5 h) results in a virtually monoexponential elimination, which could account for the historical findings. However, this elimination curve also follows a biphasic curve with a slightly higher rate of elimination initially (Shimazu et al., 2000, 016420). Differences in elimination kinetics could also be a result of the variation in CO exposure duration (Weaver et al., 2000, 016421).

The elimination of COHb is affected by a number of factors, including duration of exposure, P_aO_2, minute ventilation, the time post-exposure for analysis due to extravascular stores, as well as inter-individual variability (Bruce and Bruce, 2006, 193980; Landaw, 1973, 010803; Shimazu, 2001, 016331). The elimination rate does not seem to be dependent upon the CO exposure source (e.g., fire, non-fire CO exposure) (Levasseur et al., 1996, 080895). In addition, in a series of poisoning cases, the COHb elimination half-life was not influenced by gender, age, smoke inhalation, history of loss of consciousness, concurrent tobacco smoking, degree of initial metabolic acidosis (base excess), or the initial COHb level (Weaver et al., 2000, 016421). On the contrary, in modeling the nonlinear kinetics of CO, a subject with a higher initial COHb will detoxify and eliminate CO more rapidly (Gosselin et al., 2009, 190946). Similarly, it has been shown that the absolute elimination rates are associated positively with the initial concentration of COHb, however the relative rate of elimination, expressed as a percentage decline in COHb% after a measured time, is independent of the initial COHb concentration (Wagner et al., 1975, 010989). COHb elimination half-life falls as the fractional inspired O_2 concentration increases. While breathing air at sea level pressure, the expected half-life in adult males is approximately 285 min, but may be shorter in adult females. With inhalation of normobaric 40% O_2, the half-life falls to 75 min and further to 21 min when breathing 100% O_2 because of greater competition for Hb by O_2 (Landaw, 1973, 010803). Another study reports the half-life falls to 74 min (mean) after breathing 100% O_2, although the range in this particular study was 26-148 min (Weaver et al., 2000, 016421). In addition, COHb half-life will fall further after normocapnic hyperoxic hyperpnea (i.e., hyperventilation while maintaining normal CO_2 pressure in high O_2) (Takeuchi et al., 2000, 005675).



Source: Adapted with Permission of Lippincott Williams & Wilkins from Shimazu et al. (2000, 016420)

Figure 4-8. Changes in blood COHb after exposure to CO for a few minutes (A) or several hours (B), representing the biphasic nature of CO elimination. Note: y-axis is log-scale.

4.3.4. COHb Analysis Methods

Blood COHb saturation can be analyzed using numerous methods with various benefits and limitations. The most popular current techniques include gas chromatography (GC) and spectrophotometry, specifically using CO-oximeters. CO-oximeters are commonly used because they require little sample preparation and simultaneously measure COHb, O_2Hb, methemoglobin, and total hemoglobin concentration. However, at low concentrations of COHb relevant to ambient exposure (<5%), CO-oximeters overestimate COHb levels determined by GC (Mahoney et al., 1993, 013859; Widdop, 2002, 030493). Conversely, at higher COHb levels (>5%), CO-oximeters will underestimate COHb concentrations. In addition to the inaccuracy of the CO-oximeters, some studies report considerable imprecision in the results. Also, numerous substances or conditions can interfere with CO-oximeter measurements (i.e., temperature, bilirubin, fetal hemoglobin). Alternatively, GC is an accurate, precise, highly specific analysis method and is generally used as the reference method for COHb analysis. GC requires the CO incorporated into blood or tissue samples to first be released using a liberating agent such as potassium ferricyanide or sulfosalicylic acid (Vreman et al., 2005, 193786; Vreman et al., 2006, 098272), and then measured directly or indirectly. This methodology is more complex and time-consuming than spectrophotometry. In either analysis method, it is important to remember that COHb measured at one site in the body does not necessarily represent whole body CO distribution.

CO can also be measured directly in air or breath samples by using an electrochemical sensor that depends on the electrical signal generated by the oxidation of CO. There are conflicting reports on the correlation of exhaled CO (COex) with COHb. Multiple reports present positive correlation coefficients (r) ranging from 0.92 and 0.98 in smoking subjects (Jarvis et al., 1980, 011813; Jarvis et al., 1986, 012043; Landaw, 1973, 010803). Positive linear correlations have also been shown in diseased patients with increased COHb (De las Heras et al., 2003, 194087). Others have reported no correlation between low level COHb and COex and have suggested less correlation exists at the lower levels of COex relevant to ambient exposures (Horvath et al., 1998, 087191; Scharte et al., 2000, 194112). Finally, CO is endogenously produced in the nose and paranasal sinus which may contribute to COex concentrations (Andersson et al., 2000, 011836).

4.4. Conditions Affecting Uptake and Elimination

4.4.1. Physical Activity

Exercise is an important determinant of CO kinetics and toxicity due to the extensive increase in gas exchange. O_2 consumption can increase more than 10 fold during exercise. Similarly, ventilation, membrane and lung diffusing capacity, pulmonary capillary blood volume, and cardiac output increase proportional to work load. Also, exercise will improve the ventilation/perfusion ratio in the lung and mobilize RBC reserves from the spleen. The majority of these changes facilitate CO uptake and transport, by increasing gas exchange efficiency. Likewise, the COHb elimination rate increases with physical activity, causing a decrease in COHb half-life (Joumard et al., 1981, 011330). During a transition period from rest to exercise while exposed to CO (500 ppm/10 min), the diffusing capacity and CO uptake were reported to rise faster than O_2 consumption for each exercise intensity (Kinker et al., 1992, 086328). The two physiological variables that are most influential in the formation of COHb are alveolar ventilation and cardiac output. However, exercise did not affect the ability of the CFK equation to predict COHb saturation as long as appropriate variables were used for model analysis (Tikuisis et al., 1992, 013592).

4.4.2. Altitude

Increased altitude changes a number of factors that contribute to the uptake and elimination of CO. The relationship between altitude and CO exposure has been discussed in depth in the 2000 CO AQCD and other documents (U.S. EPA, 1978, 086321). In an effort to maintain proper O_2 transport and supply, physiological changes occur as compensatory mechanisms to combat the decreased barometric pressure and resulting altitude induced hypobaric hypoxia (HH). HH, unlike CO hypoxia, causes humans to hyperventilate, which reduces arterial blood CO_2 (hypocapnia) and increases alveolar partial pressure of O_2. Hypocapnia will lead to difficulty of O_2 dissociation and decreased blood flow, thus reducing tissue O_2 supply. HH increases blood pressure (BP) and cardiac output and leads to redistribution of blood from skin to organs and from blood vessels to extravascular compartments. Generally these changes will favor increased CO uptake and COHb formation, as well as CO elimination. In hypoxic conditions both CO and O_2 bind reduced Hb through a competitive-parallel reaction (Chakraborty et al., 2004, 193759). Sea level residents exposed to high altitude (3,658-5,800 m) for short or long visits (<1 year) experience negligible or minor changes in D_LCO, although these changes in D_LCO can be accounted for by polycythemia or increased red blood cell count and by the increased rate of reaction of carbon monoxide with hemoglobin due to hypoxia (West, 1962, 199513)(Guleria et al., 1971, 199518). Breathing CO (9 ppm) at rest at altitude produced higher COHb compared to sea level (McGrath et al., 1993, 013865), whereas high altitude exposure with exercise caused a decrease in COHb levels versus similar exposure at sea level (Horvath et al., 1988, 012725). This decrease could be a shift in CO storage or suppression of COHb formation, or both. Altitude also increases the baseline COHb levels by inducing endogenous CO production. Initial HH increased lung HO-1 protein and activity, whereas chronic HH induced endogenous CO production in nonpulmonary sites (see Section 4.5) (Carraway et al., 2000, 021096).

As the length of stay increases at high altitude, acclimatization occurs, inducing hyperventilation, polycythemia, and increased tissue capillarity and Mb content in skeletal muscle, which could also favor increased CO uptake. The D_LCO of sea level natives who are long-term residents at altitude (3,100 m) increases from sea level values (Cerny et al., 1973, 199736). Additionally, natives of high altitude (3,100-3,658 m) have increased D_LCO compared to natives of sea level or sea level natives that stay at high altitude (DeGraff et al., 1970, 199737) (Guleria et al., 1971, 199518). This has been attributed to high pulmonary capillary blood volume and membrane diffusing capacity, and altered lung structure. Most of the early adaptive changes gradually revert to sea level values after individuals return to sea level. However, differences in people raised at high altitude persist even after reacclimatization to sea level (Hsia, 2002, 193857). For example, altitude natives (3,658 m) staying at sea-level still have increased D_LCO compared to sea level natives which suggests a permanent change in the lung structure resulting in a larger diffusing surface area (Guleria et al., 1971, 199518).

4.4.3. Physical Characteristics

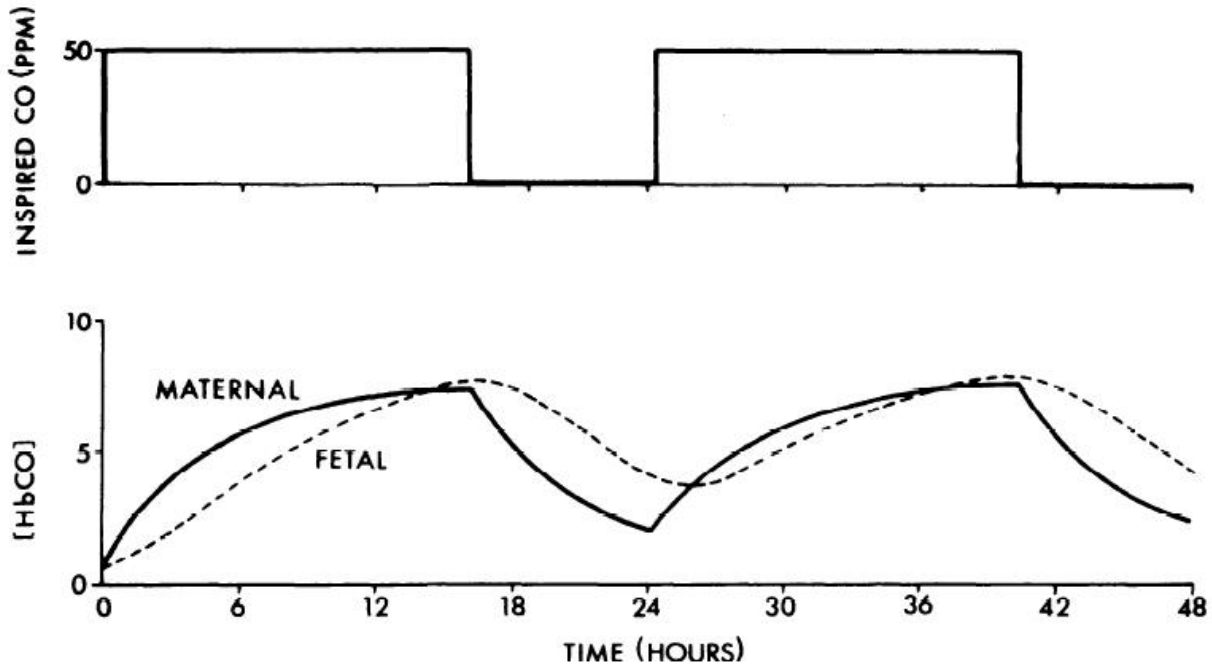
Certain physical characteristics (e.g., age, sex, pregnancy) can alter the variables that influence the uptake, distribution, and elimination of CO. Values of CO uptake and elimination change with age. Young children eliminate COHb more rapidly than adults after CO exposure (Joumard et al., 1981, 011330; Klasner et al., 1998, 087196). After infancy, the COHb half-life increases with age, nearly doubling between 2 and 70 yr (Joumard et al., 1981, 011330). The rate of this increase in CO elimination is very rapid in the growing years (2-16 yr of age), but slows beyond adolescence. Alveolar volume and D_LCO increase with increasing body length of infants and toddlers (Castillo et al., 2006, 193234), suggesting a further degree of lung development and faster CO uptake. After infancy, increasing age decreases D_LCO and increases V_A/Q mismatch, causing it to take longer to both load and eliminate CO from the blood (Neas and Schwartz, 1996, 079363).

COHb concentrations are generally lower in female subjects than in male subjects (Horvath et al., 1988, 012725), and the COHb half-life may be longer in healthy men than in women of the same age, which may be partially explained by differences in muscle mass or the slight correlation between COHb half-life and increased height (Joumard et al., 1981, 011330). However, women do have a higher rate of endogenous production while in the progesterone phase of the menstrual cycle and during pregnancy (Section 4.5). The rate of decline of D_LCO with age is lower in middle-aged women than in men; however, it evens out towards older age (Neas and Schwartz, 1996, 079363). Women also tended to be more resistant to altitude hypoxia (Horvath et al., 1988, 012725).

Ethnicity does alter physiological variables that determine CO uptake and kinetics. Lung volumes are 10-15% less in both Asian and African-American populations when compared to Caucasians. This causes a reduced alveolar surface area (20% less than estimated values) for gas exchange, leading to a 13% difference in D_LCO (Pesola et al., 2004, 193842; Pesola et al., 2006, 193855). Certain factors, such as socioeconomic status (SES), were not controlled for in these studies. SES has been shown to affect pulmonary function, including decreasing D_LCO (Hegewald and Crapo, 2007, 193923).

4.4.3.1. Fetal Pharmacokinetics

Inhaled CO by pregnant animals quickly passes the placental barriers and enters the fetal circulation (Longo, 1977, 012599). Fetal CO pharmacokinetics do not follow the same kinetics as maternal CO exposure, making it difficult to estimate fetal COHb based on maternal levels. Fetal COHb will vary as a function of maternal exposure but will also depend upon the rate of endogenous fetal CO production (Section 4.5), placental diffusing capacity of CO, the relative affinity of fetal Hb for CO compared to O_2, and the affinity of fetal blood for O_2 (Longo, 1970, 013922). Human fetal Hb has a higher affinity for CO than adult Hb, where the ratio of fetal COHb to maternal COHb at steady state in humans is approximately 1.11 (Longo, 1970, 013922)(Di Cera et al., 1989, 193998)(Hayde et al., 2000, 201602). Maternal and fetal COHb concentrations have been modeled as a function of time using a modified CFK equation (Hill et al., 1977, 011315). At steady-state conditions, the fetal COHb is up to 10-15% higher than the maternal COHb levels. For example, exposure to 30 ppm CO results in a maternal COHb of 5% and a fetal COHb of 5.75%. The fetal CO uptake lags behind the maternal for the first few hours but later may overtake the maternal values (Figure 4-9). Fetal COHb equilibrium may not be reached for 36-48 h after exposure. Similarly, during washout, the fetal COHb levels are maintained for longer, with a half-life of around 7.5 h versus the maternal half-life of around 4 h (Longo and Hill, 1977, 010802).



Source: Reprinted with Permission of the American Physiological Society from Hill et al. (1977, 011315)

Figure 4-9. Predicted maternal and fetal COHb during periodic exposure to CO (50 ppm for 16 h followed by 0 ppm for 8 h).

4.4.4. Health Status

Health status can influence the toxicity involved with CO exposure by influencing the severity of hypoxia resulting from CO exposure. Any condition that would alter the blood O_2 carrying capacity or content will result in a greater risk from COHb induced hypoxia and decreased tissue O_2 delivery. The severity of this effect depends upon the initial level of hypoxia.

Anemias are a group of diseases that result in insufficient blood O_2 or hypoxia due to Hb deficiency through hemolysis, hemorrhage, or reduced hematopoiesis. Anemia may result from pathologic conditions characterized by chronic inflammation, such as malignant tumors or chronic infections (Cavallin-Ståhl et al., 1976, 086306; Cavallin-Ståhl et al., 1976, 193239). The bodies of people with anemia compensate, causing cardiac output to increase as both heart rate and stroke volume increase. The endogenous production of CO, thus COHb, is increased in patients with hemolytic anemia due to increased heme catabolism, causing an increased baseline COHb concentration. One of the most prevalent anemias arises from a single-point mutation of Hb, causing sickle cell diseases. The Hb affinity for O_2 and O_2 carrying capacity is reduced causing a shift to the right in the O_2 dissociation curve. It is well documented that African-American populations have a higher incidence of sickle cell anemia, which may be a risk factor for CO hypoxia.

Chronic obstructive pulmonary disease (COPD) is often accompanied by a number of changes in gas exchange, including increased deadspace volume (V_D) and ventilation-perfusion ratio (V_A/Q) inequality (Marthan et al., 1985, 086334), which could slow both CO uptake and elimination. Patients with pulmonary sarcoidosis, a restrictive lung disease, may also have a decrease in lung volumes, a loss of D_LCO, and gas exchange abnormalities during exercise, including decreased arterial oxygen pressure (P_aO_2) and increased alveolar-arterial oxygen pressure difference (Lamberto et al., 2004, 193845).

Individuals with heart disease may be at a greater risk from CO exposure since they may already have compromised O_2 delivery. Time to onset of angina was reduced after exposure to

100 ppm CO, compared to clean air (Kleinman et al., 1998, 047186). Hyperlipidemic patients may have decreased CO diffusion capacity, a loss of V_A/Q gradient, and a decrease in P_aO_2 (Enzi, 1976, 195794) (Section 5.2).

4.5. Endogenous CO Production and Metabolism

Humans breathing air containing no environmental sources of CO will still have a low measurable level of circulating COHb due to endogenous CO production from heme protein catabolism. In the normal degradation of RBC Hb, the porphyrin ring of heme is broken at the α-methene bridge by HO. HO is co-localized with NADPH-flavoprotein reductase and biliverdin reductase on the endoplasmic reticulum, where it catabolizes heme in an O_2 and NADPH-dependent manner to biliverdin, ferrous iron, and CO. Biliverdin is then further broken down by biliverdin reductase into bilirubin, a powerful endogenous antioxidant. HO mediated metabolism functions as the rate-limiting enzyme step in heme degradation and endogenous CO production (Wu and Wang, 2005, 180411). Three isoforms of HO exist, but HO-1 is the only inducible form (Maines and Kappas, 1974, 193976; Maines et al., 1986, 193978; McCoubrey et al., 1997, 016715). Endogenous CO production can be increased by the up-regulation of HO-1 expression and activity by inducers such as oxidative stress, hypoxia, heavy metals, sodium arsenite, heme and heme derivatives, various cytokines, and also exogenous CO (Wu and Wang, 2005, 180411).

The major site of heme catabolism, and thus the major organ of CO production, is the liver, followed by the spleen, brain, and erythropoietic system (Berk et al., 1976, 012603). These rates of CO formation may be due to higher levels of HO activity in these tissues. The whole body production rate of CO is approximately 18.8 μmol/h (0.42 mL/h or 0.007 mL/min) and produces between 400-500 μmol CO per day (Coburn et al., 1963, 013971; Coburn et al., 1964, 013956; Coburn et al., 1966, 010984) (Figure 4-10). The endogenous rate of production varied somewhat within individuals measured on multiple days (±4.5 μmol/h and ±0.35% COHb) (Coburn et al., 1966, 010984). However, these measurements of day-to-day CO production variability were comparable to the equipment measurement error reported (±3.1 μmol/h). The endogenous rate of CO formation varies between different tissues, ranging from 0.029 nmol/mg protein/h in chorionic villi of term human placentas to 0.28 nmol/mg protein/h in cultured rat olfactory receptor neurons and rat liver perfusate (Marks et al., 2002, 030616). However, these estimations are uncertain since CO is quickly scavenged in the cytosol of living cells. CO is endogenously produced in the nose and paranasal sinus which may contribute to exhaled CO concentrations (Andersson et al., 2000, 011836). It is also important to note that increased endogenous CO production does not universally lead to an increase in COHb saturation.

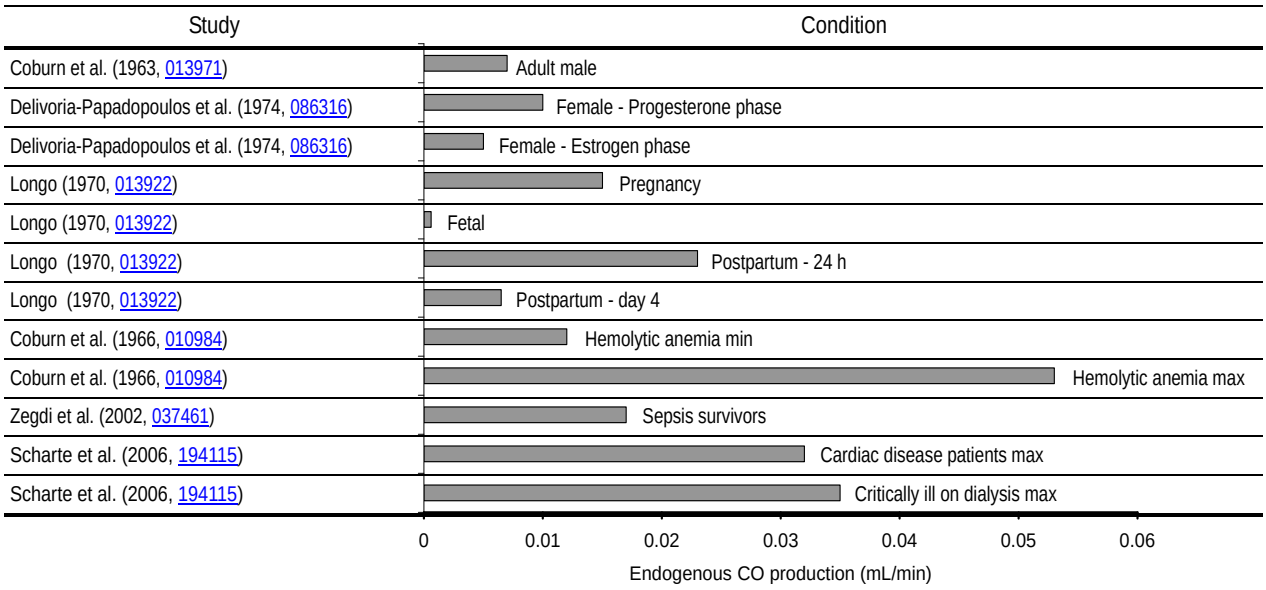


Figure 4-10. Representative estimates of endogenous CO production rates resulting from various conditions and diseases.

Not all endogenous CO production is derived from Hb breakdown. Other hemoproteins, such as Mb, cytochromes, peroxidases, and catalase, contribute 20-25% to the total amount of endogenous CO (Berk et al., 1976, 012603). All of these sources result in a normal blood COHb concentration between 0.3 and 1% (Coburn et al., 1965, 011145). The level of endogenous production can be changed by drugs or a number of physiological conditions that alter RBC destruction, other hemoprotein breakdown, or HO-1 expression and activity (Figure 4-10). Nicotinic acid (Lundh et al., 1975, 086332), allyl-containing compounds (acetamids and barbiturates) (Mercke et al., 1975, 086303), diphenylhydantoin (Coburn, 1970, 010625), progesterone (Delivoria-Papadopoulos et al., 1974, 086316), contraceptives (Mercke et al., 1975, 086308), and statins (Muchova et al., 2007, 194098) can increase CO production. Compounds such as carbon disulfide and sulfur-containing chemicals (parathion and phenylthiourea) will increase CO by acting on P450 system moieties (Landaw et al., 1970, 012605). The P450 system may also cause large increases in CO produced from the metabolic degradation of dihalomethanes, leading to very high (>10%) COHb levels (Bos et al., 2006, 194084; Manno et al., 1992, 013707) that can be further enhanced by prior exposure to hydrocarbons or ethanol (Pankow et al., 1991, 013551; Wirkner et al., 1997, 082642). Minor sources of endogenous CO include auto-oxidation of phenols, flavonoids, and halomethanes, photo-oxidation of organic compounds, and lipid peroxidation of cell membrane lipids (Rodgers et al., 1994, 076440).

Women experience fluctuating COHb levels throughout menstruation when endogenous CO production doubles in the progesterone phase (0.62 mL/h versus 0.32 mL/h in estrogen phase) (Delivoria-Papadopoulos et al., 1974, 086316; Mercke and Lundh, 1976, 086309). Similarly, endogenous CO production increases during pregnancy (0.92 mL/h) due to contributions from fetal endogenous CO production (0.036 mL/h) and altered hemoglobin metabolism (Hill et al., 1977, 011315; Longo, 1970, 013922).

Any disturbance in RBC hemostasis by accelerated destruction of hemoproteins will lead to an increased production of CO (Figure 4-11 and Figure 4-12). Pathologic conditions such as anemias, hematomas, thalassemia, Gilbert's syndrome with hemolysis, and other hematological diseases and illness will accelerate CO production (Berk et al., 1974, 012386; Hampson and Weaver, 2007, 190272; Meyer et al., 1998, 047530; Solanki et al., 1988, 012426; Sylvester et al., 2005, 191954). Patients with hemolytic anemia exhibit COHb levels at least two- to threefold higher than healthy individuals and CO production rates two- to eightfold higher (Coburn et al., 1966, 010984). Recent studies report COHb levels measured by CO-oximeter that are elevated to levels between 4.6% and 9.7% due to drug-induced hemolytic anemia (Hampson and Weaver, 2007, 190272) and between 3.9% and 6.7% due to an unstable hemoglobin disorder (Hb Zürich) (Zinkham et al., 1980, 011435).

Endogenous CO production rate varied from 0.70 to 3.18 mL/h in anemic patients (Coburn et al., 1966, 010984).

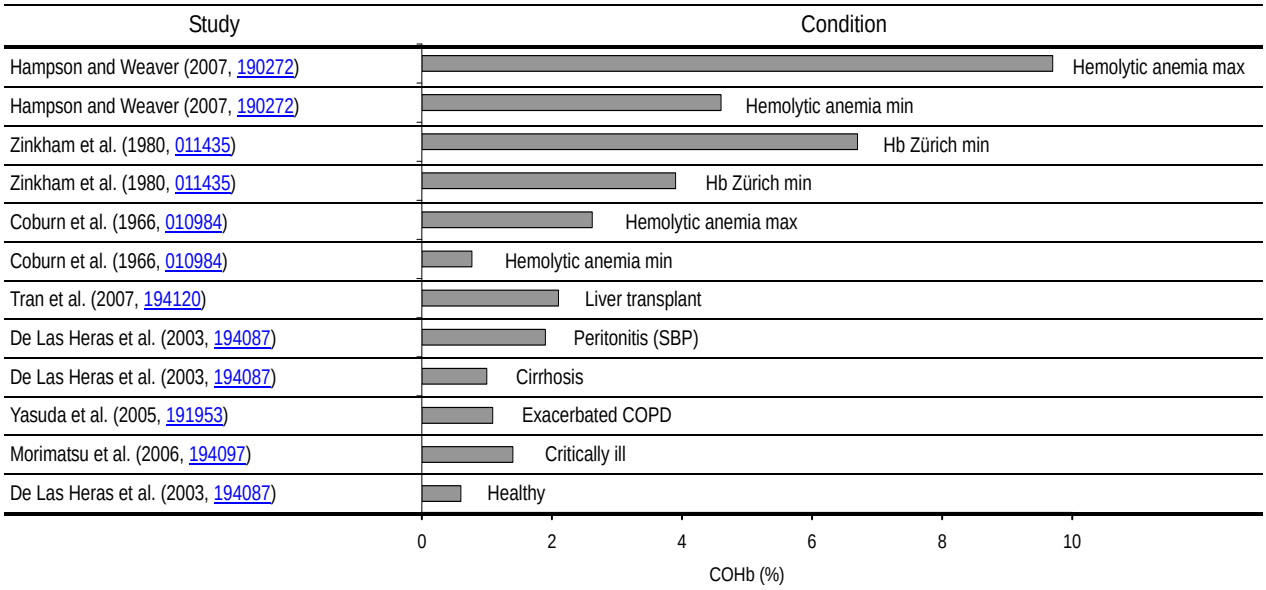


Figure 4-11. Representative COHb saturation resulting from various diseases and conditions. Measurements of COHb taken using CO-oximeter, except in Coburn et al. (1966, 010984), where COHb was measured using GC. SBP: Spontaneous bacterial peritonitis

Critically ill patients exhale more CO and have higher endogenous CO production than healthy controls, likely due to both increased heme turnover as well as upregulation of the expression and activity of HO-1 (Morimatsu et al., 2006, 194097; Scharte et al., 2000, 194112; Scharte et al., 2006, 194115) (Figure 4-12). CO production weakly correlates with the multiple organ dysfunction score (MODS), which estimates severity of organ dysfunction; however, it did not correlate with the Acute Physiology and Chronic Health Evaluation II score (APACHE II) (Scharte et al., 2006, 194115) or the sequential organ failure assessment score (SOFA) (Morimatsu et al., 2006, 194097). Critically ill patients that survived had a higher exhaled CO (COex) concentration than nonsurvivors (median 3.9 ppm versus 2.4 ppm) (Morimatsu et al., 2006, 194097). Similarly, patients that survived severe sepsis had a higher CO production than those that did not survive (14.7 ± 5.3 versus 8.5 ± 3.3 µl/kg/h) (Zegdi et al., 2002, 037461).

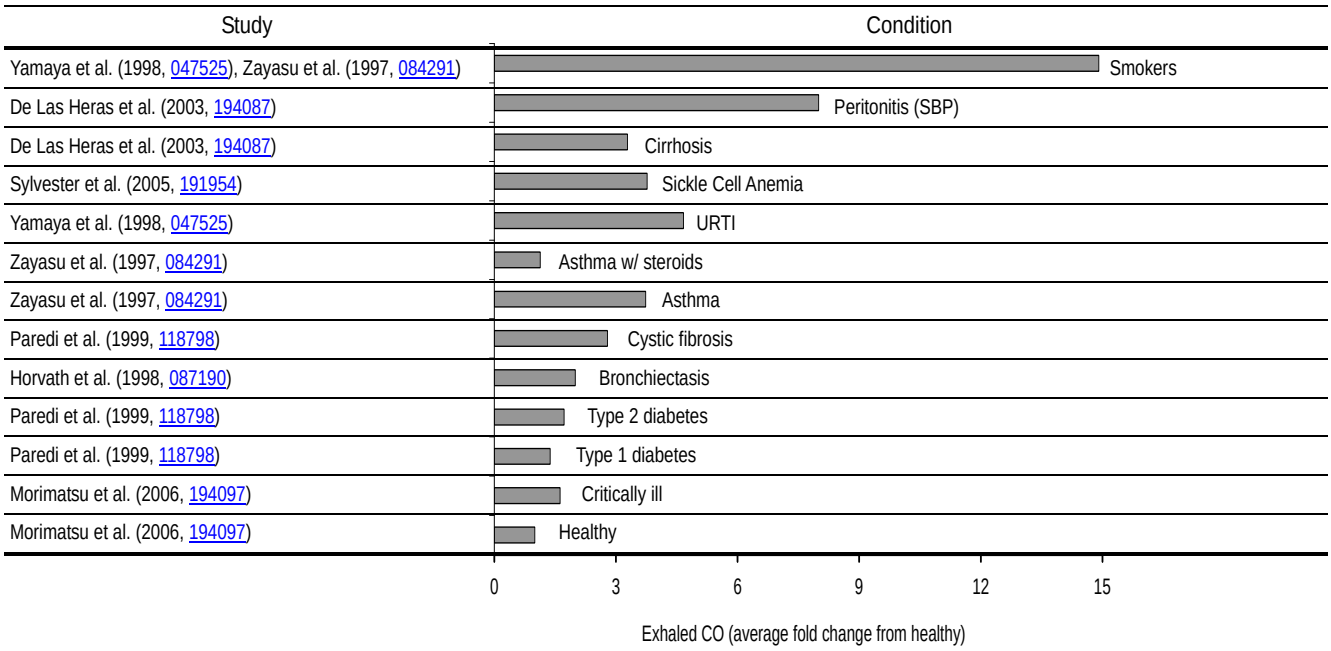


Figure 4-12. Representative exhaled CO concentrations (ppm) resulting from various conditions plotted as fold increases over healthy human controls from each study. SBP: Spontaneous bacterial peritonitis; URTI: Upper respiratory tract infection

Diseases involving inflammation and infection result in increased endogenous CO production. For example, patients with severe sepsis or septic shock have a higher COex and endogenous CO production compared to control patients, which was reduced with treatment of the disease (i.e., antibiotics, surgery) (Zegdi et al., 2002, 037461). Similarly, patients with pre-existing cardiac disease, as well as patients with renal failure who undergo dialysis, produced higher amounts of endogenous CO compared to other critically ill patients (Scharte et al., 2006, 194115). High plasma COHb levels measured by CO-oximeter were found in nonsmoking patients evaluated for liver transplantation (mean 2.1%); however, this increase was not correlated with the Model for End Stage Liver Disease (MELD) score or the Child Turcotte Pugh score, used to assess the degree of liver impairment (Tran et al., 2007, 194120). Further investigation in cirrhotic patients, with and without ascites, provided evidence for increased plasma CO concentrations, HO-1 activity in polymorphonuclear cells, exhaled CO, and blood COHb (De las Heras et al., 2003, 194087; Tarquini et al., 2009, 194117). COex, plasma CO, and COHb levels were correlated with the Child-Pugh score, and thus the severity of disease. These parameters were significantly higher in patients with ascites or with spontaneous bacterial peritonitis (SBP) (COHb, healthy: 0.6 ± 0.1%; cirrhosis: 1.0 ± 0.1%; with ascites: 1.6 ± 0.2%; with SBP: 1.9 ± 0.2%; measured by CO-oximeter). Both COex and COHb levels decreased after resolution of the infection in patients with SBP, reaching values similar to noninfected patients within 1 mo (De las Heras et al., 2003, 194087). Endotoxin concentration was correlated with plasma CO levels, suggesting a link between systemic endotoxemia and increased activity or expression of the HO/CO system (Tarquini et al., 2009, 194117). COex concentrations are also elevated in patients with diabetes (Type 1: 4.0 ± 0.7 ppm; Type 2: 5.0 ± 0.4 ppm; healthy: 2.9 ± 0.2 ppm), and correlated with blood glucose levels and duration of disease (Paredi et al., 1999, 194102). Likewise, obese Zucker rats, a model of metabolic syndrome with insulin resistance, have increased respiratory CO excretion and COHb levels compared to lean Zucker rats (3.9 ± 0.1% versus 3.0 ± 0.1% COHb), which is decreased by HO inhibition (Johnson et al., 2006, 193874).

Endogenous CO is also increased in airway inflammatory diseases. Patients with upper respiratory tract infections exhaled higher CO concentrations than normal controls and this increase was attenuated after recovery (Yamaya et al., 1998, 047525). Arterial COHb levels have been related

to disease severity in COPD patients (Yasuda et al., 2005, 191953). Bronchiectasis patients had higher COex; however, anti-inflammatory treatment did not decrease the CO levels (Horvath et al., 1998, 087191). Patients with cystic fibrosis had higher COex than normal controls (6.7 ± 0.6 ppm versus 2.4 ± 0.4 ppm), and patients treated with steroids had a decrease in CO levels (8.4 ± 1.0 ppm versus 5.1 ± 0.5 ppm) (Paredi et al., 1999, 118798). Increased arterial COHb measured by CO-oximeter was reported in patients with bronchial asthma, pneumonia, idiopathic pulmonary fibrosis, pyelonephritis, and active rheumatoid arthritis (Yasuda et al., 2002, 035206; Yasuda et al., 2004, 191955). Similarly, asthmatic patients exhibited an elevation of COex that decreased with corticosteroid therapy (nonsmoking controls: 1.5 ± 0.1 ppm; asthmatics without corticosteroids: 5.6 ± 0.6 ppm; with corticosteroids: 1.7 ± 0.1 ppm; smoking controls: 21.6 ± 2.8 ppm) (Zayasu et al., 1997, 084291). These results were confirmed and associated with increased expression of HO-1 in airway macrophages (Horvath et al., 1998, 087190). Also, COex was increased in patients with allergic rhinitis during the pollen season; however, their COex was similar to control subject levels out of season (Monma et al., 1999, 180426). Similarly, endogenous CO production and HO-1 expression in nasal mucosa was correlated with allergic rhinitis in guinea pigs as described in Section 5.1 (Shaoqing et al., 2008, 192384).

Altitude is also positively associated with baseline COHb concentrations (McGrath, 1992, 001005)(McGrath et al., 1993, 013865). This increase in COHb with altitude-induced hypoxia is associated in rats and cells with increases in the mRNA, protein, and activity of HO-1 leading to enhanced endogenous CO production (Carraway et al., 2002, 026018; Lee et al., 1997, 082641). Whether other variables such as an accelerated metabolism or a greater pool of Hb, transient shifts in body stores, or a change in the elimination rate of CO, play a role has not been explored.

Because of the sensitivity of COHb to changes in the metabolic state, ranges of endogenous COHb levels in the population are uncertain. However, baseline levels of COHb, which reflect exposure to ambient and non-ambient CO and endogenous production of CO, have been measured in the population. COHb levels measured by CO-oximeter in packed red blood cell units reserved for use between 2004 and 2005 averaged 0.78 ± 1.48%, with 10.3% of samples having COHb levels of 1.5% or greater and a maximum measurement of 12% (Ehlers et al., 2009, 194089). This study reported a decrease from a study conducted in 1982-1983 in the number of units with elevated COHb; at that time, 49% of units had COHb levels >1.5% (Aronow et al., 1984, 194083) versus 10.3% in 2004-2005. Another study calculated that 23% of donated blood units had COHb levels exceeding 1.5%, with the highest measurement being 7.2% (Aberg et al., 2009, 194082). Smoking is the main factor causing increased blood concentrations of CO. A dose-response relationship was shown to exist between COHb concentration and the number of cigarettes smoked a day (nonsmoker: 1.59 ± 1.72%; 1-5 cig/day: 2.31 ± 1.94%; 6-14 cig/day: 4.39 ± 2.48%; 15-24 cig/day: 5.68 ± 2.64%; ≥ 25 cig/day: 6.02 ± 2.86% COHb). The mean baseline COHb value for former smokers was higher than that of never smokers in this prospective cohort study (1.96 ± 1.87 versus 1.59 ± 1.72%) (Hart et al., 2006, 194092).

Endogenous CO is removed from the body mainly by expiration and oxidation. CO diffuses across the alveolar-capillary membrane and is exhaled. This event has been used as a noninvasive measurement of both endogenous and body load CO (Stevenson et al., 1979, 193767). CO can also be oxidized to CO_2 by cytochrome *c* oxidase in the mitochondria (Fenn, 1970, 010821; Young and Caughey, 1986, 012091). However, the rates of CO metabolism are much slower than the rates of endogenous CO production, with the rate of consumption representing only 10% of the rate of CO production in dogs (Luomanmäki and Coburn, 1969, 012319).

4.6. Summary and Conclusions

CO elicits various health effects by binding with and altering the function of a number of heme-containing molecules, mainly Hb. The formation of COHb reduces the O_2-carrying capacity of blood and impairs the release of O_2 from O_2Hb to the tissues. Venous COHb levels have been modeled mainly by the CFK equation, but more recent models have included venous and arterial blood mixing and Mb and extravascular storage compartments, as well as other dynamics of CO physiology. The CFK equation remains the most extensively validated and applied model for COHb prediction. Recent models have indicated that CO has a biphasic elimination curve, due to initial washout from the blood followed by a slower flux from the tissues. The flow of CO between the

blood and alveolar air or tissues is controlled by diffusion down the pCO gradient. The uptake of CO is governed not only by this CO pressure differential, but also by physiological factors, such as minute ventilation and lung diffusing capacity, that can, in turn, be affected by conditions such as exercise, age, and health. Susceptible populations, including health compromised individuals and developing fetuses, are at a greater risk from COHb induced health effects due to altered CO kinetics, compromised cardiopulmonary function, and increased baseline hypoxia levels. Altitude may also significantly affect the kinetics of COHb formation. Compensatory mechanisms, such as increased cardiac output, compensate for the decrease in barometric pressure. Altitude also increases the endogenous production of CO through upregulation of HO-1. CO is considered a second messenger and is endogenously produced from the catabolism of heme proteins by enzymes such as HO-1. A number of diseases and conditions affect endogenous CO production, possibly causing a higher endogenous COHb level. Finally, CO is removed from the body by expiration or oxidation to CO_2.

References

Aberg AM; Sojka BN; Winsö O; Abrahamsson P; Johansson G; Larsson JE (2009). Carbon monoxide concentration in donated blood: Relation to cigarette smoking and other sources. Transfusion, 49: 347-353. 194082

Abi-Esber L; El-Fadel M (2008). In-vehicle CO ingression: Validation through field measurements and mass balance simulations. Sci Total Environ, 394: 75-89. 190939

Abram SR; Hodnett BL; Summers RL; Coleman TG; Hester RL (2007). Quantitative circulatory physiology: An integrative mathematical model of human physiology for medical education. Adv Physiol Educ, 31: 202-210. 193859

Akland GG; Hartwell TD; Johnson TR; Whitmore RW (1985). Measuring human exposure to carbon monoxide in Washington, DC, and Denver, Colorado, during the winter of 1982-1983. Environ Sci Technol, 19: 911-918. 011618

Alcantara RE; Xu C; Spiro TG; Guallar V (2007). A quantum-chemical picture of hemoglobin affinity. PNAS, 104: 18451-18455. 193867

Andersson JA; Uddman R; Cardell L-O (2000). Carbon monoxide is endogenously produced in the human nose and paranasal sinuses. J Allergy Clin Immunol, 105: 269-273. 011836

Aronow WS; O'Donohue WJ Jr; Freygang J; Sketch MH (1984). Carboxyhemoglobin levels in banked blood. Chest, 85: 694-695. 194083

Arora M; Chandra J; Suri JC; Narayan S; Dutta AK (2001). Pulmonary function tests in beta thalassemia. Indian J Pediatr, 68: 239-242. 186713

Benignus VA; Coleman T; Eklund CR; Kenyon EM (2006). A general physiological and toxicokinetic (GPAT) model for simulating complex toluene exposure scenarios in humans. Toxicol Mech Meth, 16: 27-36. 151344

Benignus VA; Hazucha MJ; Smith MV; Bromberg PA (1994). Prediction of carboxyhemoglobin formation due to transient exposure to carbon monoxide. J Appl Physiol, 76: 1739-1745. 013908

Berk PD; Blaschke TF; Scharschmidt BF; Waggoner JG; Berlin NI (1976). A new approach to quantitation of the various sources of bilirubin in man. J Lab Clin Med, 87: 767-780. 012603

Berk PD; Rodkey FL; Blaschke TF; Collison HA; Waggoner JG (1974). Comparison of plasma bilirubin turnover and carbon monoxide production in man. J Lab Clin Med, 83: 29-37. 012386

Bos PM; Zeilmaker MJ; van Eijkeren JC (2006). Application of physiologically based pharmacokinetic modeling in setting acute exposure guideline levels for methylene chloride. Toxicol Sci, 91: 576-585. 194084

Bruce EN; Bruce MC (2003). A multicompartment model of carboxyhemoglobin and carboxymyoglobin responses to inhalation of carbon monoxide. J Appl Physiol, 95: 1235-1247. 193975

Bruce EN; Bruce MC; Erupaka K (2008). Prediction of the rate of uptake of carbon monoxide from blood by extravascular tissues. Respir Physiol Neurobiol, 161: 142-159. 193977

Bruce MC; Bruce EN (2006). Analysis of factors that influence rates of carbon monoxide uptake, distribution, and washout from blood and extravascular tissues using a multicompartment model. J Appl Physiol, 100: 1171-1180. 193980

Carraway MS; Ghio AJ; Carter JD; Piantadosi CA (2000). Expression of heme oxygenase-1 in the lung in chronic hypoxia. Am J Physiol, 278: L806-L812. 021096

Carraway MS; Ghio AJ; Suliman HB; Carter JD; Whorton AR; Piantadosi CA (2002). Carbon monoxide promotes hypoxic pulmonary vascular remodeling. Am J Physiol, 282: L693-L702. 026018

Castillo A; Llapur CJ; Martinez T; Kisling J; Williams-Nkomo T; Coates C; Tepper RS (2006). Measurement of single breath-hold carbon monoxide diffusing capacity in healthy infants and toddlers. Pediatr Pulmonol, 41: 544-550 . 193234

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Cavallin-Ståhl E; Mercke C; Lundh B (1976). Carbon monoxide production in patients with breast carcinoma. Br J Haematol, 32: 177-182. 086306

Cavallin-Ståhl E; Mercke C; Lundh B (1976). Erythropoiesis and carbon monoxide production in Hodgkin's disease. Br J Haematol, 32: 167-175. 193239

Cerny FC; Dempsey JA; Reddan WG (1973). Pulmonary gas exchange in nonnative residents of high altitude. J Clin Invest, 52: 2993-2999. 199736

Chace DH; Goldbaum LR; Lappas NT (1986). Factors affecting the loss of carbon monoxide from stored blood samples. J Anal Toxicol, 10: 181-189. 012020

Chakraborty S; Balakotaiah V; Bidani A (2004). Diffusing capacity reexamined: relative roles of diffusion and chemical reaction in red cell uptake of O2, CO, CO2, and NO. J Appl Physiol, 97: 2284-2302. 193759

Chung SJ (1988). Formulas predicting carboxyhemoglobin resulting from carbon monoxide exposure. Vet Hum Toxicol, 30: 528-532. 012749

Coburn RF (1967). Endogenous carbon monoxide production and body CO stores. Acta Med Scand Suppl, 472: 269-282. 011144

Coburn RF (1970). Enhancement by phenobarbital and diphenylhydantoin of carbon monoxide production in normal man. N Engl J Med, 283: 512-515. 010625

Coburn RF (1970). The carbon monoxide body stores. Ann N Y Acad Sci, 174: 11-22. 013916

Coburn RF; Blakemore WS; Forster RE (1963). Endogenous carbon monoxide production in man. J Clin Invest, 42: 1172-1178. 013971

Coburn RF; Forster RE; Kane PB (1965). Considerations of the physiological variables that determine the blood carboxyhemoglobin concentration in man. J Clin Invest, 44: 1899-1910. 011145

Coburn RF; Williams WJ; Forster RE (1964). Effect of erythrocyte destruction on carbon monoxide production in man. J Clin Invest, 43: 1098-1103. 013956

Coburn RF; Williams WJ; Kahn SB (1966). Endogenous carbon monoxide production in patients with hemolytic anemia. J Clin Invest, 45: 460-468. 010984

Cronenberger C; Mould DR; Roethig HJ; Sarkar M (2008). Population pharmacokinetic analysis of carboxyhaemoglobin concentrations in adult cigarette smokers. Br J Clin Pharmacol, 65: 30-39. 194085

DeGraff AC Jr; Grover RF; Johnson RL Jr; Hammond JW Jr; Miller JM (1970). Diffusing capacity of the lung in Caucasians native to 3,100 m. J Appl Physiol, 29: 71-76. 199737

Delivoria-Papadopoulos M; Coburn RF; Forster RE (1974). Cyclic variation of rate of carbon monoxide production in normal women. J Appl Physiol, 36: 49-51. 086316

De las Heras D; Fernández J; Ginès P; Cárdenas A; Ortega R; Navasa M; Barberá JA; Calahorra B; Guevara M; Bataller R; Jiménez W; Arroyo V; Rodés J (2003). Increased carbon monoxide production in patients with cirrhosis with and without spontaneous bacterial peritonitis. Hepatology, 38: 452-459. 194087

Di Cera E; Doyle ML; Morgan MS; De Cristofaro R; Landolfi R; Bizzi B; Castagnola M; Gill SJ (1989). Carbon monoxide and oxygen binding to human hemoglobin F0. Biochemistry, 28: 2631-2638. 193998

Douglas CG; Haldane JS; Haldane JBS (1912). The laws of combination of haemoglobin with carbon monoxide and oxygen. J Physiol, 44: 275-304. 013965

Duci A; Chaloulakou A; Spyrellis N (2003). Exposure to carbon monoxide in the Athens urban area during commuting. Sci Total Environ, 309: 47-58. 044199

Ehlers M; Labaze G; Hanakova M; McCloskey D; Wilner G (2009). Alarming levels of carboxyhemoglobin in banked blood. J Cardiothorac Vasc Anesth, 23: 336-338 . 194089

Engel LA; Wood LDH; Utz G; Macklem PT (1973). Gas mixing during inspiration. J Appl Physiol, 35: 18-24. 014336

Engel RR; Rodkey FL; O'Neal JD; Collison HA (1969). Relative affinity of human fetal hemoglobin for carbon monoxide and oxygen. Blood, 33: 37-45. 193914

Enzi G, Bevilacqua M, Crepaldi G (1976). Disturbances in pulmonary gaseous exchange in primary hyperlipoproteinemias. Bull Europ Physiol Resp, 12: 433-442. 195794

Fenn WO (1970). The burning of CO in tissues. Ann N Y Acad Sci, 174: 64-71. 010821

Forbes WH; Sargent F; Roughton FJW (1945). The rate of carbon monoxide uptake by normal men. Am J Physiol, 143: 594-608. 012850

Forster RE (1966). Diffusion of gases in the lungs. Physiologist, 9: 110-122. 180430

Gibson QH; Olson JS; McKinnie RE; Rohlfs RJ (1986). A kinetic description of ligand binding to sperm whale myoglobin. J Biol Chem, 261: 10228-10239. 016289

Gibson QH; Roughton FJ (1955). The kinetics of dissociation of the first oxygen molecule from fully saturated oxyhaemoglobin in sheep blood solutions. Proc Biol Sci, 912: 143. 193941

Gosselin NH; Brunet RC; Carrier G (2009). Determination of carboxyhaemoglobin in humans following low-level exposures to carbon monoxide. Inhal Toxicol, 21: 1077-1091. 190946

Guleria JS; Pande JN; Sethi PK; Roy SB (1971). Pulmonary diffusing capacity at high altitude. J Appl Physiol, 31: 536-543. 199518

Guyatt AR; Holmes MA; Cumming G (1981). Can carbon monoxide be absorbed from the upper respiratory tract in man? Eur Respir J, 62: 383-390. 011196

Haab P (1990). The effect of carbon monoxide on respiration. Experientia, 46: 1202-1206. 013359

Haldane J (1895). The action of carbonic oxide on man. J Physiol, 18: 430-462. 010538

Hampson NB; Weaver LK (2007). Carbon monoxide poisoning: a new incidence for an old disease. Undersea Hyperb Med, 34: 163-168. 190272

Hanel B; Teunissen I; Rabol A; Warberg J; Secher NH (1997). Restricted postexercise pulmonary diffusion capacity and central blood volume depletion. J Appl Physiol, 83: 11-17. 193918

Hart CL; Smith GD; Hole DJ; Hawthorne VM (2006). Carboxyhaemoglobin concentration, smoking habit, and mortality in 25 years in the Renfrew/Paisley prospective cohort study. Heart, 92: 321-324. 194092

Hayde M; Pollak A; Bernaschek G; Weiner CP; Vreman HJ; Stevenson DK; Widness JA (2000). Association of fetal and maternal carboxyhemoglobin levels in normal and Rh-alloimmune pregnancies. Early Hum Dev, 58: 205-212. 201602

Hegewald MJ; Crapo RO (2007). Socioeconomic status and lung function. Chest, 132: 1608-1614. 193923

Hill EP; Hill JR; Power GG; Longo LD (1977). Carbon monoxide exchanges between the human fetus and mother: A mathematical model. Am J Physiol, 232: H311-H323. 011315

Holland RA (1970). Reaction rates of carbon monoxide and hemoglobin. Ann N Y Acad Sci, 174: 154-171. 193856

Horvath I; Donnelly LE; Kiss A; Paredi P; Kharitonov SA; Barnes PJ (1998). Raised levels of exhaled carbon monoxide are associated with an increased expression of heme oxygenase-1 in airway macrophages in asthma: a new marker of oxidative stress. Thorax, 53: 668-672. 087190

Horvath I; Loukides S; Wodehouse T; Kharitonov SA; Cole PJ; Barnes PJ (1998). Increased levels of exhaled carbon monoxide in bronchiectasis: a new marker of oxidative stress. Thorax, 53: 867-870. 087191

Horvath SM; Bedi JF; Wagner JA; Agnew JW (1988). Maximal aerobic capacity at several ambient concentrations of carbon monoxide at several altitudes. J Appl Physiol, 65: 2696-2708. 012725

Hsia CC (2002). Recruitment of lung diffusing capacity: Update of concept and application. Chest, 122: 1774-1783. 193857

Jarvis MJ; Belcher M; Vesey C; Hutchison DCS (1986). Low cost carbon monoxide monitors in smoking assessment. Thorax, 41: 886-887. 012043

Jarvis MJ; Russell MAH; Saloojee Y (1980). Expired air carbon monoxide: a simple breath test of tobacco smoke intake. Br Med J, 281: 484-485. 011813

Johnson FK; Johnson RA; Durante W; Jackson KE; Stevenson BK; Peyton KJ (2006). Metabolic syndrome increases endogenous carbon monoxide production to promote hypertension and endothelial dysfunction in obese Zucker rats. Am J Physiol Regul Integr Comp Physiol, 290: 601-608. 193874

Joumard R; Chiron M; Vidon R; Maurin M; Rouzioux J-M (1981). Mathematical models of the uptake of carbon monoxide on hemoglobin at low carbon monoxide levels. Environ Health Perspect, 41: 277-289. 011330

Kinker JR; Haffor A-S; Stephan M; Clanton TL (1992). Kinetics of CO uptake and diffusing capacity in transition from rest to steady-state exercise. J Appl Physiol, 72: 1764-1772. 086328

Klasner AE; Smith SR; Thompson MW; Scalzo AJ (1998). Carbon monoxide mass exposure in a pediatric population. Acad Emerg Med, 5: 992-996. 087196

Kleinman MT; Leaf DA; Kelly E; Caiozzo V; Osann K; O'Niell T (1998). Urban angina in the mountains: effects of carbon monoxide and mild hypoxemia on subjects with chronic stable angina. Arch Environ Occup Health, 53: 388-397. 047186

Klimisch HJ; Chevalier HJ; Harke HP; Dontenwill W (1975). Uptake of carbon monoxide in blood of miniature pigs and other mammals. Toxicology, 3: 301-310. 010762

Lamberto C; Nunes H; Le Toumelin P; Duperron F; Valeyre D; Clerici C (2004). Membrane and capillary blood components of diffusion capacity of the lung for carbon monoxide in pulmonary sarcoidosis: relation to exercise gas exchange. Chest, 125: 2061-2068. 193845

Landaw SA (1973). The effects of cigarette smoking on total body burden and excretion rates of carbon monoxide. J Occup Environ Med, 15: 231-235. 010803

Landaw SA; Callahan EW Jr; Schmid R (1970). Catabolism of heme in vivo: comparison of the simultaneous production of bilirubin and carbon monoxide. J Clin Invest, 49: 914-925. 012605

Lee PJ; Jiang B-H; Chin BY; Iyer NV; Alam J; Semenza GL; Choi AMK (1997). Hypoxia-inducible factor-1 mediates transcriptional activation of the heme oxygenase-1 gene in response to hypoxia. J Biol Chem, 272: 5375-5381. 082641

Levasseur L; Galliot-Guilley M; Richter F; Scherrmann JM; Baud FJ (1996). Effects of mode of inhalation of carbon monoxide and of normobaric oxygen administration on carbon monoxide elimination from the blood. Hum Exp Toxicol, 15: 898-903. 080895

Longo LD (1970). Carbon monoxide in the pregnant mother and fetus and its exchange across the placenta. Ann N Y Acad Sci, 174: 313-341. 013922

Longo LD (1977). The biological effects of carbon monoxide on the pregnant woman, fetus, and newborn infant. Am J Obstet Gynecol, 129: 69-103. 012599

Longo LD; Hill EP (1977). Carbon monoxide uptake and elimination in fetal and maternal sheep. Am J Physiol, 232: H324-H330. 010802

Lundh B; Cavallin-Ståhl E; Mercke C (1975). Nicotinic acid and the endogenous production of carbon monoxide. J Intern Med, 197: 173-176. 086332

Luomanmäki K; Coburn RF (1969). Effects of metabolism and distribution of carbon monoxide on blood and body stores. Am J Physiol, 217: 354-363. 012319

Mahoney JJ; Vreman HJ; Stevenson DK; Van Kessel AL (1993). Measurement of carboxyhemoglobin and total hemoglobin by five specialized spectrophotometers (CO-oximeters) in comparison with reference methods. Clin Chem, 39: 1693-1700. 013859

Maines MD; Kappas A (1974). Cobalt induction of hepatic heme oxygenase; with evidence that cytochrome P-450 is not essential for this enzyme activity. PNAS, 71: 4293-4297. 193976

Maines MD; Trakshel GM; Kutty RK (1986). Characterization of two constitutive forms of rat liver microsomal heme oxygenase. Only one molecular species of the enzyme is inducible. J Biol Chem, 261: 411-419. 193978

Manier G; Moinard J; Techoueyres P; Varene N; Guenard H (1991). Pulmonary diffusion limitation after prolonged strenuous exercise. Respir Physiol, 83: 143-153. 193979

Manno M; Rugge M; Cocheo V (1992). Double fatal inhalation of dichloromethane. Hum Exp Toxicol, 11: 540-545. 013707

Marks GS; Vreman HJ; McLaughlin BE; Brien JF; Nakatsu K (2002). Measurement of endogenous carbon monoxide formation in biological systems. Antioxid Redox Signal, 4: 271-277. 030616

Marthan R; Castaing Y; Manier G; Guenard H (1985). Gas exchange alterations in patients with chronic obstructive lung disease. Chest, 87: 470-475. 086334

Marvisi M; Bassi E; Bonassi R; Civardi G; Delsignore R (2007). DLCO correlates with intestinal inflammation in ulcerative colitis, but albuminuria does not. Minerva Gastroenterol Dietol, 53: 321-7. 186702

Marvisi M; Borrello PD; Brianti M; Fornarsari G; Marani G; Guariglia A (2000). Changes in the carbon monoxide diffusing capacity of the lung in ulcerative colitis. Eur Respir J, 16: 965-8. 186703

McCartney ML (1990). Sensitivity analysis applied to Coburn-Forster-Kane models of carboxyhemoglobin formation. AIHA J, 51: 169-177. 013162

McClean PA; Duguid NJ; Griffin PM; Newth CJL; Zamel N (1981). Changes in exhaled pulmonary diffusing capacity at rest and exercise in individuals with impaired positional diffusion. Eur Respir J, 17: 179-186. 012411

McCoubrey WK Jr; Huang TJ; Maines MD (1997). Isolation and characterization of a cDNA from the rat brain that encodes hemoprotein heme oxygenase-3. FEBS J, 247: 725-732. 016715

McGrath JJ (1992). Effects of altitude on endogenous carboxyhemoglobin levels. J Toxicol Environ Health, 35: 127-133. 001005

McGrath JJ; Schreck RM; Lee PS (1993). Carboxyhemoglobin levels in humans: Effects of altitude. Inhal Toxicol, 5: 241-249. 013865

Mercke C; Cavallin-Ståhl E; Lundh B (1975). Carbon monoxide production and reticulocyte count in normal women: effect of contraceptive drugs and smoking. Acta Med Scand, 198: 155-160. 086308

Mercke C; Cavallin-Stahl E; Lundh B (1975). Heme catabolism during short-term treatment with phenobarbital, diazepam and oxazepam. Acta Med Scand, 198: 149-154. 086303

Mercke C; Lundh B (1976). Erythrocyte filterability and heme catabolism during the menstrual cycle. Ann Intern Med, 85: 322-324. 086309

Meyer J; Prien T; Van Aken H; Bone H-G; Waurick R; Theilmeier G; Booke M (1998). Arterio-venous carboxyhemoglobin difference suggests carbon monoxide production by human lungs. Biochem Biophys Res Commun, 244: 230-232. 047530

Monma M; Yamaya M; Sekizawa K; Ikeda K; Suzuki N; Kikuchi T; Takasaka T; Sasaki H (1999). Increased carbon monoxide in exhaled air of patients with seasonal allergic rhinitis. Clin Exp Allergy, 29: 1537-1541. 180426

Morimatsu H; Takahashi T; Maeshima K; Inoue K; Kawakami T; Shimizu H; Takeuchi M; Yokoyama M; Katayama H; Morita K (2006). Increased heme catabolism in critically ill patients: Correlation among exhaled carbon monoxide, arterial carboxyhemoglobin, and serum bilirubin IXalpha concentrations. Am J Physiol Lung Cell Mol Physiol, 290: L114-L119. 194097

Muchova L; Wong RJ; Hsu M; Morioka I; Vitek L; Zelenka J; Schröder H; Stevenson DK (2007). Statin treatment increases formation of carbon monoxide and bilirubin in mice: A novel mechanism of in vivo antioxidant protection. Can J Physiol Pharmacol, 85: 800-810. 194098

NCHS; Radford EP; Drizd TA (1982). Blood carbon monoxide levels in persons 3-74 years of age: United States, 1976-80; Advance Data from Vital and Health Statistics, No 76. National Center for Health Statistics; Office of Health Research, Statistics, and Technology; Public Health Service; U.S. Department of Health and Human Services. Hyattsville, MD. DHHS Pub. No. (PHS) 82-1250. 011442

Neas LM; Schwartz J (1996). The determinants of pulmonary diffusing capacity in a national sample of US adults. Am J Respir Crit Care Med, 153: 656-664. 079363

Neto CA; Yanagihara JI; Turri F (2008). A carbon monoxide transport model of the human respiratory system applied to urban atmosphere exposure analysis. J Braz Soc Mech Sci & Eng, 30: 253-260. 194672

Ocak A; Valentour JC; Blanke RV (1985). The effects of storage conditions on the stability of carbon monoxide in postmortem blood. J Anal Toxicol, 9: 202-206. 011641

Ott WR; Mage DT (1978). Interpreting urban carbon monoxide concentrations by means of a computerized blood COHb model. J Air Waste Manag Assoc, 28: 911-916. 011124

Pankow D; Matschiner F; Weigmann H-J (1991). Influence of aromatic hydrocarbons on the metabolism of dichloromethane to carbon monoxide in rats. Toxicology, 68: 89-100. 013551

Paredi P; Biernacki W; Invernizzi G; Kharitonov SA; Barnes PJ (1999). Exhaled carbon monoxide levels elevated in diabetes and correlated with glucose concentration in blood: A new test for monitoring the disease? Chest, 116: 1007-1011. 194102

Paredi P; Shah PL; Montuschi P; Sullivan P; Hodson ME; Kharitonov SA; Barnes PJ (1999). Increased carbon monoxide in exhaled air of patients with cystic fibrosis. Thorax, 54: 917-20. 118798

Penney DG (1988). A review: Hemodynamic response to carbon monoxide. Environ Health Perspect, 77: 121-130. 012519

Pesola GR; Huggins G; Sherpa TY (2006). Abnormal predicted diffusion capacities in healthy Asians: an inequality with a solution. Respiration, 73: 799-807. 193855

Pesola GR; Sunmonu Y; Huggins G; Ford JG (2004). Measured diffusion capacity versus prediction equation estimates in blacks without lung disease. Respiration, 71: 484-492. 193842

Peterson JE; Stewart RD (1970). Absorption and elimination of carbon monoxide by inactive young men. Arch Environ Occup Health, 21: 165-171. 012416

Peterson JE; Stewart RD (1975). Predicting the carboxyhemoglobin levels resulting from carbon monoxide exposures. J Appl Physiol, 39: 633-638. 010696

Prommer N; Schmidt (2007). Loss of CO from the intravascular bed and its impact on the optimised CO-rebreathing method. Eur J Appl Physiol, 100: 383-391. 180421

Proudman SM; Stevens WM; Sahhar J; Celermajer D (2007). Pulmonary arterial hypertension in systemic sclerosis: the need for early detection and treatment. J Intern Med, 37: 485-94. 186705

Reeves RB; Park HK (1992). CO uptake kinetics of red cells and CO diffusing capacity. Respir Physiol, 88: 1-21. 193847

Richardson RS; Noyszewski EA; Saltin B; Gonzalez-Alonso J (2002). Effect of mild carboxy-hemoglobin on exercising skeletal muscle: Intravascular and intracellular evidence. Am J Physiol, 283: R1131-R1139. 037513

Riediker M; Williams R; Devlin R; Griggs T; Bromberg P (2003). Exposure to particulate matter, volatile organic compounds, and other air pollutants inside patrol cars. Environ Sci Technol, 37: 2084-2093. 043761

Rodes C; Sheldon L; Whitaker D; Clayton A; Fitzgerald K; Flanagan J; DiGenova F; Hering S; Frazier C (1998). Measuring concentrations of selected air pollutants inside California vehicles [final report]. California Environmental Protection Agency, Air Resources Board; South Coast Air Quality Management District. Sacramento, CA.http://www.arb.ca.gov/research/abstracts/95-339.htm. 010611

Rodgers PA; Vreman HJ; Dennery PA; Stevenson DK (1994). Sources of carbon monoxide (CO) in biological systems and applications of CO detection technologies. Semin Perinatol, 18: 2-10. 076440

Rodkey FL; O'Neal JD; Collison HA (1969). Oxygen and carbon monoxide equilibria of human adult hemoglobin at atmospheric and elevated pressure. Blood, 33: 57-65. 008151

Roughton FJ; Forster RE (1957). Relative importance of diffusion and chemical reaction rates in determining rate of exchnage of gases in the human lung, with special reference to true diffusing capacity of pulmonary membrane and volume of blood in the lung capillaries. J Appl Physiol, 11: 290-302. 193862

Roughton FJW (1970). The equilibrium of carbon monoxide with human hemoglobin in whole blood. Ann N Y Acad Sci, 174: 177-188. 013931

Roughton FJW; Root WS (1945). The fate of CO in the body during recovery from mild carbon monoxide poisoning in man. Am J Physiol, 145: 239-252. 180418

Sakamaki F; Oya H; Nagaya N; Kyotani S; Satoh T; Nakanishi N (2002). Higher prevalence of obstructive airway disease in patients with thoracic or abdominal aortic aneurysm. J Vasc Surg, 36: 35-40. 186706

Schachter LM; Dixon J; Pierce RJ; O'Brien P (2003). Severe gastroesophageal reflux is associated with reduced carbon monoxide diffusing capacity. Chest, 123: 1932-8. 186707

Scharte M; Bone HG; Van Aken H; Meyer J (2000). Increased carbon monoxide in exhaled air of critically ill patients. Biochem Biophys Res Commun, 267: 423-426. 194112

Scharte M; von Ostrowski TA; Daudel F; Freise H; Van Aken H; Bone HG (2006). Endogenous carbon monoxide production correlates weakly with severity of acute illness. Eur J Anaesthesiol, 23: 117-122. 194115

Schoenfisch WH; Hoop KA; Struelens BS (1980). Carbon monoxide absorption through the oral and nasal mucosae of cynomolgus monkeys. Arch Environ Health, 35: 152-154. 011404

Selvakumar S; Sharan M; Singh MP (1992). Mathematical model for the exchange of gases in the lungs with special reference to carbon monoxide. Med Biol Eng Comput, 30: 525-532. 013750

Shaoqing Y; Ruxin Z; Yinjian C; Jianqiu C; Chunsheng Z; Jiangfeng T; Genhong L (2008). Possible contribution of endogenous carbon monoxide to the development of allergic rhinitis in guinea pigs. J Inflamm, 5: 23. 192384

Sharan M; Selvakumar S (1999). A mathematical model for the simultaneous transport of gases to compute blood carboxyhaemoglobin build-up due to CO exposures: application to the end-expired breath technique. Environ Pollut, 105: 231-242. 194673

Sharan M; Selvakumar S; Singh MP (1990). Mathematical model for the computation of alveolar partial pressure of carbon monoxide. Int J Bio Med Comput, 26: 135-147. 003798

Sharma VS; Schmidt MR; Ranney HM (1976). Dissociation of CO from carboxyhemoglobin. J Biol Chem, 251: 4267-4272. 193766

Shimazu T (2001). Half-life of blood carboxyhemoglobin. Chest, 119: 661-663. 016331

Shimazu T; Ikeuchi H; Sugimoto H; Goodwin CW; Mason AD Jr; Pruitt BA Jr (2000). Half-life of blood carboxyhemoglobin after short-term and long-term exposure to carbon monoxide. J Trauma, 49: 126-131. 016420

Singh MP; Sharan M; Selvakumar S (1991). A mathematical model for the computation of carboxyhaemoglobin in human blood as a function of exposure time. Proc Biol Sci, 334: 135-147. 013583

Smith MV (1990). Comparing solutions to the linear and nonlinear CFK equations for predicting COHb formation. Math Biosci, 99: 251-263. 013164

Smith MV; Hazucha MJ; Benignus VA; Bromberg PA (1994). Effect of regional circulation patterns on observed HbCO levels. J Appl Physiol, 77: 1659-1665. 076564

Sokal JA; Majka J; Palus J (1984). The content of carbon monoxide in the tissues of rats intoxicated with carbon monoxide in various conditions of acute exposure. Arch Toxicol, 56: 106-108. 011591

Solanki DL; McCurdy PR; Cuttitta FF; Schechter GP (1988). Hemolysis in sickle cell disease as measured by endogenous carbon monoxide production: A preliminary report. Am J Clin Pathol, 89: 221-225. 012426

Stevenson DK; Ostrander CE; Johnson JD (1979). Effect of erythrocyte destruction on the pulmonary excretion rate of carbon monoxide in adult male Wistar rats. J Lab Clin Med, 94: 649-654. 193767

Stewart RD; Peterson JE; Baretta ED; Bachand RT; Hosko MJ; Herrmann AA (1970). Experimental human exposure to carbon monoxide. Arch Environ Health, 21: 154-164. 013972

Stewart RD; Peterson JE; Fisher TN; Hosko MJ; Baretta ED; Dodd HC; Herrmann AA (1973). Experimental human exposure to high concentrations of carbon monoxide. Arch Environ Occup Health, 26: 1-7. 012428

Sylvester KP; Patey RA; Rafferty GF; Rees D; Thein SL; Greenough A (2005). Exhaled carbon monoxide levels in children with sickle cell disease. Eur J Pediatr, 164: 162-165. 191954

Takeuchi A; Vesely A; Rucker J; Sommer LZ; Tesler J; Lavine E; Slutsky AS; Maleck WA; Volgyesi G; Fedorko L; Iscoe S; Fisher JA (2000). A simple "new" method to accelerate clearance of carbon monoxide. Am J Respir Crit Care Med, 161: 1816-1819. 005675

Tarquini R; Masini E; La Villa G; Barletta G; Novelli M; Mastroianni R; Romanelli RG; Vizzutti F; Santosuosso U; Laffi G (2009). Increased plasma carbon monoxide in patients with viral cirrhosis and hyperdynamic circulation. Am J Gastroenterol, 104: 891-897. 194117

Terzano C; Conti V; Petroianni A; Ceccarelli D; De Vito C; Villari P (2009). Effect of Postural Variations on Carbon Monoxide Diffusing Capacity in Healthy Subjects and Patients with Chronic Obstructive Pulmonary Disease. Respiration, 77: 51-57. 108046

Tikuisis P (1996). Modeling the uptake and elimination of carbon monoxide. In Penney DG (Ed.),Carbon Monoxide (pp. 45-67). Boca Raton, FL: CRC Press, Inc / Lewis Publishers. 080960

Tikuisis P; Buick F; Kane DM (1987). Percent carboxyhemoglobin in resting humans exposed repeatedly to 1,500 and 7,500 ppm CO. J Appl Physiol, 63: 820-827. 012219

Tikuisis P; Kane DM; McLellan TM; Buick F; Fairburn SM (1992). Rate of formation of carboxyhemoglobin in exercising humans exposed to carbon monoxide. J Appl Physiol, 72: 1311-1319. 013592

Tikuisis P; Madill HD; Gill BJ; Lewis WF; Cox KM; Kane DM (1987). A critical analysis of the use of the CFK equation in predicting COHb formation. Am Ind Hyg Assoc J, 48: 208-213. 012138

Topping DL (1975). Acute effects of carbon monoxide on the metabolism of perfused rat liver. Biochem J, 152: 425-427. 193784

Tran TT; Martin P; Ly H; Balfe D; Mosenifar Z (2007). Carboxyhemoglobin and its correlation to disease severity in cirrhotics. J Clin Gastroenterol, 41: 211-215. 194120

Tyuma I; Ueda Y; Imaizumi K; Kosaka H (1981). Prediction of the carbonmonoxyhemoglobin levels during and after carbon monoxide exposures in various animal species. Jpn J Physiol, 31: 131-143. 011226

U.S. Census Bureau (2008). American Housing Survey for the United States: 2007. U.S. Government Printing Office. Washington, DC. 194013

U.S. EPA (1978). Altitude as a factor in air pollution. U.S. Envrionmental Protection Agency. Research Triangle Park, NC. EPA-600/9-78-015. 086321

U.S. EPA (1991). Air quality criteria for carbon monoxide. U.S. Environmental Protection Agency. Research Triangle Park, NC. EPA/600/8-90/045F. http://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=3000554R.txt. 017643

U.S. EPA (2000). Air quality criteria for carbon monoxide. National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency. Research Triangle Park, NC. EPA 600/P-99/001F. 000907

Vreman HJ; Wong RJ; Kadotani T; Stevenson DK (2005). Determination of carbon monoxide (CO) in rodent tissue: effect of heme administration and environmental CO exposure. Anal Biochem, 341: 280-289. 193786

Vreman HJ; Wong RJ; Stevenson DK; Smialek JE; Fowler DR; Li L; Vigorito RD; Zielke HR (2006). Concentration of Carbon Monoxide (CO) in Postmortem Human Tissues: Effect of Environmental CO Exposure. J Forensic Sci, 51: 1182-1190. 098272

Wagner JA; Horvath SM; Dahms TE (1975). Carbon monoxide elimination. Respir Physiol Neurobiol, 23: 41-47. 010989

Weaver LK; Howe S; Hopkins R; Chan K (2000). Carboxyhemoglobin half-life in carbon monoxide-poisoned patients treated with 100% oxygen at atmospheric pressure. Chest, 117: 801-808. 016421

Weller PA; Price M; Isenberg H; Edwards YH; Jeffreys AJ (1986). Myoglobin expression: early induction and subsequent modulation of myoglobin and myoglobin mRNA during myogenesis. Mol Cell Biol, 6: 4539-4547. 187298

West JB (1962). Diffusing capacity of the lung for carbon monoxide at high altitude. J Appl Physiol, 17: 421-426. 199513

Widdop B (2002). Analysis of carbon monoxide. Ann Clin Biochem, 39: 378-391. 030493

Wirkner K; Damme B; Poelchen W; Pankow D (1997). Effect of long-term ethanol pretreatment on the metabolism of dichloromethane to carbon monoxide in rats. Toxicol Appl Pharmacol, 143: 83-88. 082642

Wittenberg BA; Wittenberg JB; Caldwell PRB (1975). Role of myoglobin in the oxygen supply to red skeletal muscle. J Biol Chem, 250: 9038-9043. 012436

Wu L; Wang R (2005). Carbon monoxide: endogenous production, physiological functions, and pharmacological applications. Pharmacol Rev, 57: 585-630. 180411

Yamaya M; Sekizawa K; Ishizuka S; Monma M; Mizuta K; Sasaki H (1998). Increased carbon monoxide in exhaled air of subjects with upper respiratory tract infections. Am J Respir Crit Care Med, 158: 311-314. 047525

Yasuda H; Sasaki T; Yamaya M; Ebihara S; Maruyama M; Kanda A; Sasaki H (2004). Increased arteriovenous carboxyhemoglobin differences in patients with inflammatory pulmonary diseases. Chest, 125: 2160-2168. 191955

Yasuda H; Yamaya M; Nakayama K; Ebihara S; Sasaki T; Okinaga S; Inoue D; Asada M; Nemoto M; Sasaki H (2005). Increased arterial carboxyhemoglobin concentrations in chronic obstructive pulmonary disease. Am J Respir Crit Care Med, 171: 1246-1251. 191953

Yasuda H; Yamaya M; Yanai M; Ohrui T; Sasaki H (2002). Increased blood carboxyhaemoglobin concentrations in inflammatory pulmonary diseases. Thorax, 57: 779-783. 035206

Yerushalmi R; Kramer MR; Rizel S; Sulkes A; Gelmon K; Granot T; Neiman V; Stemmer SM (2009). Decline in pulmonary function in patients with breast cancer receiving dose-dense chemotherapy: a prospective study. Ann Oncol, 20: 437-440. 186711

Young LJ; Caughey WS (1986). Mitochondrial oxygenation of carbon monoxide. Biochemistry, 239: 225-227. 012091

Zayasu K; Sekizawa K; Okinaga S; Yamaya M; Ohrui T; Sasaki H (1997). Increased carbon monoxide in exhaled air of asthmatic patients. Am J Respir Crit Care Med, 156: 1140-1143. 084291

Zegdi R; Perrin D; Burdin M; Boiteau R; Tenaillon A (2002). Increased endogenous carbon monoxide production in severe sepsis. Intensive Care Med, 28: 793-796. 037461

Zinkham WH; Houtchens RA; Caughey WS (1980). Carboxyhemoglobin levels in an unstable hemoglobin disorder (Hb Zürich): effect on phenotypic expression. Science, 209: 406-408. 011435

Chapter 5. Integrated Health Effects

5.1. Mode of Action of CO Toxicity

5.1.1. Introduction

The diverse effects of CO are dependent upon concentration and duration of exposure as well as on the cell types and tissues involved. Responses to CO are not necessarily due to a single process and may instead be mediated by a combination of effects including COHb-mediated hypoxic stress and other mechanisms such as free radical production and the initiation of cell signaling. However, binding of CO to reduced iron in heme proteins with subsequent alteration of heme protein function is the common mechanism underlying the biological responses to CO.

5.1.2. Hypoxic Mechanisms

As discussed in the 2000 CO AQCD (U.S. EPA, 2000, 000907), the most well-known pathophysiologic effect of CO is tissue hypoxia caused by binding of CO to Hb. Not only does the formation of COHb reduce the O_2-carrying capacity of blood, but it also impairs the release of O_2 from O_2Hb. Compensatory alterations in hemodynamics, such as vasodilation and increased cardiac output, protect against tissue hypoxia. Depending on the extent of CO exposure, these compensatory changes may be effective in people with a healthy cardiovascular system. However, hemodynamic responses following CO exposure may be insufficient in people with decrements in cardiovascular function, resulting in health effects as described in Section 5.2.

The 2000 CO AQCD (U.S. EPA, 2000, 000907) reported changes in vasodilation due to CO levels between 500-2,000 ppm (Kanten et al., 1983, 011333; MacMillan, 1975, 012909). In one study, the vasodilatory response to CO in cerebral blood vessels was attributed to decreased O_2 availability (Koehler et al., 1982, 011341). In another study, exposure of rats to 1,000 ppm CO resulted in increased cerebral blood flow which was not triggered by tissue hypoxia since no changes in intramitochondrial NADH levels preceded vasodilation (Meilin et al., 1996, 079919). However, the response was blocked by the inhibition of NOS indicating a role for the free radical species NO in CO-mediated vasodilation (Meilin et al., 1996, 079919).

Increased cardiac output was also discussed in the 2000 CO AQCD (U.S. EPA, 2000, 000907) as a compensatory response to CO-mediated tissue hypoxia. Findings of studies which measured hemodynamic alterations following CO exposure were equivocal and sometimes contradictory (Penney, 1988, 012519). While most studies reported a positive correlation between COHb and cardiac output at COHb levels above 20%, one study demonstrated increased cardiac output in humans following acute exposure to 5% CO which resulted in the rapid rise in COHb levels to ~9% (Ayres et al., 1973, 193943). However, there was no increase in cardiac output following a more gradual increase in COHb levels to ~9% achieved by exposure to 0.1% CO over a longer period of time (Ayres et al., 1973, 193943). Increased heart rate and stroke volume (SV) were observed in response to CO exposure in one study (Stewart et al., 1973, 012428); however, some experiments found no change in SV in humans with 18-20% COHb (Vogel and Gleser, 1972, 010898) or 12.5% COHb (Klausen et al., 1968, 193936). The 2000 CO AQCD (U.S. EPA, 2000, 000907) reported that blood pressure was generally unchanged in human CO exposure studies, while a number of animal studies demonstrated CO-induced hypotension (Penney, 1988, 012519). No changes in forearm blood flow, blood pressure, or heart rate were reported in humans with approximately 8% COHb

Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at http://epa.gov/hero. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISAs) and the Integrated Risk Information System (IRIS).

(Hausberg and Somers, 1997, 083450). However, high-concentration exposures (3,000-10,000 ppm) in animals resulted in diminished organ blood flow (Brown and Piantadosi, 1992, 013441). In-depth discussion of hemodynamic changes resulting from CO exposure in recent human clinical studies can be found in Section 5.2.4.

Binding of CO to Mb, as discussed in the 2000 CO AQCD (U.S. EPA, 2000, 000907) and in Section 4.3.2.3, can also impair the delivery of O_2 to tissues. Mb has a high affinity for CO, about 25 times that of O_2; however, pathophysiologic effects are seen only after high-dose exposures to CO, resulting in COMb concentrations far above baseline levels. High-energy phosphate production in cardiac myocytes was inhibited when COMb concentrations exceeded 40%, corresponding to an estimated COHb level between 20-40% (Wittenberg and Wittenberg, 1993, 013909). Conversely, rat hearts perfused with solutions containing 6% CO (60,000 ppm) exhibited no change in high-energy phosphate production, respiration rate, or contractile function (Chung et al., 2006, 193987; Glabe et al., 1998, 086704).

5.1.3. Nonhypoxic Mechanisms

Nonhypoxic mechanisms underlying the biological effects of CO were discussed in the 2000 CO AQCD (U.S. EPA, 2000, 000907) and are summarized below. Most of these mechanisms are related to CO's ability to bind heme-containing proteins other than Hb and Mb (Raub and Benignus, 2002, 041616). Since then, additional experiments have confirmed and extended these findings. While the majority of the older studies utilized concentrations of CO far higher than ambient levels, many of the newer studies have employed more environmentally-relevant concentrations of CO.

5.1.3.1. Nonhypoxic Mechanisms Reviewed in the 2000 CO AQCD

Inhibition of heme-containing proteins such as cytochrome *c* oxidase and cytochrome P450 reductases may alter cellular function. CO interacts with the ferrous heme *a*3 of the terminal enzyme of the electron transport chain, cytochrome *c* oxidase (Petersen, 1977, 193764). Cytochrome *c* oxidase inhibition not only interrupts cellular respiration and energy production but can also enhance reactive oxygen species (ROS) production. In vivo studies observed CO binding to cytochrome *c* oxidase under conditions where COHb concentrations were above 50% (Brown and Piantadosi, 1992, 013441). It is unlikely that this could arise under physiologic conditions or under conditions relevant to ambient exposures.

A series of studies from the laboratory of Thom, Ischiropoulos and colleagues indicated that CO exposure produced a pro-oxidant cellular environment by liberation of NO. Exposure to CO concentrations of 10-20 ppm and above caused isolated rat platelets, as well as cultured bovine pulmonary endothelial cells, to release NO (Thom and Ischiropoulos, 1997, 085644). This response was blocked by treatment with an NOS inhibitor, indicating that the NO released was dependent on NOS activity. An increase in available NO was also seen in the lung and brain of CO-exposed rats (Ischiropoulos et al., 1996, 079491; Thom et al., 1999, 016757). Reaction of NO with superoxide to form the highly active oxidant species, peroxynitrite (Thom et al., 1997, 084337), was thought to lead to the activation and sequestration of leukocytes in brain vessels (Thom et al., 2001, 193779) and aorta (Thom et al., 1999, 016753), oxidation of plasma lipoproteins (Thom et al., 1999, 016753), and the formation of protein nitrotyrosine (Ischiropoulos et al., 1996, 079491; Thom et al., 1999, 016757; Thom et al., 1999, 016753). NO release by CO was attributed to the displacement of NO from nitrosyl-bound heme proteins. The rate of this event was slow; however, it occurred at environmentally-relevant concentrations of CO (Thom et al., 1997, 084337).

CO exposure also increased the production of other pro-oxidant species, including hydrogen peroxide (H_2O_2) and hydroxyl radical (OH). High-level CO exposure (2,500 ppm) increased OH in rat brain, and this response was distinct from tissue hypoxia (Piantadosi et al., 1997, 081326). The mechanism for enhanced H_2O_2 production was unclear. The release of H_2O_2 in the lung of CO-exposed rats was dependent upon the production of NO, as it was inhibited by pretreatment with an NOS inhibitor (Thom et al., 1999, 016757). It is possible that peroxynitrite formed after CO exposure inhibited electron transport at complexes I through III, or that cytochrome *c* oxidase inhibition led to mitochondrial dysfunction and ROS production.

Evidence was presented for CO-mediated vasorelaxation by three different mechanisms. First, CO may inhibit the synthesis of vasoconstrictors by P450 heme proteins (Wang, 1998, 086074).

Vasodilation in isolated vessels was demonstrated via this P450-dependent mechanism using high concentrations of CO (approximately 90,000 ppm) (Coceani et al., 1988, 040493). In the case of cytochrome P450 enzymes, tissue CO levels may need to be abnormally high to elicit a response since the Warburg binding coefficients (the ratio of CO to O_2 at which half the reactive sites are occupied by CO) for cytochrome P450s range from 0.1-12 (Piantadosi, 2002, 037463). P450 inhibition may reduce the hypoxia-induced expression of mitogens such as erythropoietin (EPO), vascular endothelial growth factor (VEGF), endothelin-1 (ET-1), and platelet derived growth factor (PDGF), which may decrease smooth muscle proliferation in response to hypoxia (Wang, 1998, 086074). CO also interfered with the metabolism of barbiturates and other drugs; however, this was probably due to the hypoxic actions of CO rather than to P450 inhibition (Roth and Rubin, 1976, 012703; Roth and Rubin, 1976, 012420).

Secondly, CO has been shown to play a physiological role in vasomotor control and in signal transduction by activation of soluble guanylate cyclase (sGC), causing a conversion of GTP to cyclic GMP (cGMP). CO reversibly ligates the heme core of sGC, and the resulting protoporphyrin IX intermediate triggers cGMP production (Ndisang et al., 2004, 180425). CO caused vascular relaxation, independent of the endothelium, in human arterial rings (Achouh et al., 2008, 179918), rat tail artery (Wang et al., 1997, 084341), and rat thoracic aorta (Lin and McGrath, 1988, 012773), but not in cerebral vessels (Andresen et al., 2006, 180449; Brian et al., 1994, 076283). Activation of sGC by CO has been linked to neurotransmission, vasodilation, bronchodilation, inhibition of platelet aggregation, and inhibition of smooth muscle proliferation (Brüne and Ullrich, 1987, 016535; Cardell et al., 1998, 086700; Cardell et al., 1998, 011534; Morita et al., 1997, 085345; Verma et al., 1993, 193999).

CO-mediated vasorelaxation can also be caused by activation of voltage- or Ca^{2+}-activated potassium (K^+) channels in smooth muscle cells, which leads to membrane hyperpolarization, voltage-dependent Ca^{2+} channel closing, reduction of resting Ca^{2+} concentration and vascular tissue relaxation (Farrugia et al., 1993, 013826; Wang et al., 1997, 084341). This effect may be linked to sGC activity; however, it has also been reported to occur independently (Dubuis et al., 2003, 180439; Naik and Walker, 2003, 193852). Developmental stage and tissue type will determine whether K^+ channels or the sGC/cGMP pathway play more of a role in vasorelaxation (Ndisang et al., 2004, 180425).

Collectively, these older studies demonstrated that exposures to high concentrations of CO resulted in altered functions of heme proteins other than Hb and Mb. Decreased cellular respiration and energy production and increased ROS following cytochrome *c* oxidase inhibition would likely predispose towards cellular injury and death. The release of NO from sequestered stores could contribute to the pro-oxidant status if superoxide levels are simultaneously increased. Furthermore, increased ROS and reactive nitrogen species are known to promote cell signaling events leading to inflammation and endothelial dysfunction. An inappropriate increase in vasorelaxation due to inhibition of vasoconstrictor production or to activation of vasodilatory pathways (sGC and ion channels) could potentially limit compensatory alterations in hemodynamics. Alternatively, CO-binding to sGC could result in decreased vasorelaxation by interfering with the binding of NO to sGC. NO can also activate sGC, and with a 30-fold greater affinity than CO, is 1,000-fold more potent with respect to vasodilation and sGC activation (Stone and Marletta, 1994, 076455). CO could further contribute to endothelial dysfunction by this mechanism. Although the 2000 CO AQCD (U.S. EPA, 2000, 000907) made no definitive links between these nonhypoxic mechanisms of CO and CO-mediated health effects, it did document the potential for CO to interfere with basic cellular and molecular processes that could lead to dysfunction and/or disease.

5.1.3.2. Recent Studies of Nonhypoxic Mechanisms

Since the 2000 CO AQCD (U.S. EPA, 2000, 000907), new studies have provided additional evidence for nonhypoxic mechanisms of CO which involve the binding of CO to reduced iron in heme proteins. These mechanisms, which may be interrelated, are described below and include:

- Alteration in NO signaling
- Inhibition of cytochrome c oxidase
- Heme loss from protein

- Disruption of iron homeostasis
- Alteration in cellular redox status

Recent studies have also demonstrated nonhypoxic mechanisms of CO which are either indirectly linked to heme protein interactions or not yet understood. These mechanisms are described below and include:

- Alteration in ion channel activity
- Modulation of protein kinase pathways

This assessment evaluates these nonhypoxic mechanisms in terms of their potential to contribute to health effects associated with environmentally-relevant CO exposures. As discussed above, CO at high concentrations may promote oxidative stress, cell injury and death, inflammation and endothelial dysfunction. Whether lower CO concentrations trigger these same processes is of key interest since they may potentially contribute to adverse health effects following ambient exposures.

In addition, a large number of studies published since the 2000 CO AQCD (U.S. EPA, 2000, 000907) have focused on the role of CO derived from HO-catalyzed heme metabolism as an endogenous signaling molecule and on the potential therapeutic effects of exogenous CO administered at high concentrations. This assessment addresses aspects of these topics pertaining to the evaluation of health effects associated with environmentally-relevant CO exposures.

Alteration in NO Signaling

Work by Thorup et al. (1999, 193782) demonstrated altered NO signaling in isolated rat renal resistance arteries. In one set of experiments, rapid release of NO was observed in response to exogenous CO. This response was biphasic, peaking at 100 nM CO in the perfusate and declining at higher concentrations. It was also NOS-dependent as it required L-arginine and was blocked by a NOS inhibitor. The authors attributed the effects of CO on NO release to either stimulated eNOS or to displacement of preformed NO from intracellular binding sites. These findings are similar to those of Thom and colleagues (Ischiropoulos et al., 1996, 079491; Thom and Ischiropoulos, 1997, 085644; Thom et al., 1994, 076459; Thom et al., 1997, 084337; Thom et al., 1999, 016753; Thom et al., 1999, 016757; Thom et al., 2000, 011574; Thom et al., 2006, 098418) who demonstrated NO release, presumably from sequestered stores in platelets, endothelial cells, aorta and lung in response to CO (see above). Furthermore in a second set of experiments, Thorup et al. (1999, 193782) demonstrated inhibition of agonist-stimulated NOS activity in isolated rat renal resistance arteries. Here rapid NOS-dependent release of NO following carbachol stimulation was blocked by pretreatment with 100 nM CO or by upregulation of intracellular HO-1. Additional experiments using blood-perfused isolated juxtamedullary afferent arterioles demonstrated a biphasic response to CO with rapid vasodilation observed at lower, but not higher, concentrations of CO. These same higher concentrations of CO inhibited agonist-stimulated vasodilation in the arterioles. In order to determine whether CO had a direct effect on the activity of NOS, which is a heme protein, purified recombinant eNOS was exposed in vitro to CO in the presence of the necessary substrates and cofactors. A dose-dependent inhibition of NOS by CO was observed, suggesting that CO-mediated NO release in the isolated vessels was not due to stimulated NOS activity. The authors concluded that CO effects on vascular tone were due to the liberation of NO from intracellular binding sites at lower concentrations and to the inhibition of NOS at higher concentrations.

These findings illustrate the potential of CO to alter processes dependent on endogenous NO either by enhancing intracellular concentrations of free NO (increased vasodilatory influence) or by inhibiting agonist-induced NO production by NOS (decreased vasodilatory influence). In addition, CO may compete with NO for binding to sGC as discussed above. Since NO activates sGC to a greater extent than CO, NO-dependent vasodilation may be significantly impaired in the presence of CO. In fact, a recent study in transgenic mice demonstrated that chronic overexpression of HO-1 in vascular smooth muscle resulted in attenuated NO-mediated vasodilation and elevated blood pressure (Imai et al., 2001, 193864). Results of this study suggested that decreased sensitivity of sGC to NO contributed to the changes in vascular function. The considerations mentioned above, however, do not preclude an important role for CO in maintaining vasomotor tone in vessels where

CO and NO do not compete for available heme sites on sGC. This could occur when both mediators are present at low concentrations compared with sGC or in situations where NOS does not co-localize with sGC, as discussed by Thorup et al. (1999, 193782).

Inhibition of Cytochrome *c* Oxidase

High concentrations of CO are known to inhibit cytochrome c oxidase, the terminal enzyme in the mitochondrial electron transport chain, resulting in inhibition of mitochondrial respiration and the formation of superoxide from mitochondrial substrates. Several recent studies demonstrated CO-mediated decreases in cytochrome *c* oxidase activity in model systems ranging from isolated mitochondria to whole animals. In a study by Alonso et al. (2003, 193882), exposure of isolated mitochondria from human skeletal muscle to 50-500 ppm CO for 5 min decreased cytochrome *c* oxidase activity. Similarly, exposure of cultured macrophages to 250 ppm CO for 1 h inhibited cytochrome *c* oxidase (Zuckerbraun et al., 2007, 193884). In this latter study, increased ROS were observed following exposure to 250 ppm CO, as well as to CO concentrations as low as 50 ppm, for 1 h. Animal studies demonstrated that exposure of rats to 250 ppm CO for 90 min inhibited cytochrome *c* oxidase activity in myocardial fibers (Favory et al., 2006, 184462). Exposure of mice to 1,000 ppm CO for 3 h, resulting in COHb levels of 61%, decreased cytochrome *c* oxidase activity in heart mitochondria (Iheagwara et al., 2007, 193861).

Heme Content Loss from Proteins

In addition to decreasing the activity of cytochrome *c* oxidase, exposure of mice to 1,000 ppm CO for 3 h resulted in decreased protein levels and heme content of cytochrome *c* oxidase in heart mitochondria (Iheagwara et al., 2007, 193861). CO-mediated heme release was also seen in a study by Cronje et al. (2004, 180440) and was followed by increased endogenous CO production through the activation of HO-2 and the induction of HO-1. Loss of heme from proteins leads to loss of protein function and often to protein degradation.

Disruption of Iron Homeostasis

Exposure of rats to 50 ppm CO for 24 h increased levels of iron and ferritin in the bronchoalveolar lavage fluid (BALF), decreased lung non-heme iron and increased liver non-heme iron (Ghio et al., 2008, 096321). Furthermore in this same study, exposure of cultured human respiratory epithelial cells to 10-100 ppm CO for 24 h caused a dose-dependent decrease in cellular non-heme iron and ferritin. Heme loss, which was observed in other studies (Cronje et al., 2004, 180440; Iheagwara et al., 2007, 193861), may also contribute to disruption of iron homeostasis. Iron homeostasis is critical for the sequestration of free iron and the prevention of iron-mediated redox cycling which leads to ROS generation and lipid peroxidation.

Alteration in Cellular Redox Status

Recent studies demonstrated that exposure to low, moderate, and high levels of CO increased cellular oxidative stress in cultured cells (Kim et al., 2008, 193961; Zuckerbraun et al., 2007, 193884). A dose-dependent increase in dichlorofluorescein (DCF) fluorescence (an indicator of ROS) occurred following 1-h exposure to 50-500 ppm CO in macrophages and following 1-h exposure to 250 ppm CO in hepatocytes. NOS inhibition had no effect on the increase in DCF fluorescence in CO-treated macrophages, indicating that the effects were not due to an interaction of CO and NO (Zuckerbraun et al., 2007, 193884). Mitochondria were identified as the source of the increased ROS since mitochondria-impaired cells (rho zero cells and treatment with antimycin A) did not respond to CO with an increase in DCF fluorescence. Furthermore, 1-h exposure to 250 ppm CO inhibited mitochondrial cytochrome *c* oxidase enzymatic activity in macrophages (Zuckerbraun et al., 2007, 193884). Recently, inhibition of cytochrome *c* oxidase was demonstrated in HEK-293 cells transfected with HO-1 and in macrophages with induced HO-1; this effect was attributed to

endogenously produced CO (D'Amico et al., 2006, 193992). In hepatocytes, exposure to 250 ppm CO for 1 h resulted in Akt phosphorylation and nuclear translocation of nuclear factor kappa B (NF-κB), effects which were blocked by antioxidants (Kim et al., 2008, 193961). Significant increases in apoptosis were also observed in this model. Thus in this study, CO exposure led to uncoupled mitochondrial respiration and ROS-induced programmed cell death.

Further evidence for cellular redox stress is provided by studies in which glutathione stores were altered following CO exposure in vitro (Kim et al., 2008, 193961; Patel et al., 2003, 043155). In addition, mitochondrial redox stress was observed in livers of rats exposed to 50 ppm CO (Piantadosi et al., 2006, 180424). Furthermore, an adaptive increase in intracellular antioxidant defenses (i.e., superoxide dismutase) was observed in endothelial cells exposed to 10 ppm CO for 40 min (Thom et al., 2000, 011574), and mitochondrial biogenesis was observed in hearts of mice exposed to 250 ppm CO for 1 h (Suliman et al., 2007, 193768).

Several mechanisms could contribute to the cellular redox stress elicited by CO exposure. First, inhibition of cytochrome *c* oxidase could result in increased mitochondrial superoxide generation. Secondly, interactions of CO with heme proteins could lead to the release of heme and free iron and subsequently to the generation of ROS. As mentioned above, increased ROS generation has been linked to cellular injury and death, inflammation, and endothelial dysfunction.

Two of the above-mentioned studies demonstrated that CO-mediated mechanisms were unrelated to hypoxia by showing that hypoxic conditions failed to mimic the results obtained with CO. Hence, the mitochondrial redox stress and mitochondrial pore transition observed in livers from rats exposed to CO (Piantadosi et al., 2006, 180424) and the cardiac mitochondrial biogenesis observed in mice exposed to CO (Suliman et al., 2007, 193768) were attributed specifically to nonhypoxic mechanisms of CO.

Alteration in Ion Channel Activity

Work by Dubuis et al. (Dubuis et al., 2002, 193911) demonstrated increased current through Ca^{2+}-activated K^{+} channels in smooth muscle cells from pulmonary arteries of rats exposed to 530 ppm CO for 3 wk. These findings provide further evidence for non-cGMP-dependent vasodilatory actions of CO.

Modulation of Protein Kinase Pathways

Endogenously produced CO is a gaseous second messenger molecule in the cell. Work from numerous laboratories has demonstrated the potential for CO to be used as a therapeutic gas with numerous possible clinical applications since it can produce anti-inflammatory, anti-apoptotic, and anti-proliferative effects (Durante et al., 2006, 193778; Ryter et al., 2006, 193765). These studies generally involved pretreatment with CO followed by exposure to another agent 12-24 h later. There is extensive literature on this topic as reviewed by Ryter et al. (2006, 193765), Durante et al. (2006, 193778) and others. A number of these processes are mediated through cGMP while others involve redox-sensitive kinase pathways, possibly secondary to CO-dependent generation of ROS. For example, 250 ppm CO inhibited growth of airway smooth muscle cells by attenuating the activation of the extracellular signal-regulated kinase 1/2 (ERK 1/2) pathway, independent of sGC and other MAP kinases (Song et al., 2002, 037531). A second example is provided by the study of Kim et al. (2005, 193959) where 250 ppm CO inhibited PDGF- induced smooth muscle cell proliferation by upregulating $p21^{Waf1/Cip1}$ and caveolin-1, and down-regulating cyclin A expression. In this case, effects were dependent upon cGMP and the p38 MAPK pathway (Kim et al., 2005, 193959). Thirdly, rat endothelial cells exposed to 15 ppm CO escaped anoxia/reoxygenation-induced apoptosis via modulation of the signaling pathways involving phosphoinositide 3-kinase (PI3K), Akt, p38 MAP kinase, Signal Transducers and Activators of Transcription (STAT-1) and STAT-3 (Zhang et al., 2005, 184460). In a fourth study, Akt was found to be responsible for the CO-induced activation of NF-κB, protecting against hepatocyte cell death (Kim et al., 2008, 193961). While research focusing on therapeutic applications of CO generally involves high-level short-term exposure to CO (i.e., 250-1,000 ppm for up to 24 h), some studies found effects below 20 ppm (Zhang et al., 2005, 184460). Few if any studies on the therapeutic effects of CO have explored the dose-response relationship

between CO and pathway activation/deactivation, so it remains unclear how these effects may be related to environmentally-relevant exposures.

Concentration-Response Relationships

In many cases, the concentrations of exogenous CO required for these nonhypoxic effects were much higher (Alonso et al., 2003, 193882; Favory et al., 2006, 184462; Iheagwara et al., 2007, 193861; Thorup et al., 1999, 193782) than concentrations of CO in ambient air. However, in some studies the effects were mimicked by upregulation of HO-1 which would result in increased local production of CO as well as of iron and biliverdin (D'Amico et al., 2006, 193992; Imai et al., 2001, 193864; Thorup et al., 1999, 193782). For example, HO-1 upregulation or overexpression attenuated carbachol-mediated NO release and NO-mediated vasodilation, similar to the effects of exogenous CO in these same models (Imai et al., 2001, 193864; Thorup et al., 1999, 193782). In the study by D'Amico et al. (2006, 193992), overexpression of HO-1 in cells inhibited cellular respiration by 12% and decreased cytochrome c oxidase activity by 23%. It is not clear how comparable these conditions involving increased intracellular concentrations of endogenous CO are to increased intracellular concentrations of CO resulting from exogenous CO exposures. Neither is it clear what concentrations of intracellular CO are generated locally within cells as a result of HO-catalyzed heme metabolism. However, a small amount of a relatively high local concentration of endogenous CO produced in a regulated manner by HO-1 and HO-2 may be sufficient to react with local targets (e.g., heme proteins), while a larger amount of exogenous CO may be required to reach the same targets. This may be due to indiscriminate reactions of exogenous CO with other target proteins or to other issues related to compartmentalization. It is conceivable that acute or chronic exposures to ambient CO could "sensitize" (or "desensitize") targets of endogenous cellular CO production, but there is no experimental evidence to support this mechanism.

There is a growing appreciation that nonhypoxic mechanisms may contribute to the effects associated with CO toxicity and poisoning (Ischiropoulos et al., 1996, 079491; Thom et al., 1994, 076459; Weaver et al., 2007, 193939). On the other hand, recent studies suggest that exogenous CO at lower concentrations may have beneficial anti-inflammatory, anti-proliferative and cytoprotective effects under certain circumstances (Durante et al., 2006, 193778; Ryter et al., 2006, 193765). Since the focus of this assessment is on mechanisms which are relevant to ambient exposures, it is important to understand which mechanisms may occur at "low" (50 ppm and less) and "moderate" (50-250 ppm CO) concentrations of CO. Hence, both recent animal studies and relevant older ones which add to the understanding of mechanisms in this range of CO concentrations are briefly summarized in Table 5-1. It should be noted that most of the above-mentioned nonhypoxic mechanisms were demonstrated at CO concentrations of 50 ppm and less.

Table 5-1. Responses to CO exposures at low and moderate concentrations.

Study	Model System	CO Exposure	Response	Notes
IN VITRO				
Alonso et al. (2003, 193882)	Human muscle mitochondria	50, 100, 500 ppm 5 min	Decreased cytochrome c oxidase activity	
Thom and Ischiropoulos (1997, 085644)	Rat platelets	10 ppm	Increased free NO	
Thom et al. (1997, 084337)	Bovine pulmonary artery endothelial cells	20 ppm 30-60 min	Increased free NO and peroxynitrite	Reported to correspond to 7% COHb
Thom et al. (2000, 011574)	Bovine pulmonary artery endothelial cells	10 ppm 40 min	Increased MnSOD and protection against toxic effects of 100 ppm CO	Adaptive responses
Song et al. (2002, 037531)	Human aortic smooth muscle cells	50-500 ppm 24 h	Inhibition of cellular proliferation	Blocked activation of ERK1/2 pathway, independent of sGC and other MAP kinases
Kim et al. (2005, 193959)	Rat pulmonary artery smooth muscle cells	250 ppm 1 h	Inhibited PDGF- induced smooth muscle cell proliferation	Upregulated $p21^{Waf1/Cip1}$ and caveolin-1, and down-regulated cyclin A expression.
Kim et al. (2008, 193961)	Rat hepatocytes	250 ppm 1 h 2x per day 250 ppm 1 h	Blocked spontaneous apoptosis Increased mitochondrial ROS generation, increased mitochondrial glutathione oxidation, and decreased cellular ascorbic acid	CO induced Akt phosphorylation via ROS production CO activated NFκB
Zhang et al. (2005, 184460)	Rat pulmonary artery endothelial cells	15 ppm 0.5-24 h	Blocked anoxia-reoxygenation mediated apoptosis	Modulation of PI3K/Akt/p38 MAP kinase and STAT-1 and STAT-3
Zuckerbraun et al. (2007, 193884)	Mouse macrophages	50 and 250 ppm 1 h	Increased ROS generation (dose dependent response for 50-500 ppm CO)	Mitochondrial derived ROS and cytochrome c oxidase inhibition demonstrated for 250 ppm
Ghio et al. (2008, 096321)	Human bronchial epithelial cells	10-100 ppm 24 h	Dose-dependent decrease in cellular non-heme iron (effect at 10 ppm was significant, effect at 50 ppm maximal) Dose-dependent decrease in cellular ferritin at 50-100 ppm 50 ppm blocked iron uptake by cells 50 ppm increased iron release from cells	Compare with in vivo experiments in same paper
IN VIVO				
Ghio et al. (2008, 096321)	Rats	50 ppm 24 h	Mild neutrophil accumulation in BALF Increased lavage MIP-2, protein, LDH Lavage iron and ferritin were increased by CO Lung non-heme iron was decreased by CO Liver non-heme iron was increased by CO	Compare with in vitro experiments in same paper
Thom et al. (1999, 016753)	Rats	50 ppm 1 h 100 ppm 1 h	Increased nitrotyrosine in aorta Leukocyte sequestration in aorta after 18 h Albumin efflux from skeletal muscle microvasculature 3 h after CO LDL oxidation	Effects blocked by NOS inhibitor
Thom et al. (1999, 016757)	Rats	100 ppm 1 h 50 ppm 1 h	Elevated free NO during CO exposure (EPR) Elevated nitrotyrosine in lung homogenates Lung capillary leakage 18 h after exposure	Inhibition of NOS abrogated CO effects
Sorhaug et al. (2006, 180414)	Rats	200 ppm 72 wk	No changes in lung morphology No pulmonary hypertension No atherosclerotic lesions in systemic vessels Ventricular hypertrophy	
Loennechen et al. (1999, 011549)	Rats	100 and 200 ppm 1-2 wk	Increased ET-1 mRNA in the heart ventricles, increased right and left ventricular weight	12 and 23% COHb
Favory et al. (2006, 184462)	Rats	250 ppm 90 min	Complex IV inhibition in myocardial fibers Inhibition of vasodilatory response to acetylcholine and SNP, Increased coronary perfusion pressure and contractility	11% COHb
Piantadosi et al. (2006, 180424)	Rats	50 ppm CO or hypobaric hypoxia for 1, 3, or 7 days	Liver mitochondrial oxidative and nitrosative stress, altered mitochondrial permeability pore transition sensitivity	CO effects not mimicked by hypobaric hypoxia
Suliman et al. (2007, 193768)	Mice	250 ppm 1 h	Cardiac mitochondrial biogenesis	Activation of GC involved. No role for NOS. Increased mitochondrial H_2O_2 and activation of Akt proposed
Wellenius et al. (2004, 087874)	Rats Model of MI	35 ppm 1 h	Decreased delayed ventricular beat frequency	Altered arrhythmogenesis
Wellenius et al. (2006, 156152)	Rats Model of MI	35 ppm 1 h	Decreased supraventricular ectopic beats	Altered arrhythmogenesis

Study	Model System	CO Exposure	Response	Notes
Carraway et al. (2002, 026018)	Rats Model of hypoxic pulmonary vascular remodeling	Hypobaric hypoxia ± 50 ppm CO 3 wk	CO promoted remodeling and increased pulmonary vascular resistance	
Gautier et al. (2007, 096471)	Rats Model of right ventricle hypertrophy secondary to chronic hypoxia	3 wk of hypobaric hypoxia with 50 ppm CO during last week	Rats with pulmonary hypertension were more sensitive to CO which altered the right ventricular adaptive response to pulmonary hypertension leading to ischemic lesions	
Melin et al. (2005, 193833)	Rats Model of right ventricle hypertrophy secondary to chronic hypoxia	50 ppm 10 wk	CO increased cardiac dilation and decreased left ventricular function	
Melin et al. (2002, 037502)	Rats Model of right ventricle hypertrophy secondary to chronic hypoxia	50 ppm 10 wk	CO increased right ventricular hypertrophy, decreased right ventricular diastolic function and increased left ventricular weights	

5.1.3.3. Implications of Nonhypoxic Mechanisms

A key issue in understanding the biological effects of environmentally-relevant exposures to CO is whether the resulting partial pressures of CO (pCO) in cells and tissues can initiate cell signaling which is normally mediated by endogenously generated CO or perturb signaling which is normally mediated by other signaling molecules such as NO.

Several aspects need to be considered. First of all, during a period of exogenous CO uptake, Hb acts as a buffer for most cells and tissues by limiting the availability of free CO. Nevertheless, COHb delivers CO to cells and tissues. This delivery involves CO's dissociation from Hb followed by its diffusion down a pCO gradient. Hence, greater release of CO from COHb will occur under conditions of low cell/tissue pCO. Conversely, higher cell/tissue pCO in cells/tissues than in the blood will lead to the egress of CO from cells/tissues.

A second consideration is the role played by O_2 in competing with CO for binding to intracellular heme protein targets. In general, heme proteins (e.g., cytochrome *c* oxidase) are more sensitive to CO when O_2 is limited. Hence, hypoxic conditions would be expected to enhance the effects of CO. This concept is demonstrated in the study by D'Amico et al. (2006, 193992). NO, which also competes with O_2 and CO for binding to heme proteins, may have a similar impact.

A third consideration is whether certain cell types serve as primary targets for the effects of CO. Besides the blood cells (including leukocytes and platelets), the first cells encountering CO following its dissociation from Hb are the endothelial cells which line blood vessels. An exception to this situation is in the lungs where epithelial and inflammatory cells found in airways and alveoli are exposed to free CO prior to CO binding to Hb. These lung cells may also serve as unique targets for CO. Processes such as pulmonary microvascular endothelial dysfunction, inflammatory cell activation, and respiratory epithelial injury may ensue as a result of preferential targeting of these cell types.

Since there is potential for exogenous CO to affect endogenous pools of CO, the concentrations of CO in cells and tissues before and after exogenous exposures are of great interest. Table 5-2 summarizes findings from four recent studies relevant to this issue. It should be noted that exposure to 50 ppm CO resulted in a three- to fivefold increase in tissue CO concentration.

Table 5-2. Tissue concentration of CO following inhalation exposure.

Study	CO Exposure	Tissue CO Concentrations	COHb	Notes
Cronje et al. (2004, 180440)	Rat 2,500 ppm 45 min	Blood: 27,500 (800) pmol/mg Heart: 800 (300) pmol/mg Muscle: 90 (80) pmol/mg Brain: 60 (40) pmol/mg Control levels in parentheses	66-72%	CO concentration increased in the heart but not in brain or skeletal muscle after CO exposure A later report stated that these tissue CO values were too high due to a computational error (Piantadosi et al., 2006, 180424)
Vreman et al. (2005, 193786)	Mice 500 ppm 30 min	Blood: 2648 ± 400 (45) pmol/mg Heart: 100 ± 18 (6) pmol/mg Muscle: 14 ± 1 (10) pmol/mg Brain: 18 ± 4 (2) pmol/mg Kidney: 120 ± 12 (7) pmol/mg Spleen: 229 ± 55 (6) pmol/mg Liver: 115 ± 31 (5) pmol/mg Lung: 250 ± 2 (3) pmol/mg Intestine: 9 ± (4) pmol/mg Testes: 6 ± 3 (2) pmol/mg Control levels in parentheses	28%	CO concentration relative to 100% blood: Lung: 9.4% Spleen: 8.6% Kidney: 4.5% Liver: 4.3% Heart: 3.8% Brain: 0.7% Muscle: 0.5% Intestine: 0.3%, Testes: 0.2%
Piantadosi et al. (2006, 180424)	Rats 50 ppm 1-7 days	Liver: 30-40 pmol/mg Control liver 10 pmol/mg	4-5% Control 1%	CO concentration reached a plateau after 1 day
Vreman et al. (2005, 193786)	Mice 50, 250 and 1,250 ppm 1 h	Heart (left ventricle) 50 ppm: 50 pmol/mg 250 ppm: 95 pmol/mg 1250 ppm: 160 pmol/mg Control heart: 9 pmol/mg		No mention of COHb% but exposures were similar to those in Cronje et al. (2004, 180440)

Data is expressed as pmol CO/mg tissue wet weight

Furthermore, endogenous CO production is known to be increased during inflammation, hypoxia, increased heme availability and other conditions of cellular stress where HO-1 or HO-2 activity is increased. A few studies reported cell and tissue concentrations of CO along with accompanying COHb levels resulting from enhanced endogenous CO production; Table 5-3 summarizes these findings. Additional measurements of CO levels in cells and tissues following increased endogenous production and following inhalation of exogenous CO may provide further insight into the relationship between the CO tissue concentration and biological responses.

Table 5-3. Tissue concentration of CO following increased endogenous production.

Study	Exposure	Tissue CO	COHb	Notes
Carraway et al. (2000, 021096)	Rats Hypobaric hypoxia for 21 days		1.5-2.8% Control 0.5%	COHb highest after days 1 and 21 at three- to fourfold higher than controls
Piantadosi et al. (2006, 180424)	Rats Hypobaric hypoxia 1-7 days	Liver: 5-12 pmol/mg Control liver 10 pmol/mg	1-1.25% Control 1%	CO concentration reached a plateau after 1 day
Vreman et al. (2005, 193786)	Mice 30 μM heme	Blood: 88 ± 10 (45) pmol/mg Heart: 14 ± 3 (6) pmol/mg Muscle: 7 ± 1 (10) pmol/mg Brain: 2 ± 0 (2) pmol/mg Kidney: 7 ± 2 (7) pmol/mg Spleen: 11 ± 1 (6) pmol/mg Liver: 8 ± 3 (5) pmol/mg Lung: 8 ± 3 (3) pmol/mg Intestine: 3 ± 1 (4) pmol/mg Testes: 2 ± 0 (2) pmol/mg Control levels in parentheses	0.9%	CO concentration relative to 100% blood: Heart: 16% Spleen: 13% Lung: 9% Liver: 9% Kidney: 8% Muscle: 8% Intestine: 3% Brain: 2% Testes: 2%

Data is expressed as pmol CO/mg tissue wet weight

It should be noted that increased cellular and tissue concentrations of biliverdin and iron accompany the increased endogenous production of CO by HO-1 and HO-2. Biliverdin and iron have known biological effects, with biliverdin exhibiting antioxidant properties and iron exhibiting pro-oxidant properties (Piantadosi et al., 2006, 180424), which could complicate interpretation of results from studies in which HO-1 and HO-2 activities are increased. In addition, indiscriminate reactions occurring in the case of exogenous CO would likely lead to less specific responses than those mediated by reactions of endogenously-produced CO with local targets. Hence, the situations of increased endogenous CO production and of exogenous CO exposure are not equivalent.

A further consideration is that in the numerous conditions and disease states where HO-1 is induced, increased levels of endogenously produced CO may represent an adaptive response to stress (Durante et al., 2006, 193778; Piantadosi, 2008, 180423). These increases and the accompanying increases in COHb generally fall in the range of 1.5- to 4-fold, with the exception of some situations of hemolytic anemia and hemoglobin disorders (see Figure 4-11 for results in humans). The resulting excess endogenous CO may react intracellularly with heme proteins or diffuse into the blood according to the gradient of pCO in the cell/tissue and blood compartments. In many cases, beneficial effects or compensatory mechanisms may result as a result of short-term induction of HO-1, as reviewed by Ryter et al. (2006, 193765) and Durante et al. (2006, 193778). Longer term increases in HO-1 are sometimes associated with protective responses, as in the case of atherosclerosis (Cheng et al., 2009, 193775; Durante et al., 2006, 193778), and sometimes with pathophysiologic responses as demonstrated in hypoxic pulmonary vascular remodeling (Carraway et al., 2002, 026018) and models of salt-sensitive hypertension (Johnson et al., 2003, 193868; Johnson et al., 2004, 193870) and metabolic syndrome (Johnson et al., 2006, 193874). Increased endogenous CO in hearts of individuals with ischemic heart disease and in lungs of individuals with various forms of inflammatory lung disease might also be expected (Scharte et al., 2006, 194115; Yamaya et al., 1998, 047525; Yasuda et al., 2005, 191953) (Figure 4-12). It is conceivable that prolonged increases in endogenous CO production in chronic disease states may result in less of a reserve capacity to handle additional intracellular CO resulting from exogenous exposures, but there is no experimental evidence to support this mechanism. Perhaps these circumstances lead to dysregulated functions or toxicity. Thus, CO may be responsible for a continuum of effects from cell signaling to adaptive responses to cellular injury (Piantadosi, 2008, 180423), depending on intracellular concentrations of CO, heme proteins and molecules which modulate CO binding to heme proteins.

5.1.3.4. Summary

CO is a ubiquitous cell signaling molecule with numerous physiological functions. The endogenous generation and release of CO from heme by HO-1 and HO-2 is tightly controlled, as is any homeostatic process. However, exogenously-applied CO has the capacity to disrupt multiple heme-based signaling pathways due to its nonspecific nature. Only a limited amount of information is available regarding the impact of exogenous CO on tissue and cellular levels of CO and on signaling pathways. However recent animal studies demonstrated increased tissue CO levels and biological responses following exposure to 50 ppm CO. Whether or not environmentally-relevant exposures to CO lead to adverse health effects through altered cell signaling is an open question for which there are no definitive answers at this time. However, experiments demonstrating oxidative/nitrosative stress, inflammation, mitochondrial alterations and endothelial dysfunction at concentrations of CO within one or two orders of magnitude higher than ambient concentrations suggest a potential role for such mechanisms in pathophysiologic responses. Furthermore, prolonged increases in endogenous CO resulting from chronic diseases may provide a basis for the enhanced sensitivity of susceptible populations to CO-mediated health effects such as is seen in individuals with coronary artery disease.

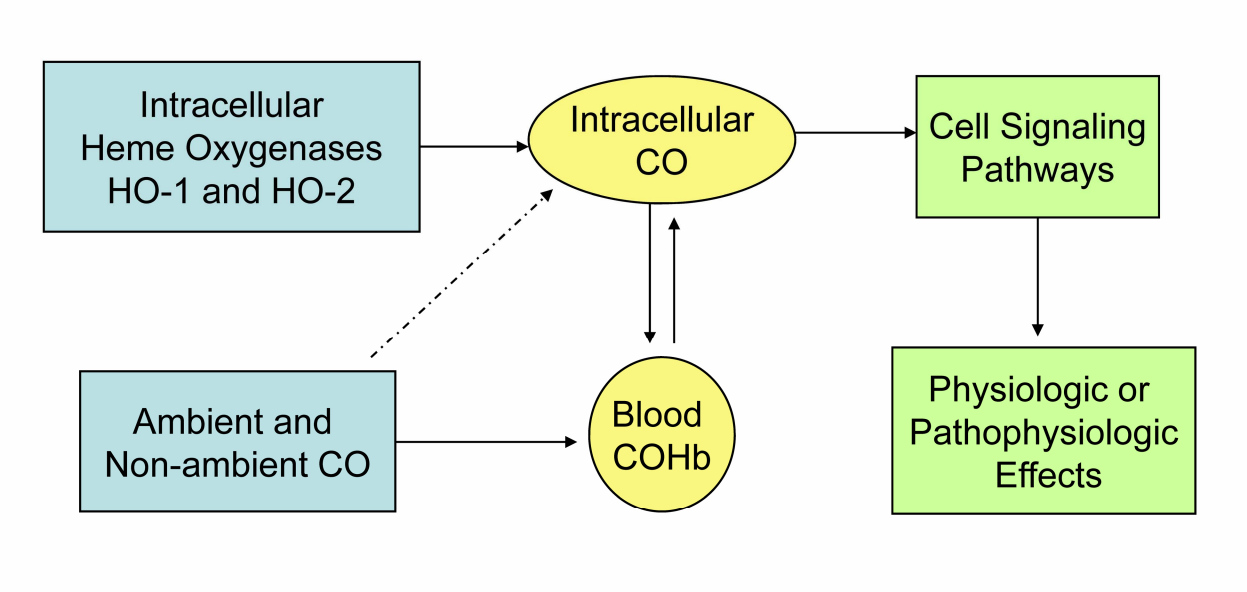


Figure 5-1. Direct effects of CO. The dashed line refers to uptake of inhaled CO by respiratory epithelial cells and resident macrophages in the lung. The uptake of CO by all other cells and tissues is dependent on COHb.

5.2. Cardiovascular Effects

5.2.1. Epidemiologic Studies with Short-Term Exposure

The 2000 CO AQCD (U.S. EPA, 2000, 000907) examined the association between short-term variations in ambient CO concentrations and cardiovascular morbidity. While the results presented by these studies did provide suggestive evidence of ambient CO levels being associated with exacerbation of heart disease, the AQCD determined that the evidence was inconclusive. The reasons

for this conclusion were given as: internal inconsistencies and lack of coherence of the reported results within and across studies; the degree to which average ambient CO levels derived from fixed-site monitors are representative of spatially heterogeneous ambient CO values or of personal exposures that often include nonambient CO; and the lack of biological plausibility for any harmful effects occurring with the very small changes in COHb levels (from near 0 up to 1.0%) over typical baseline levels (about 0.5%) that would be expected with the low average ambient CO concentrations reported in the epidemiologic studies (generally <5.0 ppm, 1-h daily max) (U.S. EPA, 2000, 000907). These reasons were also cited in the discussion of the effects of short-term exposure to CO on mortality and other types of morbidity. The AQCD posited that ambient CO concentrations used as exposure indices in epidemiologic studies may be surrogates for ambient air mixtures produced by combustion sources and/or other constituents of such mixtures. In addition, the AQCD noted that the epidemiologic evidence was stimulating increased scientific interest regarding ambient CO exposures as a potential risk factor for exacerbation of heart disease and other health effects, although the epidemiologic studies were subject to considerable biological and statistical uncertainty.

The following section reviews the literature since the 2000 CO AQCD, including numerous new studies on relevant cardiac endpoints and biomarkers and additional studies of daily hospital admissions for heart disease. New epidemiologic evidence addresses some of the aforementioned uncertainties, including consistency and coherence of results and the possibility that CO may be acting as a surrogate for other combustion-derived air pollutants.

5.2.1.1. Heart Rate and Heart Rate Variability

Heart rate variability (HRV) refers to the beat-to-beat alterations in the heart rate (HR) and is generally determined by analyses of time and frequency domains measured by electrocardiograms (ECG). The time domains often analyzed are (a) normal-to-normal (NN or RR) time interval between each QRS complex, (b) standard deviation of the normal-to-normal interval (SDNN), and (c) mean squared differences of successive difference normal-beat to normal-beat intervals (rMSSD). Shorter time domain variables results in lower HRV. The frequency domains often analyzed are (a) the ratio of low energy frequency (LF) to high energy frequency (HF), and (b) the proportion of interval differences of successive normal-beat intervals greater than 50 ms (PNN_{50}), reflecting autonomic balance. Decreased HRV is associated with a variety of adverse cardiac outcomes such as arrhythmia, myocardial infarction (MI), and heart failure (Deedwania et al., 2005, 195134; De Jong and Randall, 2005, 193996; Huikuri et al., 1999, 184464; Rajendra et al., 2006, 193787).

Three studies investigated the association between ambient air pollution, including CO, and HRV in Boston, MA and reported inconsistent results. The earlier of these studies recruited 21 active residents aged 53-87 yr and performed up to 12 ECG assessments on each subject over a period of 4 mo (summer 1997). Particles (PM_{10}, $PM_{2.5}$) and several gaseous pollutants (O_3, NO_2, and SO_2) were monitored at fixed sites (up to 4.8 mi from the study site), while CO was monitored 0.25 mi from each participant's residence. Lag periods for the preceding 1 h, 4 h, and 24 h before each subject's HRV assessment were analyzed, and results showed that only $PM_{2.5}$ and O_3 were associated with HRV parameters (Gold et al., 2000, 011432).

A similar study by the same group of researchers 2 yr later involved 28 older subjects (aged 61-89 yr) who were living at or near an apartment complex located on the same street as the Harvard School of Public Health. The subjects were seen once a week for up to 12 wk, and HRV parameters (SDNN, r-MSSD, PNN_{50}, LF/HF ratio) were measured for 30 min each session. Data for $PM_{2.5}$, BC, and CO were recorded at the Harvard School of Public Health (<1 km from the residence) while data for NO_2, O_3, and SO_2 were collected from government regulatory monitoring sites. There were moderate correlations between CO and $PM_{2.5}$ (r = 0.61) and between CO and NO_2 (r = 0.55) but not with SO_2 (r = 0.18) or O_3 (r = 0.21). Similarly, $PM_{2.5}$ was associated with HRV, whereas in contrast to the previous study, CO was associated[1] with a negative change in SDNN (% change: -13 [95% CI: -24.06 to -1.88]), r-MSSD (% change: -31.88 [95% CI: -38 to -7.5]), and PNN_{50} (% change: -46.25 [95% CI -103.95 to -9.38] per 0.5 ppm increase in 24-h avg CO concentration) (Schwartz et al., 2005, 074317).

[1] The effect estimates from epidemiologic studies have been standardized to a 1 ppm increase in ambient CO for 1-h max CO concentrations, 0.75 ppm for 8-h max CO concentrations, and 0.5 ppm for 24-h avg CO concentrations throughout this section (text, tables, and figures).

An additional Boston, MA study examined HRV parameters (SDNN, LF, HF, LF/HF ratio) among 603 persons from the Normative Aging Study, a longitudinal study that originally recruited 2,280 men in the greater Boston area during 1963. The cohort members were examined (November 2000-October 2003) and the ECG data were linked to air pollution data for $PM_{2.5}$, particle number concentration, BC, O_3, NO_2, SO_2, and CO. Lagged pollutant effects for a 4-h, 24-h, and 48-h ma were examined. The main pollutant effects were with $PM_{2.5}$ and O_3, while CO was not associated with HRV (Park et al., 2005, 057331).

A study in Mexico City selected 30 subjects from the outpatient clinic at the National Institute of Cardiology and followed them for ~10 h (starting at 9:00 a.m.) (Riojas-Rodriguez et al., 2006, 156913). Each subject was connected to a Holter ECG monitor (e.g., a portable ECG monitor) and also given personal $PM_{2.5}$ and CO monitors. The subjects went about their usual daily activities, and the personal $PM_{2.5}$ and CO data were linked to various ECG parameters (HR, R-R, LF, HF) at various lags. In copollutant models with $PM_{2.5}$, personal CO exposure for the same 5-min period was significantly associated with a decrease in LF and very low energy frequency (VLF) parameters with coefficients equal to -0.024 (95% CI: -0.041 to -0.007) and -0.034 (95% CI: -0.061 to -0.007), respectively, for a 1 ppm increase in 1-h CO concentration.

In an additional study conducted in Mexico City, 34 residents from a nursing home underwent HRV analysis every other day for 3 mo (Holguin et al., 2003, 057326). Exposure assessment for ambient $PM_{2.5}$ was based on data recorded at a monitor on the roof of the nursing home, while exposures to ambient O_3, NO_2, SO_2, and CO were derived from data recorded at a fixed site 3 km from the nursing home. Exposures for the same day and 1-day lags were analyzed, and only O_3 and $PM_{2.5}$ were positively associated with HRV.

Wheeler et al. (2006, 088453) examined 18 individuals with COPD and 12 individuals with recent MI living in Atlanta, GA. Morning ECG readings were collected by a Holter system by a field technician in the subjects' homes. Ambient air pollution exposures for $PM_{2.5}$, O_3, NO_2, SO_2 and CO were derived from data recorded at fixed sites throughout metropolitan Atlanta. Three exposure periods were analyzed: the hour of the ECG reading, 4-h mean, and 24-h mean before the reading. While positive effects were reported for NO_2 and $PM_{2.5}$, no quantitative results were reported for CO.

After reviewing 2,000 patient charts, Dales (2004, 099036) recruited 36 subjects with CAD from the Toronto Western Hospital's noninvasive cardiac diagnostic unit. HR and HRV (SDNN, N-N, HF, LF, HF/LH ratio) were assessed 1 day each week for up to 10 wk by a Holter monitoring system. Personal air sampling for $PM_{2.5}$ and CO was carried out for the same 24-h period while subjects went about their usual daily activities for that period. Stratified results showed that among those not on beta-receptor-blockers, personal CO exposure was positively associated with SDNN ($p = 0.02$). However, in the group taking beta blockers, there was a negative association ($p = 0.06$). Personal exposure to $PM_{2.5}$ was not associated with HRV.

Peters et al. (1999, 011554) examined HR among a sub-sample of the Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) study (n = 2,681) in Augsburg, Germany. Total suspended particles (TSP), SO_2, and CO data were collected from a single monitoring station located in the center of the city and linked to each subject to estimate exposures on the same day and 5 days prior. A 0.5 ppm change in 24-h CO concentration was associated with an increase in HR of approximately 1 beat per minute, whereas CO based on a 5-day exposure had no effect on HR.

Thirty-one subjects with CHF had their pulse rate recorded daily over a 2-mo period, and the correlation between pulse rate and air pollutants was examined (Goldberg et al., 2008, 180380). There was weak evidence for a decrease in pulse rate associated with the lag 1 SO_2 concentration after adjustment for personal and meteorological factors and no evidence for an effect associated with any of the other air pollutants (adjusted mean difference for CO: 0.245 [95% CI -0.209 to 0.700] lag 0-2).

Liao et al (2004, 056590) investigated men and women aged 45-64 yr from the Atherosclerosis Risk in Communities (ARIC) study (Washington County, MD; Forsyth County, NC; and selected suburbs of Minneapolis, MN). The sample sizes were 4,899, 5,431, 6,232, 4,390 and 6,784 for analyses involving PM_{10}, O_3, CO, NO_2, and SO_2, respectively. County-level exposure estimates for 24-h CO were calculated for 1, 2, and 3 days prior to clinical examination. A 0.5 ppm increase in 24-h CO concentration (at lag 1) was associated with an increase in HR (beats/minute) ($\beta = 0.357$, $p < 0.05$). CO was not significantly associated with changes in SDNN.

The Exposure and Risk Assessment for Fine and Ultrafine Particles in Ambient Air (ULTRA) study was carried out in three European cities: Amsterdam, The Netherlands; Erfurt, Germany; and

Helsinki, Finland; a panel of subjects with CAD was followed for 6 mo with biweekly clinical visits, which included an ECG reading to assess HRV (Timonen et al., 2006, 088747). The time-domain measures of HRV (SDNN and rMSSD) were analyzed along with frequency-domain measures, which included power spectrum densities for LF and HF. Exposures to ambient air pollution ($PM_{2.5}$, PM_{10}, NO_2, CO) were derived from data recorded at fixed-monitoring site networks within each city. Correlation coefficients for NO_2 and CO ranged from 0.32 to 0.86 in the three cities. CO was moderately correlated with PM_{10} in Helsinki (r = 0.40), with $PM_{2.5}$ in Amsterdam (r = 0.58), and more highly correlated with PM_{10} in Erfurt (r = 0.77). Various lag periods were examined, including lag 0 (24 h prior to the clinical visit) through a 0- to 2-day avg lag and a 0- to 4-day avg lag. In total there were 1,266 ECG recordings used in the final analyses. In the pooled analyses (e.g., across cities) a 0.5 ppm increase in 24-h CO concentration was associated with a decrease in LF/HF ratio at lag 1-day (β -16.4 [95% CI: -29.9 to -0.3]), and a decrease in SDNN and HF at lag 2-day (β -3.4 [95% CI: -6.1 to -0.4]; β= -17.6 [95% CI: -34.4 to -0.9], respectively). However, the same study reported no effect for CO on BP and HR (Ibald-Mulli et al., 2004, 087415).

A small panel study in Kuopio, Finland, which was designed as the pilot study for the ULTRA study, examined simultaneous ambulatory ECG and personally monitored CO readings among 6 male patients with CAD (Tarkiainen et al., 2003, 053625). The patients were asked to follow their usual daily activities, but data were recorded only three times with 1-wk intervals. The CO exposures were divided into low (≤ 2.7 ppm) and high (>2.7 ppm) and during the high CO exposure r-MSSD increased on average by 2.4 ms; however, there was no effect on RR or SDNN.

A study in Taiwan recruited 83 patients (aged 40-75 yr) from the National Taiwan University Hospital, Taipei, and conducted ambulatory ECG readings using a Holter system (Chan et al., 2005, 088988). Ambient air pollution exposures for PM_{10}, NO_2, SO_2, and CO were derived from 12 fixed-site monitoring stations across Taipei. Lag periods of 1 h to 8 h prior to the ECG reading were analyzed, and only NO_2 was associated with HRV parameters (SDNN and LF); CO was not associated with HRV.

Min et al. (2009, 199514) investigated the effects of CO on cardiac autonomic function by measuring HRV in patients with and without metabolic syndrome. Several criteria were used to classify metabolic syndrome, including waist circumference, triglycerides and cholesterol levels, blood pressure, and fasting glucose level. The group classified as having metabolic syndrome showed significant decreases in SDNN and HF, and those declines were significantly associated with CO exposure with a 1- to 2-day lag. Copollutant models with PM_{10} and NO_2 gave similar results.

In summary, few studies have examined the effect of CO on HR, and while two of the three studies reported a positive association, further research is warranted to corroborate the current results. Similarly, while a larger number of studies have examined the effect of CO on various HRV parameters, mixed results have been reported throughout these studies. Furthermore, with several HRV parameters often examined, there are mixed results across the studies as to the HRV parameters that are positively associated with CO exposure. Table 5-4 presents a summary of the reviewed studies. Due to the heterogeneity of endpoints (see column "cardiac endpoint" in Table 5-4), these studies do not lend themselves to a quantitative meta-analysis or inclusion in a summary figure.

Table 5-4. Summary of studies investigating the effect of CO exposure on HRV parameters.

Study	Location Sample Size	Cardiac Endpoint	Upper CO Concentrations from AQS[a] in ppm	CO Concentrations Reported by Study Authors in ppm	Copollutants
Gold et al. (2000, 011432)	Boston, MA (n = 21)	HR, SDNN, r-MSSD	98th%: 0.80-2.48 99th%: 0.89-2.57 (24 h)t	Mean: 0.47(24 h) Range: 0.12-0.82	PM_{10}, $PM_{2.5}$, O_3, NO_2, SO_2
Schwartz et al. (2005, 074317)	Boston, MA (n = 28)	SDNN, r-MSSD, PNN, LF/HF	98th%: 0.95-2.14 99th%: 0.96-2.60 (24 h)	25th, 50th, 75th percentiles: 0.38, 0.45, 0.54	$PM_{2.5}$, BC, NO_2, O_3
Park et al. (2005, 057331)	Boston, MA (n = 4 97)	SDNN, LF, HF, LF/HF	98th%: 0.92-1.45 99th%: 0.99-1.66 (24 h)	Mean: 0.50 (24 h) Range: 0.13-1.8	$PM_{2.5}$, BC, O_3, NO_2, SO_2
Riojas-Rodriguez et al. (2006, 156913)	Mexico City, Mexico (n = 30)	HF, LF, VLF, HR, R-R	NA	Mean: 2.9 (11 h) Range: 0.1-18	$PM_{2.5}$
Holguin et al. (2003, 057326)	Mexico City, Mexico (n = 34)	HF,LF, LF/HF	NA	Mean: 3.3(24 h) Range: 1.8-4.8	$PM_{2.5}$, O_3, NO_2, SO_2
Wheeler et al. (2006, 088453)	Atlanta, GA (n = 30)	SDNN, r-MSSD, PNN, LF, HF, LF/HF	98th%: 2.8-3.1 99th%: 2.9-3.8 (8 h)	Mean: 362 ppb (4h) 25th, 50th, 75th percentiles: 221.5, 304.3, 398.1	$PM_{2.5}$, O_3, NO_2, SO_2
Dales (2004, 099036)	Toronto, Canada (n = 36)	SDNN, HF, LF, LF/HF, N-N	NA	Mean: 2.4[b] Range: 0.4-16.5	$PM_{2.5}$
Peters et al. (1999, 011554)	Augsburg, Germany (n = 2681)	HR	NA	Mean: 3.6 Range: 1.5-7.1	TSP, SO_2
Goldberg et al. (2008, 180380)	Montreal, Canada (n-31)	Pulse rate	NA	NR; IQR: 1.8 ppm	NO_2, O_3, SO_2, $PM_{2.5}$
Liao et al. (2004, 056590)	Maryland, North Carolina, Minnesota, (n = 4899-6784)	HR, SDNN, LF, HF	98th%: 0.39-2.29 99th%: 0.43-2.66 (24 h)	Mean: 0.65 (24 h)	PM_{10}, O_3, NO_2, SO_2
Timonen et al. (2006, 088747)	Amsterdam, The Netherlands; Erfurt, Germany; Helsinki, Finland (n = 131)	SDNN, HF, LF/HF	NA	Mean: 0.35-0.52 Range: 0.09-2.17	$PM_{2.5}$, PM_{10}, NO_2
Ibald-Mulli et al. (2004, 087415)	Amsterdam, The Netherlands; Erfurt, Germany; Helsinki, Finland (n = 131)	BP, HR	NA	Mean: 0.35-0.52 Range: 0.09-2.17	UFP, PM_{10}, $PM_{2.5}$, NO_2, SO_2
Tarkiainen et al. (2003, 053625)	Kuopio, Finland (n = 6)	PNN, SDNN, r-MSSD	NA	Mean: 4.6 Range: 0.5-27.4	None
Chan et al. (2005, 088988)	Taipei, Taiwan (n = 83)	SDNN, r-MSSD, LF	NA	Mean: 1.1 Range: 0.1-7.7	PM_{10}, NO_2, SO_2
Min et al. (2009, 199514)	South Korea (n=986)	SDNN, HF, LF	NA	Mean: 0.45 Range: 0.10-7.20	PM_{10}, NO_2, SO_2

NA: Not Available
[a] Includes range across individual monitors in study site; AQS data available for U.S. studies only
[b] 95th percentile of 24-h levels

5.2.1.2. ECG Abnormalities Indicating Ischemia

The ST-segment of an ECG represents the period of slow repolarization of the ventricles and ST-segment depression can be associated with adverse cardiac outcomes, including ischemia. Gold et al. (2005, 087558) recruited a panel of 28 older adults living at or near an apartment complex located within 0.5 km of a monitoring site in Boston, MA. Each subject underwent weekly ECGs for 12 wk in summer 1999 with the main outcome of interest being the ST-segment. Air pollution data in the form of $PM_{2.5}$, BC, and CO were collected from a central site within 0.5 km of the residences of the subjects and averaged over various lag periods (1- to 24-h, 12-h, and 24-h ma) before the ECG. The final analyses included 24 subjects with 269 observations, and results showed consistent negative associations of ST-segment change with increased BC with the strongest association with the 5-h lag. CO during the same lag period also showed a negative association with ST-segment change; however, only BC remained significant in multipollutant models.

The most recent study by this group of researchers utilized a repeated-measures study to investigate the associations between ambient air pollution and ST-segment level changes averaged over 30-min periods in patients with coronary artery disease (CAD) (Chuang et al., 2008, 155731).

The authors reported that increases in mean $PM_{2.5}$, BC, NO_2 and SO_2 concentrations predicted depression of 30-min averaged ST-segment levels. No association of ST-segment depression was observed with CO or O_3.

5.2.1.3. Arrhythmia

Cardiac arrhythmia refers to a broad group of conditions where there is irregular electrical activity in the heart. The main types of arrhythmias are fibrillation, tachycardia, and bradycardia, all resulting from dysfunction of the upper (atria) and lower (ventricle) chambers of the heart. Briefly, fibrillation refers to when a chamber of the heart quivers chaotically rather than pumps in an orderly fashion, tachycardia refers to a rapid heart beat (e.g., >100 beats/min), while bradycardia refers to a slow heart beat (e.g., <60 beats/min). A few air pollution panel studies have examined the occurrence of cardiac arrhythmias by analyzing data recorded by implantable cardioverter defibrillators (ICDs) among cardiac patients. The majority of these studies were conducted in North America, with the main outcome investigated being tachycardia. Results of these studies provide little evidence for an association between cardiac arrhythmia and ambient CO.

For example, Dockery and colleagues (2005, 078995) analyzed the relationship between ambient air pollution and the daily incidence of ventricular tachyarrhythmia among 203 patients with ICDs in Boston, MA. An hourly city average for the Boston metropolitan area was calculated for CO, O_3, NO_2, SO_2, SO_4^{2-}, BC, and $PM_{2.5}$. Although positive associations between ventricular arrhythmic episode days were found for all mean pollutant levels on the same day and previous days, none of these associations approached statistical significance. However, when the analyses were stratified by patients who had a previous incidence of ventricular arrhythmia within 3 days or greater than 3 days to the day of interest, a 0.5 ppm increase in 24-h CO concentration was positively associated with incidence of ventricular arrhythmia (OR: 1.68 [95% CI: 1.18-2.41]) among those who had a ventricular arrhythmia within the last 3 days.

A similar study in eastern Massachusetts examined cardiac arrhythmia by analyzing defibrillator discharges precipitated by either ventricular tachycardia or fibrillation among 100 cardiac patients (Peters et al., 2000, 011347). Exposure to ambient CO was estimated for the same day, 1-day, 2-day, 3-day, and a 5-day mean lag period. CO was moderately correlated with PM_{10} ($r = 0.51$) and $PM_{2.5}$ ($r = 0.56$) and more highly correlated with NO_2 ($r = 0.71$). When analyzing patients who had at least one defibrillator discharge ($n = 33$), there was no association with CO. However, when analyzing patients who had at least 10 discharges ($n = 6$), a 0.5 ppm increase in 24-h CO concentration (lag 0-4) was associated with an increased odds of a defibrillator discharge (OR: 1.66 [95% CI: 1.01-2.76]).

In contrast, other air pollution panel studies conducted in St Louis, MO (among 56 subjects) (Rich et al., 2006, 089814), Atlanta, GA (among 518 subjects) (Metzger et al., 2007, 092856), Boston, MA (among 203 subjects) (Rich et al., 2005, 079620), and Vancouver, Canada (Rich et al., 2004, 055631; Vedal et al., 2004, 055630) (among 34 and 50 subjects respectively) did not find an association between short-term changes in ambient CO and occurrence of cardiac arrhythmia in patients with implantable defibrillators. The study in Boston also examined atrial fibrillation episodes among the same group of subjects and did not find an association with ambient CO (Rich et al., 2005, 079620).

An alternative method used to assess the relationship between cardiac arrhythmia and ambient air pollution is to analyze cardiac data recorded via ECG. Two studies have employed this method and reported inconsistent results. A study in Steubenville, OH, which is located in an industrial area, examined weekly ECG data among 32 nonsmoking older adults for 24 wk during summer and fall (Sarnat et al., 2006, 090489). Ambient exposures for up to 5 days prior to the health assessment (based on a 5-day ma) were calculated for $PM_{2.5}$, SO_4^{2-}, elemental carbon (EC), O_3, NO_2, SO_2, and CO from data recorded at one central monitoring site. Increases in ambient CO were not associated with increased odds of having at least one arrhythmia during the study period.

In contrast, a study in Germany examined the relationship between ambient air pollution and the occurrence of supraventricular (atria) and ventricular tachycardia recorded via monthly 24-h ECGs among 57 subjects over a 6-mo period (Berger et al., 2006, 098702). Exposure estimates were calculated for ambient ultrafine particles, $PM_{2.5}$, CO, NO, NO_2, and SO_2 for various lag periods (0-23 h, 24-47 h, 48-71 h, 72-95 h, and 5-day avg) prior to the ECG. Results showed that a 0.5 ppm increase in ambient 24-h CO concentration (lag 0-4 days prior to ECG) was positively associated

with the occurrence of supraventricular tachycardia (OR: 1.36 [95% CI: 1.08-1.74]). However, ambient CO was not associated with ventricular tachycardia.

In summary, the studies that have examined associations between CO and the occurrence of cardiac arrhythmias provided little evidence of a CO effect on cardiac arrhythmias. While most studies analyzed data from ICDs, very few reported significant associations, which is similar to the studies that analyzed ECG data to evaluate cardiac arrhythmias in association with CO exposures. Table 5-5 summarizes the reviewed studies.

Table 5-5. Summary of studies investigating the effect of CO exposure on cardiac arrhythmias.

Study	Location, Sample Size	Cardiac Endpoint	Upper CO Concentrations from AQS[a] in ppm	CO Concentrations Reported by Study Authors in ppm	Copollutants
ARRHYTHMIAS (AMONG PATIENTS WITH ICDS)					
Dockery et al. (2005, 078995)	Boston, MA (n = 203)	Ventricular tachycardia	98th%: 0.89-2.33 99th%: 0.99-2.55 (24 h)	25th, 50th, 75th, 95th, percentiles: 0.53, 0.80, 1.02, 1.37 (2-day)	$PM_{2.5}$, BC, O_3, NO_2, SO_2, SO_4^{2-}
Peters et al. (2000, 011347)	Massachusetts, US (n = 100)	Ventricular fibrillation or tachycardia	98th%: 1.60-2.58 99th%: 1.75-2.71 (24 h)	Mean: 0.58 (24 h) Max: 1.66	$PM_{2.5}$, PM_{10}, BC, O_3, NO_2, SO_2, SO_4^{2-}
Rich et al. (2006, 089814)	Boston, MA (n = 56)	Ventricular arrhythmia	98th%: 0.89-2.33 99th%: 0.99-2.55 (24 h)	25th, 50th, 75th percentiles: 0.4, 0.5, 0.6 (24 h)	$PM_{2.5}$, EC, O_3, NO_2, SO_2
Metzger et al. (2007, 092856)	Atlanta, GA (n = 518)	Ventricular tachycardia	98th%: 5.0 99th%: 5.6 (1 h)	Mean: 1.7 (1 h) Range: 0.1-7.7	PM_{10}, $PM_{2.5}$, O_3, NO_2, SO_2
Rich et al. (2005, 079620)	Boston, MA (n = 203)	Atrial fibrillation	98th%: 0.89-2.33 99th%: 0.99-2.55 (24 h)	25th, 50th, 75th, 95th, percentiles: 0.53, 0.80, 1.02, 1.37 (2-day)	$PM_{2.5}$, BC, O_3, NO_2, SO_2
Rich et al. (2004, 055631)	Vancouver, Canada (n = 34)	ICD discharge due to arrhythmia	NA	Mean: 0.55 (24 h) IQR: 0.16	$PM_{2.5}$, PM_{10}, EC, O_3, NO_2, SO_2, SO_4^{2-}
Vedal et al. (2004, 055630)	Vancouver, Can (n = 50)	ICD discharge due to arrhythmia	NA	Mean: 0.6 (24 h) Range: 0.3-1.6	PM_{10}, O_3, NO_2, SO_2
ARRHYTHMIAS (VIA ECG)					
Sarnat et al. (2006, 090489)	Steubenville, OH (n = 32)	Atrial or ventricular tachycardia	98th%: 1.42 99th%: 1.81 (24 h)	Mean: 0.2 (24 h) Range: 0.1, 1.5	$PM_{2.5}$, O_3, NO_2, SO_2, SO_4^{2-}, EC
Berger et al. (2006, 098702)	Erfurt, Germany (n = 57)	Atrial or ventricular tachycardia	NA	Mean: 0.45 (24 h) Min, Med, Max 0.10, 0.38, 1.68	PM_{10}, $PM_{2.5}$, NO_2, NO, SO_2, UF

NA: Not Available

[a] Includes range across individual monitors in study site; AQS data available for U.S. studies only.

5.2.1.4. Cardiac Arrest

Cardiac arrest refers to the abrupt loss of heart function due to failure of the heart to contract effectively during systole, which can lead to sudden cardiac death if not treated immediately. Very

few studies have investigated the association between ambient CO exposure and the risk of cardiac arrest, and none reported a significant association between increased CO exposure and the occurrence of cardiac arrest.

Two studies (Levy et al., 2001, 017171; Sullivan et al., 2003, 043156) were evaluated that examined the association between ambient CO and cardiac arrest. Both studies were conducted in Seattle, WA, using a case-crossover study design and found no association between short-term exposure to CO and cardiac arrest.

These studies examined air pollution exposures for black smoke particles (BSP), PM_{10}, SO_2, and CO. The correlation coefficient for PM_{10} and CO was 0.8 in both studies. The first of these studies examined paramedic-attended out-of-hospital primary cardiac arrests among 362 cases (1998-1994) in Seattle and King County, WA, whereby lags of 0-5 days were analyzed (Levy et al., 2001, 017171). There was no indication of association between CO and out-of-hospital primary cardiac arrest (RR 0.99 [95% CI: 0.83-1.18]). The second of these studies examined out-of-hospital primary cardiac arrest for a 10-yr period (1985-1994) among subjects within a health organization database (the Group Health Cooperative of Puget Sound), whereby 0- through 2-day lags were analyzed (Sullivan et al., 2003, 043156). The relative risk of primary cardiac arrest was 0.95 (95% CI: 0.85-1.05; lag 0).

5.2.1.5. Myocardial Infarction

As previously stated, MI is commonly referred to as "heart attack" and is another cardiac outcome that has received limited attention within the area of air pollution research. Only one study has investigated the association between short-term changes in ambient CO and the onset of MI. Peters and colleagues (2001, 016546) employed a case-crossover study design to analyze short_term exposures (0-5 h and 0-5 days before the onset of MI) to particles (PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, BC) and gases (CO, O_3, NO_2, SO_2) among 772 patients with MI in the greater Boston area. While all pollutants showed positive associations with the onset of MI, only $PM_{2.5}$ reached statistical significance with the main exposure period (2 h before the onset) (OR for CO: 1.22 [95% CI: 0.89-1.67]).

5.2.1.6. Blood Pressure

Only two studies have investigated whether short-term exposure to CO influences BP. The earlier of these two studies examined BP among 2,607 men and women aged 25-64 yr who participated in the Augsburg, Germany, MONICA study (Ibald-Mulli et al., 2001, 016030). Exposures to ambient TSP, SO_2 and CO (from one monitor in the center of the city) during the same day as the BP reading and an average over the 5 days prior were examined. Results showed that ambient CO had no association with BP.

Similarly, the second of these studies extracted baseline and repeated measures of cardiac rehabilitation data from a Boston, MA, hospital for 62 subjects with 631 visits and analyzed ambient air pollution exposures (with particular focus on $PM_{2.5}$) averaged over various periods up to 5 days before the visit (Zanobetti et al., 2004, 087489). While results showed significant associations between increased BP and ambient $PM_{2.5}$, SO_2, O_3, and BC, there was no significant effect for CO (results not presented quantitatively).

5.2.1.7. Vasomotor Function

Gaseous pollutants, including SO_2, NO and CO, were found to affect large artery endothelial function among 40 healthy white male nonsmokers in Paris, France, whereas PM was found to exaggerate the dilatory response of small arteries to ischemia (Briet et al., 2007, 093049). Changes in amplitude of flow-mediated dilatation were highly dependent on changes in 5-day lag concentrations of SO_2, NO and CO, but not NO_2, $PM_{2.5}$ or PM_{10}. The effect attributed to CO (β coefficient: -0.68 [95% CI: -1.22 to -0.15]) was the smallest in magnitude when compared to those for SO_2 and NO, but overall the effect estimates were similar and all were statistically significant. Similarly, $PM_{2.5}$, PM_{10}, NO_2 and CO were positively correlated with small artery reactive hyperemia, and the effect attributed to CO was the smallest in magnitude when compared to those for $PM_{2.5}$, PM_{10}, and NO_2; but overall, the effect estimates were similar and all were statistically significant.

5.2.1.8. Blood Markers of Coagulation and Inflammation

Several studies have investigated the association between ambient CO and various blood markers related to coagulation and inflammation. The main endpoints analyzed have been plasma fibrinogen, B-type natriuretic peptide (BNP), endothelial function, Factor VII, C-reactive protein (CRP), prothrombin, intercellular adhesion molecule (ICAM-1), and white blood cell count (WBC).

Delfino et al. (2008, 156390) measured blood plasma biomarkers in a panel of 29 nonsmoking, elderly subjects with a history of CAD living in retirement communities in the Los Angeles, CA, air basin, in order to identify associations with systemic inflammation. The blood plasma biomarkers included CRP, fibrinogen, tumor necrosis factor-α (TNF- α) and its soluble receptor-II (sTNF-RII), interleukin-6 (IL-6) and its soluble receptor (IL-6sR), fibrin D-dimer, soluble platelet selectin (sP-selectin), soluble vascular cell adhesion molecule-1 (sVCAM-1), soluble ICAM-1, and myeloperoxidase (MPO). Overall, there were statistically significant associations for many of the biomarker and pollutant combinations, with some of the strongest effects for CRP, IL-6 and sTNF-RII with indoor and outdoor concentrations of NO_2 and CO. Only the outdoor concentrations indicated an effect of PM for these three biomarkers of inflammation. There was weak evidence for an effect of outdoor and indoor CO on the biomarker of platelet activation (sP-selectin), and for an effect of many of the air pollutants examined on fibrinogen, TNF- α, sVCAM-1, sICAM-1, and MPO. Parameter estimates for fibrin D-dimer were close to zero for most models. Overall, the results suggest that traffic related pollutants, including $PM_{2.5}$, UFPs, OC and CO, lead to increases in systemic inflammation and platelet activation in elderly people with a history of CAD.

Delfino et al. (2009, 200844) added a second year of data from 31 additional subjects to data used in their previous analysis of 29 subjects (Delfino et al., 2008, 156390). This updated panel study of 60 elderly individuals with CAD investigated the relationship of air pollutants to changes in circulating biomarkers of inflammation, platelet activation and antioxidant capacity. The updated analysis focused on the biomarkers that were most informative in the previous analysis (Delfino et al., 2008, 156390) and included IL-6, TNF-α, sTNF-RII, CRP, and sP-selectin. Additionally, frozen-thawed erythrocyte lysates were assayed spectrophotometrically for activities of two antioxidant enzymes, glutathione peroxidase-1 (GPx-1) and copper-zinc superoxide dismutase (Cu,Zn-SOD). Hourly outdoor home-air pollutants were measured over 9 days before each blood draw. There was evidence for an association of CO with IL-6, P-selectin, TNF-RII and CRP, but not for TNF- α, Cu,Zn-SOD, or GPx-1. Many positive associations were found for IL-6, sP-selectin, sTNF-RII, TNF- α, and CRP with markers of traffic-related air pollution (EC, OC, BC, NO_X, and CO), confirming the earlier finding that traffic related pollutants may lead to increases in systemic inflammation and platelet activation in elderly people with a history of CAD.

Circulating levels of BNP are directly associated with cardiac hemodynamics and symptom severity in patients with heart failure and serve as a marker of functional status. Wellenius et al. (2007, 092830) examined the association between BNP levels and short-term changes in ambient air pollution levels among 28 patients with chronic stable heart failure and impaired systolic function. The authors reported no association between CO along with the other pollutants examined and measures of BNP at any lag.

Pekkanen et al. (2000, 013250) examined the association between daily concentrations of air pollution and concentrations of plasma fibrinogen measured among 4,982 male and 2,223 female office workers in Whitehall, London, U.K., between September 1991 and May 1993. Plasma fibrinogen data were linked to ambient exposure to BS, PM_{10}, O_3, NO_2, SO_2, and CO, where the exposures were derived from data recorded at 5 fixed sites across London. There was a high correlation between levels of CO and NO_2 ($r = 0.81$) and more moderate correlations of CO with PM_{10} ($r = 0.57$) and SO_2 ($r = 0.61$). The pollution data on the same day when the blood sampling was done (lag 0) and on the 3 previous days (lags 1-3) were analyzed. Results showed that ambient CO at all lags was associated with an increase in plasma fibrinogen. Results were similar for NO_2, while all other pollutants were not associated with an increase in plasma fibrinogen.

Liao et al. (2005, 088677) examined associations between various air pollutants and hemostatic and inflammatory markers (fibrinogen, factor VIII-C, von Willebrand factor, serum albumin, WBC) among 10,208 middle-aged males and females from the ARIC study. Exposure estimates for ambient PM_{10}, NO_2, SO_2, O_3 and CO were calculated for days 1-3 prior to the blood sampling. A 0.5 ppm increment in 24-h CO concentration was significantly associated with 0.015 g/dL decrease in serum albumin among persons with a history of cardiovascular disease (CVD). CO was not associated with other hemostatic or inflammatory factors.

In Israel, Steinvil et al. (2008, 188893) examined WBC, fibrinogen, and CRP among 3,659 study subjects enrolled in the Tel-Aviv Sourasky Medical Center inflammation survey, in which subjects lived <11 km from an ambient air pollution monitor. Air pollution data in the form of PM_{10}, NO_2, SO_2, O_3, and CO were derived from data recorded at fixed sites. The correlation coefficients were high between CO and NO_2 (r = 0.86) and PM_{10} (r = 0.75). Exposures for lag days 0-7 were analyzed, and ambient CO had a negative effect on fibrinogen only among males. Negative associations were reported for lag 0 (e.g., same day) and lags 2-5 with the decrease in fibrinogen ranging from -5.5 mg/dL to -9.8 mg/dL per 0.5 ppm increase in 24-h CO concentration. A similar negative effect for CO was observed on WBC among males only. The average CO exposure over the week prior to the sampling yielded the largest reduction in WBC (-263 cells/μL).

In a German study, Rückerl and colleagues (Ruckerl et al., 2006, 088754) recruited 57 nonsmoking male patients with CHD who were scheduled for 12 subsequent clinical visits where samples of blood were collected. The authors tested the primary hypothesis that CRP would increase in association with a rise in air pollution levels. CRP is an acute phase protein that increases during inflammatory processes in the body. Other markers of inflammation (serum amyloid A [SAA]), cell adhesion (E-selectin, von Willebrand factor antigen [vWF], ICAM-1), and coagulation (fibrinogen, factor VII [FVII], prothrombin fragment 1+2) were also examined. Ambient air pollution in the form of PM_{10}, UFP, EC, NO_2, and CO was monitored at one central site, and a 24-h avg immediately preceding the clinic visit (lag 0) and up to 5 days (lags 1-4) was calculated for each patient. For CRP, the odds of observing concentrations above the 90th percentile (8.5 mg/L) were 2.41 (95% CI: 1.23-5.02) in association with a 0.5 ppm increase in 24-h CO concentration (lag 2). CO concentration during lags 1 and 2 was associated with observing ICAM-1 concentrations above the 90th percentile (OR: 2.41 [95% CI: 1.49-4.04]; OR: 3.17 [95% CI: 1.77-6.11], respectively). CO concentration (lag 0-3) was associated with a decrease in FVII.

A similar study by Rückerl and colleagues (2007, 156931) was conducted among 1,003 MI survivors across six European cities (Athens, Greece; Augsburg, Germany; Barcelona, Spain; Helsinki, Finland; Rome, Italy; Stockholm, Sweden). The study compared repeated measurements of interleukin-6 (IL-6), CRP and fibrinogen with concurrent ambient levels of air pollution (particle number count [PNC], PM_{10}, $PM_{2.5}$, NO, NO_2, O_3, SO_2, CO) from fixed sites across each city. Lags 0-1 and the 5-day mean prior to the blood sampling were analyzed and ambient CO was not associated with any of the inflammatory endpoints.

Baccarelli et al. (2007, 090733) recruited 1,218 healthy individuals from the Lombardia region in Italy and assessed whether blood coagulability is associated with ambient air pollution. The main blood coagulability endpoints of interest were prothrombin time (PT) and activated partial thromboplastin time (APTT), which are measures of the quality of the coagulation pathways, assuming that, if shortened these measures would reflect hypercoagulability. Air pollution data (PM_{10}, O_3, NO_2, and CO) were obtained from 53 fixed stations across the Lombardia region, which was divided into 9 different study areas, and a network average for each pollutant was calculated across the available monitors within each of the 9 study areas. The analyses examined air pollution at the time of the blood sampling, as well as averages for the 7 days prior and 30 days prior. Results showed that ambient CO at the time of blood sampling was associated with a decrease in PT (coefficient = -0.11 [95% CI: -0.18 to -0.05], $p < 0.001$), indicating hypercoagulability. However, PM_{10} and NO_2 at the time of blood sampling were also associated with a decrease in PT and results from multipollutant models were not reported. Acute phase reactants such as fibrinogen and naturally occurring anticoagulants such as antithrombin, protein C and protein S were examined and none were associated with ambient air pollution.

Rudez et al. (2009, 193783) collected 13 consecutive blood samples within a 1-yr period and measured light-transmittance platelet aggregometry, thrombin generation, fibrinogen and CRP in 40 healthy individuals in Rotterdam, The Netherlands. In general, air pollution increased platelet aggregation as well as coagulation activity but had no clear effect on systemic inflammation. Specifically, there were notable associations between maximal aggregation and CO, NO and NO_2 and between late aggregation and CO. The effects for CO were the highest in magnitude and persisted over most of the lag times investigated. There also was evidence of an increase in endogenous thrombin potential and peak thrombin generation associated with CO, NO, NO_2 and O_3, but no clear associations between PM_{10} and peak height or lag time of thrombin generation. In addition, there was no evidence for an effect of any of the air pollutants examined on CRP or fibrinogen levels. These prothrombotic effects may partly explain the relationship between air pollution and the risk of ischemic cardiovascular disease.

Ljungman et al. (2009, 191983) investigated the effect of CO and NO_2 on inflammation in certain genetic subpopulations of MI survivors. Specifically, they examined whether IL-6 and fibrinogen gene variants could affect plasma IL-6 response to CO or NO_2. The study included 955 MI survivors from 6 European cities. This study provides evidence of gene-environment interaction where IL-6 and fibrinogen gene polymorphisms modified the effects of CO and NO_2 on IL-6 levels in this panel of subjects with existing cardiovascular disease. Subjects with the homozygous major allele genotypes for all 3 IL-6 polymorphisms examined showed larger IL-6 responses to increased CO, and there was evidence of a genetic interaction with NO_2 for one of the polymorphisms. Subjects with the homozygote minor allele genotype for one fibrinogen polymorphism showed both a larger and clearer effect modification for the IL-6 response to increased CO compared to the IL-6 polymorphisms. Similar magnitudes of effect modification were seen for NO_2, but the effect modification pattern was not statistically significant. A second fibrinogen polymorphism did not modify the response to air pollution. Overall, this study provides evidence for the influence of CO on IL-6 levels in subjects with genetic polymorphisms of the IL-6 and fibrinogen genes. In this study, 16% of the subjects had a polymorphism combination that resulted in a statistically significant gene-gene-environment interaction potentially implicating a higher risk of health effects from air pollution in these patients with ischemic heart disease.

In summary, a growing number of studies provide some evidence of a link between CO exposure and blood markers of coagulation and inflammation. Further studies are required to determine whether the prothrombotic effects characterized by many of the blood markers may partly explain the relationship between CO and the risk of ischemic cardiovascular disease. The results of a recent gene-gene-environment interaction study are particularly interesting. Table 5-6 summarizes the reviewed studies. Due to the heterogeneity of endpoints (see column "cardiac endpoint" in Table 5-6), these studies do not lend themselves to a quantitative meta-analysis or inclusion in a summary figure.

Table 5-6. Summary of studies investigating the effect of CO exposure on blood markers of coagulation and inflammation.

Study	Location, Sample Size	Cardiac Endpoint	Upper CO Concentrations from AQS[a] in ppm	CO Concentrations Reported by Study Authors in ppm	Copollutants
Delfino et al. (2008, 156390)	Los Angeles, CA (n=29)	CRP, fibrinogen, TNF-α, IL-6, fibrin D-dimer, sP-selectin, sVCAM-1, sICAM-1, MPO	98th%: 2.9 99th%: 3.1 (1 h)	Outdoor Mean: 0.71 (1 h) Indoor Mean: 0.78 (1 h)	O_3, NO_2, EC, OC, BC, $PM_{0.25}$, $PM_{0.25-2.5}$, $PM_{2.5-10}$
Delfino et al. (2009, 200844)	Los Angeles, CA (n=60)	CRP, TNF-α, IL-6, sP-selectin, sTNF-RII, Cu,Zn-SOD, GPx-1	NA	Outdoor mean: 0.50-0.58 (1h)	O_3, NO_2,NO_x, EC, OC, BC, SOC, PN, $PM_{0.25}$, $PM_{0.25-2.5}$, $PM_{2.5-10}$
Wellenius et al. (2007, 092830)	Boston, MA (n=28)	BNP	98th%: 0.75-2.22 99th%: 0.92-2.48 (24 h)	Mean: 0.44 (24 h)	$PM_{2.5}$, SO_2, NO_2, O_3, BC
Pekkanen et al (2000, 013250)	London, U.K. (n = 7205)	Plasma fibrinogen	NA	Mean: 1.22 (24 h) 10th, 50th, 90th, Max: 0.61, 1.04, 2.0, 8.61	PM_{10}, BS, O_3, NO_2, SO_2
Liao et al (2005, 088677)	US (n = 10.208)	Fibrinogen, VII-C, WBC, albumin, vWF	98th%: 0.39-2.29 99th%: 0.43-2.66 (24 h)	Mean: 1.4 (24 h)	PM_{10}, O_3, NO_2, SO_2
Steinvil et al (2008, 188893)	Tel-Aviv, Israel (n = 3659)	CRP, fibrinogen, WBC	NA	Mean: 0.8 25th, 50th, 75th percentiles: 0.7, 0.8, 1.0	PM_{10}, O_3, NO_2, SO_2
Rückerl et al (2006, 088754)	Erfurt, Germany (n = 57)	CRP, SAA, cell adhesions and coagulation	NA	Mean: 0.45 (24 h) Range: 0.10, 1.68	PM_{10}, $PM_{2.5}$, UFP, EC, NO_2
Rückerl et al (2007, 156931)	Six European cities (n = 1003)	IL-6, CRP, fibrinogen	NA	Mean: 0.29-1.48 (24 h)	PM_{10}, $PM_{2.5}$, O_3, NO_2, SO_2
Baccarelli et al (2007, 090733)	Lombardia Region, Italy (n = 1218)	PT, APTT, fibrinogen, anticoagulants	NA	Mean: 1.14-3.11 Max: 5.52-11.43	PM_{10}, O_3, NO_2, SO_2
Rudez et al. (2009, 193783)	Rotterdam, The Netherlands (n=40)	Platelet aggregation, thrombin generation, fibrinogen, CRP	NA	Median: 0.29 (24 h)	PM_{10}, NO, NO_2, O_3
Ljungman et al. (2009, 191983)	Six European cities (n=955)	IL-6 and fibrinogen polymorphisms	NA	Mean: 0.25-1.29 (24 h)	NO_2, PM_{10}, $PM_{2.5}$

NA: Not Available

[a] Includes range across individual monitors in study site; AQS data available for U.S. studies only.

5.2.1.9. Hospital Admissions and Emergency Department Visits

Since the 2000 CO AQCD (U.S. EPA, 2000, 000907) there have been a number of studies that investigated the effect of ambient CO on hospital admissions and ED visits for CVD. Some of these studies have focused solely on one specific CVD outcome, and these studies are discussed first. The subsequent sections provide a discussion of the studies that investigated hospital admissions and ED visits for all CVD outcomes (e.g., nonspecific) or a variety of specific CVD outcomes.

Coronary Heart Disease

Ischemic heart disease (IHD), also known as CHD, is caused by inadequate circulation of the blood to the heart muscle, which is a result of the coronary arteries being blocked by cholesterol deposits or by vasospasm. CHD can lead to sudden episodes such as MI or death, as well as chronic conditions such as angina pectoris (chest pain).

Ischemic Heart Disease

A number of studies have focused directly on hospitalizations for IHD. There is a lot of variation among these studies with regard to methods employed and results reported. It should be noted that within these studies IHD included MI and angina pectoris (ICD-9 codes 410-414; ICD-10 codes 120, 121-123, 124). A multicity time-series study was conducted to estimate the risk of CVD hospitalization associated with short-term CO exposure in 126 U.S. urban counties from 1999-2005 for over 9 million Medicare enrollees 65 yr old and older (Bell et al., 2009, 193780). The analyses yielded positive associations between same-day CO concentration adjusted for NO_2 concentration and increased risk of hospitalization for IHD 1.004 (95% PI: 1.001-1.007). Cause-specific effect estimates were not presented for CO alone (without adjustment for NO_2).

Mann and colleagues (2002, 036723) investigated the modifying effect of secondary diagnosis of arrhythmia and congestive heart failure (CHF) on the relationship between hospital admissions for IHD (ICD-9: 410-414) and ambient air pollutants for the period of 1988-1995 in southern California. There were 54,863 visits analyzed and a 0.75 ppm increase in 8-h max CO concentration was associated with a 2.69% (95% CI: 1.21-4.19) increase in same-day IHD admissions among persons with a secondary diagnosis of CHF, a 2.23% (95% CI: 1.35-3.13) increase among persons with a secondary diagnosis of arrhythmia, and a 1.21% (95% CI: 0.49-1.94) increase among persons without either secondary diagnosis. Of all the pollutants examined (PM_{10}, NO_2, O_3, CO), only NO_2 showed positive effects estimates similar in magnitude to CO. Although no multipollutant models were analyzed, a moderate to high correlation between CO and NO_2 was found across the seven regions ranging from 0.64 to 0.86. This study indicated that people with IHD and underlying CHF and/or arrhythmia represent a potentially susceptible population relative to the effects of ambient air pollution.

By using a time-series approach, ED visits for IHD (ICD-9: 410-414) in Montreal, Canada, (1997-2002) were examined in relation to ambient CO concentrations (lags 0 and 1) (Szyszkowicz, 2007, 193793). A total of 4,979 visits were analyzed, and results showed significant positive effects with a 0.5 ppm increase in 24-h CO concentration (lag 0), resulting in a 14.1% (95% CI: 5.8-20.6) increase in daily ED visits among all patients. Stratified analyses showed that this effect was mostly among male patients (19.8% [95% CI: 9.2-31.6]). NO_2 was the only other pollutant examined, and it too showed significant positive associations with ED visits for IHD for same-day exposure; however, no multipollutant models were examined.

Lee and colleagues (2003, 095552) examined daily counts of hospital admissions for IHD in Seoul, Korea, for the period from December 1997 to December 1999. Single-day lags 0-5 were analyzed, and the lag period with the strongest association for each pollutant was presented by the authors. For CO, lag 5 showed the strongest effect, with a 1 ppm increase in 1-h maximum (max) CO concentration associated with a daily increase in the number of hospital admissions for IHD; however, this was only among patients 64+ yr of age (RR: 1.07 [95% CI: 1.01-1.13]). All other pollutants (PM_{10}, O_3, NO_2) except SO_2 showed similar significant effects and in a copollutant model with PM_{10} the CO effect was somewhat attenuated (RR 1.04 [95% CI: 0.98-1.11]).

Other studies have examined hospital admissions for IHD while investigating a broad group of CVD outcomes. A study was conducted in Atlanta, GA, where over 4 million ED visits from 31 hospitals for the period 1993-2000 were analyzed (Study of Particles and Health in Atlanta [SOPHIA]). Several articles have been published from this research, with two examining cardiovascular admissions in relation to CO concentrations. The first of these (Metzger et al., 2004, 044222) used a time-series design and analyzed a 3-day ma over single-day lags 0-2 as the a priori lag structure. Although of borderline statistical significance, CO was positively associated with an increase in ED visits for IHD (RR 1.016 [95% CI: 0.999-1.034] per 1 ppm increase in 1-h max CO concentration).

The second of these reports (Peel et al., 2007, 090442) examined the association of ambient air pollution levels and cardiovascular-related ED visits with and without specific secondary conditions

(e.g., comorbidity). Within a time-stratified case-crossover design using the same lag structure previously mentioned, the main results showed that a 1 ppm increase in 1-h max CO concentration was associated with an increase in IHD among those without diabetes (OR: 1.023 [95% CI: 1.004-1.042]), and without CHF (OR: 1.024 [95% CI: 1.006-1.042]).

Two Australian studies have also examined associations between ambient CO concentrations and increased hospital admissions for various CVD outcomes. The first of these studies (Barnett et al., 2006, 089770) analyzed data from five of the largest cities in Australia (Brisbane, Canberra, Melbourne, Perth, Sydney) and two New Zealand cities (Auckland, Christchurch) for the period 1998-2001. A time-stratified case-crossover design was employed, and the age groups of 15-64 yr and ≥ 65 yr were analyzed for the 0-1 lag period. The pooled estimates across all cities showed that a 0.75 ppm increase in 8-h max CO concentration was associated with a 1.9% (95% CI: 0.7-3.2) increase in admissions for IHD among the elderly group (≥ 65 yr). No association was observed for the younger age group.

The second of the Australian studies (Jalaludin et al., 2006, 189416) examined ED visits for CVD outcomes in the elderly (65+ yr) in Sydney for the period 1997-2001. Using a time-series approach, single-day lags of 0, 1, 2, 3, and an average over lags 0 and 1 were examined. A 0.75 ppm increase in 8-h max CO concentration (lag 0) was associated with increases in IHD emergency department visits of 3.1% (95% CI: 1.3-4.9).

Angina Pectoris

In the current literature, only one study was identified that focused solely on angina pectoris as an endpoint. Admissions data for angina pectoris were collected from 25 academic hospitals in Tehran, Iran, and linked to ambient air pollution for the period of 1996-2001 (Hosseinpoor et al., 2005, 087413). Using a time-series approach, single-day lags of 0-3 were analyzed and a 0.5 ppm increase in 24-h avg CO concentration at lag 1 was associated with increased hospital admissions for angina (OR: 1.005 [95% CI: 1.003-1.007]). This result persisted in a multipollutant model that also included NO_2, PM_{10}, and O_3 (OR: 1.005 [95% CI: 1.001-1.008]).

Myocardial Infarction

Linn et al. (2000, 002839) examined the association between ambient air pollution and hospital admissions for cardiopulmonary illnesses in metropolitan Los Angeles for the years 1992-1995. Using a time-series approach, a 0.5 ppm increase in same-day 24-h avg CO concentration was associated with a 2.0% increase in MI hospital admissions among people aged >30 yr. When the analyses were stratified by season, no significant effects were observed (no quantitative seasonal effects reported).

A time-series study in Denver, Colorado, investigated daily hospital admissions for various CVD outcomes among older adults (>65 yr) across 11 hospitals (Koken et al., 2003, 049466). Data between July and August for the period 1993-1997 were analyzed. Single-day lags 0-4 were examined and CO showed no association with hospital admissions for MI (quantitative results were not reported).

As part of the Health Effects of Air Pollution among Susceptible Subpopulations (HEAPSS) study, Lanki et al. (2006, 089788) investigated the association between traffic-related exposure to air pollutants and hospitalization for first acute myocardial infarction (AMI). Data were collected from five European cities with either AMI registers (Augsburg, Barcelona) or hospital discharge registers (Helsinki, Rome, Stockholm). Correlation coefficients between CO and NO_2 ranged from 0.43 to 0.75 across the five cities, and between CO and PM_{10} the range was 0.21 to 0.56. A total of 26,854 hospital admissions were analyzed, and pooled estimates from all five cities showed that there was a weak positive association with AMI hospital admissions and 24-h avg CO concentrations at lag 0 (RR: 1.014 [95% CI: 1.000-1.029] per 0.5 ppm increase), but more so when only using data from the three cities (Helsinki, Rome, Stockholm) with hospital discharge registers (RR: 1.020 [95% CI: 1.003-1.035] per 0.5 ppm increase). When analyses were stratified by fatality and age, results showed that the CO effect was significantly associated with fatal AMI among the <75-yr age group (RR: 1.080 [95% CI: 1.017-1.144]) and with non-fatal AMI in the ≥ 75-yr age group (RR: 1.044 [95% CI: 1.011-1.076]).

Further analyses within the HEAPSS cohort were conducted using the event of cardiac readmission among the first MI survivors (n = 22, 006) (Von Klot et al., 2005, 088070). The readmissions of interest were those with primary diagnosis of AMI, angina pectoris, dysrhythmia,

and heart failure that occurred at least 29 days after the index event. Single-day lags 0-3 were examined, and pooled estimates from all 5 cities showed that a 0.5 ppm increase in same-day (lag 0) CO was associated with an increase in cardiac (e.g., any of the diagnoses) readmissions (RR: 1.041 [95% CI: 1.003-1.076]); this persisted in two-pollutant models that included either PM_{10} or O_3. Correlation coefficients with CO ranged from 0.21 to 0.57 for PM_{10} and 0.44 to 0.75 for NO_2.

A study in Rome, Italy, also found an association between ambient CO and hospitalizations for first-episode MI among 6,531 subjects (January 1995-June 1997) (D'Ippoliti et al., 2003, 074311). A case-crossover design with stratification of time into separate months was used to select referent days as the days falling on the same day of the week within the same month as the index day. CO concentration was positively associated with lag 2 (OR: 1.019 [95% CI: 1.001-1.037]). The other pollutants analyzed were NO_2 and TSP, both of which exhibited a significant positive effect at lag 0. TSP also showed a significant positive effect at lag 0-2 and, when entered into a model with CO, the CO effect did not persist.

The previously mentioned Australian and New Zealand study that analyzed data from seven cities (Brisbane, Canberra, Melbourne, Perth, Sydney, Auckland, and Christchurch) for the period 1998-2001 also reported an association between CO and MI hospital admissions (Barnett et al., 2006, 089770). The pooled estimates across all cities showed that a 0.75 ppm increase in 8-h max CO concentration was associated with a 2.4% (95% CI: 0.6-4.1) increase in admissions for MI, but only among older adults (≥ 65 yr). Table 5-7 shows a summary of the CHD hospital admission studies that examined CO exposures.

In summary, the majority of studies reported significant increases in the daily number of admissions for IHD, angina and MI in relation to CO exposures. In studies that stratified by age groups and/or sex, the effects were larger among the elderly and males. Among the different lag periods being examined, the associations were more commonly observed with same day CO (lag 0) or an average over the same day and previous day (lag 0-1). Figure 5-2 shows the effect estimates associated with daily admissions for various forms of CHD from selected studies.

Study	Location	Lag	Age	Group/Outcome	Effect Estimate (95% CI)
Metzger et al. (2004, 044222)	Atlanta, GA	0-2			IHD
Peel et al. (2007, 090442)	Atlanta, GA	0-2			
Mann et al.(2002, 036723)	California, US	0-3			
	California, US	0-3		sCHF	
	California, US	0-3		sARR	
Barnett et al. (2006, 089770)	Australia, New Zealand	0-1	15-64 yr		
	Australia, New Zealand	0-1	65+ yr		
Jalaludin et al. (2006, 189416)	Sydney, Australia	0-1	65+ yr		
Szyszkowicz (2007, 193793)	Montreal, Canada	0	All ages		
	Montreal, Canada	0	All ages	Males	
	Montreal, Canada	0	All ages	Females	
	Montreal, Canada	0	65+ yr	Males and Females	
	Montreal, Canada	0	65+ yr	Males	
	Montreal, Canada	0	65+ yr	Females	
Lee et al. (2003, 095552)	Seoul, Korea	5	All ages		
	Seoul, Korea	5	64+ yr		
von Klot et al. (2005, 088070)	Multicity, Europe	0	35+ yr		Angina
Hosseinpoor et al. (2005, 087413)	Tehran, Iran	1	All ages		
Linn et al. (Linn et al., 2000, 002839)	Los Angeles, CA	0		All year	MI
Barnett et al. (2006, 089770)	Australia, New Zealand	0-1	15-64 yr		
	Australia, New Zealand	0-1	65+ yr		
Lanki et al. (2006, 089788)	Multicity, Europe	0	35+ yr	All cities	
	Multicity, Europe	0	<75 yr	Nonfatal	
	Multicity, Europe	0	<75 yr	Fatal	
	Multicity, Europe	0	75+ yr	Nonfatal	
	Multicity, Europe	0	75+ yr	Fatal	
von Klot et al. (2005, 088070)	Multicity, Europe	0	35+ yr		
D'Ippoliti et al. (2003, 074311)	Rome, Italy	0-2	18+ yr		
	Rome, Italy	0-2	18-64 yr		
	Rome, Italy	0-2	65-74 yr		
	Rome, Italy	0-2	75+ yr		

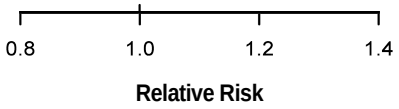


Figure 5-2. Summary of effect estimates (95% confidence intervals) associated with hospital admissions for various forms of CHD. Effect estimates have been standardized to a 1 ppm increase in ambient CO for 1-h max CO concentrations, 0.75 ppm for 8-h max CO concentrations, and 0.5 ppm for 24-h avg CO concentrations.

Table 5-7. Summary of CHD hospital admission studies.[a]

Study	Location	Endpoints Examined	Copollutants	Lags Examined	Upper CO Concentrations from AQS[c] in ppm	CO Concentrations Reported by Study Authors in ppm
STUDIES THAT FOCUSED SOLELY ON CHD						
Mann et al. (2002, 036723)	Southern California (1988-1995)	IHD	PM_{10}, NO_2, O_3	0,1,2, 2-4ma	98th%: 1.0-13.8 99th%: 1.3-15.9 (8 h)	Mean: 2.07 (8h)
Szyszkowicz (2007, 193793)	Montreal, Can (1997-2002)	IHD	NO_2	0,1	NA	Mean: 0.5 (24 h)
Lee et al.(2003, 095552)	Seoul, Korea (1997-1999)	IHD	PM_{10}, NO_2, SO_2, O_3	0,1,2,3,4,5	NA	Mean: 1.8
Lanki et al. (2006, 089788)[b]	5 European cities (1992-2000)	MI (first acute)	PM_{10}, NO_2, O_3, PNC	0,1,2,3	NA	Highest city was Rome. 25th = 1.5 75th = 2.6
von Klot et al. (2005, 088070)[b]	5 European cities (1992-2001)	MI, Angina, Cardiac[a]	PM_{10}, NO_2, O_3, PNC	0,1,2,3	NA	Mean: highest city was Rome: 1.9 (24 h)
D'Ippoliti et al. (2003, 074311)[b]	Rome, Italy (1995-1997)	MI	TSP, NO_2, SO_2	0,1,2,3,4, 0-2	NA	Mean: 3.8 (24 h)
Hosseinpoor et al. (2005, 087413)[b]	Tehran, Iran (1996-2001)	Angina	PM_{10}, NO_2, SO_2, O_3	0,1,2,3	NA	Mean: 9.4 (24 h)
STUDIES THAT EXAMINED CHD AMONG OTHER CVDS						
Metzger et al.(2004, 044222)	Atlanta, GA (1993-2000)	IHD, All CVD, CD, CHF, PVCD	PM_{10}, NO_2, SO_2, O_3	0-2ma	98th%: 5.0-5.1 99th%: 5.5-5.9 (1 h)	Mean: 1.8 (1 h)
Peel et al. (2007, 090442)	Atlanta, GA (1993-2000)	IHD, All CVD, CD, CHF, PVCD	PM_{10}, NO_2, SO_2, O_3	0-2ma	98th%: 5.0-5.1 99th%: 5.5-5.9 (1 h)	Mean: 1.8 (1 h)
Barnett et al. (2006, 089770)	Australia and New Zealand (1998-2001)	IHD, MI, All CVD, CA, Stroke	PM_{10}, NO_2, O_3	Lag 0-1	NA	Mean: (8 h) 0.5- 2.1
Jalaludin et al. (2006, 189416)	Sydney, Australia (1997-2001)	IHD, All CVD, Stroke, Cardiac	PM_{10}, NO_2, SO_2, O_3	0,1,2,3, 0-1	NA	Mean: 0.82 (8 h)
Linn et al. (2000, 002839)	Los Angeles, CA (1992-1995)	MI, All CVD, CHF, CA, OS	PM_{10}, NO_2, O_3	0	98th%: 1.0-7.8 99th%: 1.1-8.3 (24 h)	Mean: (24 h) Winter 1.7, Spring 1.0, Summer 1.2, Fall 2.1
Koken et al.(2003, 049466)	Denver, CO (1993-1997)	MI, CAth, PHD, CD, CHF	PM_{10}, NO_2, SO_2, O_3	0,1,2,3,4	98th%: 1.2-2.0 99th%: 1.3-2.0 (24 h)	Mean: 0.9 ppm (24 h)

[a] Cardiac = AMI, angina, dysrhythmia, or HF; CA = Cardiac arrhythmia; CAth = Cardiac atherosclerosis; CD = cardiac dysrhythmias; CHF = Congestive heart failure; PHD = Pulmonary heart disease; OS = Occlusive stroke; PVCD = peripheral vascular and cerebrovascular disease, ma = moving average.

[b] These studies presented CO concentrations in the units mg/m^3. The concentrations were converted to ppm using the conversion factor 1 ppm = 1.15 mg/m^3, which assumes standard atmosphere and temperature.

[c] Includes range across individual monitors in study site; AQS data available for U.S. studies only.

NA: Not Available

Stroke

A stroke is the result of either the blood supply to the brain being blocked (e.g., embolism), which refers to an ischemic stroke (80% of strokes), or the occurrence of a burst blood vessel or hemorrhaging, referred to as a hemorrhagic stroke. Hemorrhagic stroke has two main groupings; intracerebral hemorrhagic stroke (10% of strokes), which is when a blood vessel in the brain leaks, and subarachnoid hemorrhage (3% of strokes), which is bleeding under the outer membranes of the brain. The third type of stroke is a transient ischemic attack (TIA) or ministroke, which has the same early symptoms as a normal stroke but the symptoms disappear within 24 h, leaving no apparent deficits. A limited number of air pollution studies have investigated hospital admissions for the three main forms of stroke and generally report small, positive associations or no association with ambient CO concentrations measured during lag periods between 0 and 3 days.

In the multicity time-series study conducted by Bell et al. (2009, 193780), the analyses yielded small, positive associations between same-day CO concentration adjusted for NO_2 concentration and increased risk of hospitalization for cerebrovascular outcomes 1.005 (95% PI: 1.002-1.009). Cause-specific effect estimates were not presented for CO alone (without adjustment for NO_2).

A U.S. study across 9 cities investigated hospital admissions for ischemic and hemorrhagic stroke among Medicare beneficiaries aged 65+ yr of age (155,503 ischemic and 19,314 hemorrhagic admissions from the ED) (Wellenius et al., 2005, 088685). Single-day lags 0-2 were examined and based on a pooled estimate, same-day CO (lag 0) was associated with an increase in ischemic stroke admissions of 1.98% (95% CI: 0.86-3.12) per 0.5 ppm increase in 24-h CO concentration), but not hemorrhagic stroke admissions (-1.14%, 95% CI: -3.40 to 1.18). All other pollutants examined (PM_{10}, NO_2, SO_2) were also associated with an increase in ischemic stroke admissions but not hemorrhagic stroke admissions.

Villeneuve and colleagues (2006, 090191) studied ED visits for hemorrhagic strokes, acute ischemic strokes and transient ischemic attacks among individuals 65+ yr of age at 5 hospitals within the Edmonton, Canada, area between April 1992 and March 2002 (12,422 visits). Within a time-stratified case-crossover design, the analyses were stratified by two seasonal groups (October-March and April-September). CO was found to only have an effect on ischemic stroke during April-September (OR: 1.32 [95% CI 1.09-1.60] per a 0.5 ppm increase in 24-h CO concentration) for a 3-day avg across lags 0-2. CO had no effect on any other stroke subtype. In two-pollutant models the CO effect on ischemic stroke persisted after controlling for PM_{10}, $PM_{2.5}$, SO_2, and O_3.

In Kaohsiung City, Taiwan, CO averaged over lags 0-2 was associated with increased admissions for stroke across 63 hospitals (Tsai et al., 2003, 080133). From 1997 through 2000 a total of 23,179 admissions were analyzed, and on warm days ($\geq$ 20°C) the odds ratios for primary intracerebral hemorrhage and ischemic stroke were 1.39 (95% CI: 1.16-1.66) and 1.39 (95% CI: 1.25-1.53) respectively for a 0.5 ppm increase in 24-h CO concentration. For the same increase in CO on cool days (<20°C) the odds ratios were 1.33 (95% CI: 0.38-2.55) for intracerebral hemorrhage and 2.68 (95% CI: 1.59-4.49) for ischemic stroke. These results persisted in two-pollutant models that included PM_{10}, SO_2, and O_3 but did not persist when controlling for NO_2.

Earlier research conducted in metropolitan Los Angeles examined hospital admissions for cardiopulmonary illnesses from 1992-1995 (Linn et al., 2000, 002839). Using a time-series approach, a 0.5 ppm increase in 24-h CO concentration (lag 0) was associated with a 2.18% (95% CI: 1.73-2.62) increase in occlusive (ischemic) stroke hospital admissions among people aged >30 yr. When the analyses were stratified by season, there was a 1.8% (p=0.017) increase during winter, a 4.55% (p=0.039) increase during summer, and a 1.6% (p=0.015) increase during fall (results for spring were not reported).

A study in Taipei, Taiwan, analyzed 8,582 emergency admissions for cerebrovascular diseases, hemorrhagic stroke, ischemic stroke, and all strokes during 1997-2002 (Chan et al., 2006, 090193). Single-day lags 0-3 were analyzed, and a 0.75 ppm increase in 8-h max CO concentration (lag 2) was associated with an increase in cerebrovascular diseases (OR: 1.03 [95% CI: 1.01-1.05]) and all strokes (OR: 1.03 [95% CI: 1.01-1.05]). These results persisted in two- and three-pollutant models that included O_3 and PM_{10}. There was no association with individual ischemic or hemorrhagic stroke. CO was moderately correlated with PM_{10} (r = 0.47) and $PM_{2.5}$ (r = 0.44), and the correlation was higher with NO_2 (r = 0.77).

A time-series study that focused specifically on stroke hospital admissions conducted in Dijon, France, did not report a significant association with ambient CO (Henrotin et al., 2007, 093270). Hospital admissions for different types of first-ever stroke (e.g., ischemic, hemorrhagic) among

subjects >40 yr were analyzed for the period 1994-2004. A bidirectional case-crossover study design was employed where single-day lags between 0-3 days were examined and CO had no significant association for any lag. This was also the case when the analyses were stratified by gender and types of ischemic stroke (large arteries, lacunar, cardioembolic, transient). Of all pollutants examined (PM_{10}, NO_X, O_3, SO_2, CO), only O_3 showed a significant effect.

Two Australian studies examined associations between ambient CO and hospital admissions for various CVDs. The first of these studies analyzed data from five of the largest cities in Australia (Brisbane, Canberra, Melbourne, Perth, Sydney) and two New Zealand cities (Auckland, Christchurch) for the period 1998-2001 (Barnett et al., 2006, 089770). A time-stratified case-crossover design was employed and the age groups of 15-64 yr and ≥ 65 yr were analyzed for the 0-1 lag period (average over lag 0 and 1). The pooled estimates across all cities showed that CO had no effect on stroke admissions (quantitative results not reported).

The second of the Australian studies examined ED visits for CVDs in older adults (65+ yr) in Sydney for the period 1997-2001 (Jalaludin et al., 2006, 189416). Using a time-series approach, single-day lags of 0-3 and an average over lags 0 and 1 (e.g., lag 0-1) were examined, and CO showed no effect on stroke ED visits. When the analyses were stratified by cool and warm periods, a 0.75 ppm increase in 8-h max CO concentration during the cool period was associated with a 3.8% (95% CI: 0.76-6.94) increase in stroke ED visits.

In summary, there was limited evidence that increased ambient CO concentrations might be associated with hospital admissions for stroke. The largest positive effects came from the Taiwan study in Kaohsiung (Tsai et al., 2003, 080133), with slightly larger effects during the warmer period (>20°C). Similarly, in the Canadian study by Villeneuve and colleagues (2006, 090191), there was a stronger effect during the warmer period (April-September). Studies in France and Australia reported no association between ambient CO concentrations and increased hospital admissions or ED visits for stroke. Figure 5-3 shows the effect estimates associated with daily admissions for stroke from selected studies; Table 5-8 shows a summary of the stroke hospital admission studies that examined CO exposures.

Study	Location	Lag	Outcome/Group	Effect Estimate (95% CI)
Wellenius et al. (2005, 088685)	Multicity, US	0-2	65+ yr	Ischemic Stroke
Villeneuve et al. (2006, 090191)	Edmonton, Can	0-2	IS, 65+ yr, All Seasons	
Villeneuve et al. (2006, 090191)	Edmonton, Can	0-2	IS, 65+ yr, Apr-Sep	
Villeneuve et al. (2006, 090191)	Edmonton, Can	0-2	IS. 65+ yr, Oct-Mar	
Villeneuve et al. (2006, 090191)	Edmonton, Can	0-2	CIS, 65+ yr, All Seasons	
Villeneuve et al. (2006, 090191)	Edmonton, Can	0-2	CIS, 65+ yr, Apr-Sep	
Villeneuve et al. (2006, 090191)	Edmonton, Can	0-2	CIS. 65+ yr, Oct-Mar	
Tsai et al. (2003, 080133)	Kaohsiung, Taiwan	0-2	<20°C Temp	
Tsai et al. (2003, 080133)	Kaohsiung, Taiwan	0-2	>20°C Temp	
Linn et al. (2000, 002839)	Los Angeles, CA	0		
Chan et al. (2006, 090193)	Taipei, Taiwan	1		
Henrotin et al. (2007, 093270)	Dijon, France	3		
Wellenius et al. (2005, 088685)	Multicity, US	0-2	65+ yr	Hemorrhagic Stroke
Villeneuve et al. (2006, 090191)	Edmonton, Can	0-2	65+ yr, All Seasons	
Villeneuve et al. (2006, 090191)	Edmonton, Can	0-2	65+ yr, Apr-Sep	
Villeneuve et al. (2006, 090191)	Edmonton, Can	0-2	65+ yr Oct-Mar	
Tsai et al. (2003, 080133)	Kaohsiung, Taiwan	0-2	<20°C Temp	
Tsai et al. (2003, 080133)	Kaohsiung, Taiwan	0-2	>20°C Temp	
Chan et al. (2006, 090193)	Taipei, Taiwan	1		
Henrotin et al. (2007, 093270)	Dijon, France	1		
Chan et al. (2006, 090193)	Taipei, Taiwan	2		Stroke (nonspecific)
Jalaludin et al. (2006, 189416)	Sydney, Australia	0-1		

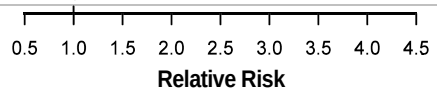


Figure 5-3. Summary of effect estimates (95% confidence intervals) associated with ED visits and hospital admissions for stroke. Effect estimates have been standardized to a 1 ppm increase in ambient CO for 1-h max CO concentrations, 0.75 ppm for 8-h max CO concentrations, and 0.5 ppm for 24-h avg CO concentrations. IS=ischemic stroke, CIS=cerebral ischemic stroke.

Table 5-8. Summary of stroke hospital admission studies.[a]

Study	Location	Type Of Stroke Examined	Copollutants	Lags Examined	Upper CO Concentrations from AQS[c] in ppm	CO Concentrations Reported by Study Authors in ppm
STUDIES THAT FOCUSED SOLELY ON STROKE						
Wellenius et al. (2005, 088685)	9 US cities (1993-1999)	Isch, Hem	PM_{10}, NO_2, SO_2	0,1, 2	98th%: 0.9-5.9 99th%: 1.2-7.1 (24 h)	25th, 50th, 75th percentiles: 0.73, 1.02, 1.44
Villeneuve et al. (2006, 090191)	Edmonton, Can (1992-2002)	Isch, Hem, TIA	NO_2, SO_2, O_3	0,1, 0-2	NA	Mean: 0.8 (24 h)
Tsai et al. (2003, 080133)	Kaohsiung, Taiwan (1997-2000)	Isch, Hem	PM_{10}, NO_2, SO_2, O_3	0-2	NA	Mean: 0.79 (24 h)
Chan et al. (2006, 090193)	Taipei, Taiwan (1997-2002)	All, Isch, Hem	PM_{10}, NO_2, SO_2, O_3	0,1,2,3	NA	Mean: 1.7 (8h)
Henrotin et al. (2007, 093270)[b]	Dijon, France (1994-2004)	Isch, Hem	PM_{10}, NO_X, SO_2, O_3	0,1,2,3	NA	Mean: 0.59 (24 h)
STUDIES THAT EXAMINED STROKE AMONG OTHER CVDS						
Linn et al. (2000, 002839)	Los Angeles, CA (1992-1995)	Isch	PM_{10}, NO_2, O_3	Lag 0	98th%: 1.0-7.8 99th%: 1.1-8.3 (24 h)	Mean: (24 h) Winter 1.7, Spring 1.0, Summer 1.2, Fall 2.1
Barnett et al. (2006, 089770)	Australia and New Zealand (1998-2001)	All	PM_{10}, NO_2, O_3	Lag 0-1	NA	Mean: (8h) 0.5-2.1
Jalaludin et al. (2006, 189416)	Sydney, Australia (1997-2001)	All	PM_{10}, NO_2, SO_2, O_3	0,1,2,3, 0-1	NA	Mean: 0.82 (8h)

[a] Isch = Ischemic; Hem = Hemorrhagic; TIA = transient ischemic attack
[b] These studies presented CO concentrations in the units mg/m^3. The concentrations were converted to ppm using the conversion factor 1 ppm = 1.15 mg/m^3, which assumes standard atmosphere and temperature.
[c] Includes range across individual monitors in study site; AQS data available for U.S. studies only.
NA: Not Available

Congestive Heart Failure

Heart failure (HF) is a condition in which the heart is unable to adequately pump blood to the rest of the body. It does not refer to the cessation of the heart but more to the inability of the heart to operate at an optimal capacity. HF is often called congestive heart failure (CHF), which refers to when the inadequate pumping leads to a buildup of fluid in the tissues. The underlying causes of CHF are hypertension, CAD, MI, and diabetes.

In the multicity time-series study conducted by Bell et al. (2009, 193780), the analyses yielded positive associations between same-day CO concentration adjusted for NO_2 concentration and increased risk of hospitalization for HF (1.009 [95% PI: 1.005-1.012]). Cause-specific effect estimates were not presented for CO alone (without adjustment for NO_2).

Wellenius and colleagues (2005, 087483) examined the rate of hospitalization for CHF among 55,019 Medicare recipients (≥ 65 yr) residing in Allegheny County, PA, during 1987-1999. A time-stratified case-crossover design was employed and single-day lags of 0-3 were analyzed. A 0.5 ppm increase in 24-h avg CO concentration on the same-day (lag 0) was associated with a 4.1% (95% CI: 3.0-5.3) increase in the rate of hospitalization for CHF. This result persisted in copollutant models that included PM_{10}, NO_2, O_3, and SO_2. CO was moderately correlated with SO_2 ($r = 0.54$) and PM_{10} ($r = 0.57$) and more highly correlated with NO_2 ($r = 0.70$).

Another U.S. study recruited 125 patients diagnosed with CHF who were admitted to Johns Hopkins Bayview Medical Center in Baltimore, MD (Symons et al., 2006, 091258). The patients were interviewed after admission through the ED during their stays in overnight wards. The

interview was designed to collect information about symptom onset, health conditions, and factors related to air pollution exposure. Various lag periods (single day and cumulative days 0-3) prior to the onset of symptoms were analyzed and although the focus of this study was exposure to $PM_{2.5}$, of all the pollutants examined ($PM_{2.5}$, CO, NO_2, O_3) only 8-h max CO concentration at lag 2 was significantly associated with the onset of CHF symptoms (OR: 1.68 [95% CI: 1.28-2.80]).

Earlier research conducted in metropolitan Los Angeles, CA examined hospital admissions for cardiopulmonary illnesses (1992-1995) (Linn et al., 2000, 002839). Using a time-series approach, a 0.5 ppm increase in same-day 24-h avg CO concentration was associated with a 1.25% increase in CHF hospital admissions among people >30 yr. When the analyses were stratified by seasons, only summer showed a significant increase (3.7%); however, the study did not report the results for the other seasons.

A time-series study in Denver, CO, investigated daily admissions for various CVDs among older adults (>65 yr) across 11 hospitals (Koken et al., 2003, 049466). Single-day lags 0-4 were examined, and an increase of 0.5 ppm in 24-h avg CO concentration for lag 3 was associated with an 18% (95% CI: 0.2-39.3) increase in risk of hospitalization for CHF.

As stated earlier, a study was conducted in Atlanta, GA, where over 4 million ED visits from 31 hospitals for the period 1993-2000 were analyzed (Metzger et al., 2004, 044222). A time-series design was used and a 3-day ma over single-day lags 0-2 as the a priori lag structure was analyzed. Results showed that 1-h max CO concentration was not associated with an increase in ED visits for CHF (RR: 1.010 [95% CI: 0.988-1.032] per 1 ppm increase). Peel et al. (2007, 090442) examined the same cardiovascular-related effects among those with and without specific secondary conditions (e.g., comorbidity) and found that 1-h max CO concentration was associated with an increase in ED visits for CHF only among those with COPD (OR: 1.058 [95% CI: 1.003-1.115] per 1 ppm increase).

In Kaohsiung city, Taiwan, a study analyzed 13,475 admissions for CHF across 63 hospitals for the period 1996 through 2004 (Lee et al., 2007, 090707). A 0.5 ppm increase in 24-h avg CO concentration averaged over lag days 0-2 was positively associated with CHF hospital admissions on cool days (<25°C) (OR: 1.70 [95% CI: 1.43-2.01]), with a slightly weaker effect on warm days (>25˚ C) (OR: 1.32 [95% CI: 1.15-1.55]). These results persisted in two-pollutant models that included PM_{10}, SO_2, O_3, and models with NO_2 only on warmer days, not with NO_2 on cooler days.

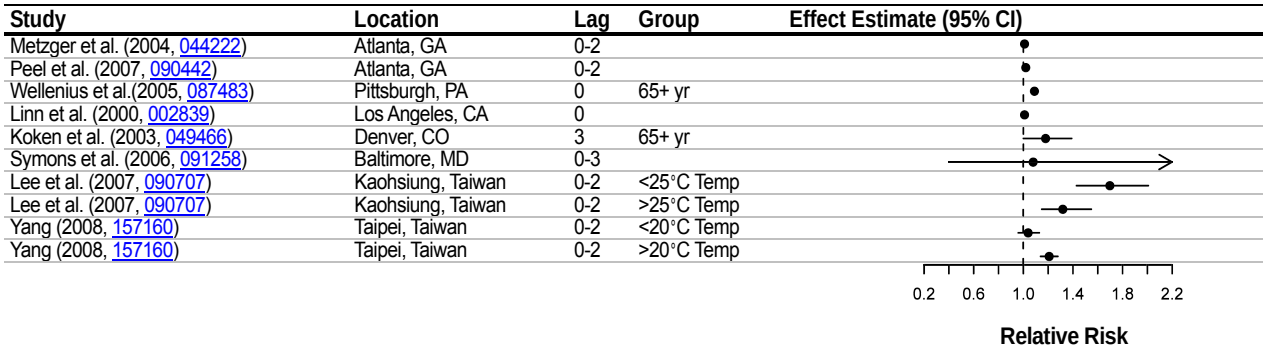


Figure 5-4. Summary of effect estimates (95% confidence intervals) associated with hospital admissions for CHF. Effect estimates have been standardized to a 1 ppm increase in ambient CO for 1-h max CO concentrations, 0.75 ppm for 8-h max CO concentrations, and 0.5 ppm for 24-h avg CO concentrations.

A case-crossover analysis was undertaken to examine the association between levels of ambient air pollutants and hospital admissions for CHF among individuals residing in Taipei, Taiwan, from 1996 through 2004 (Yang, 2008, 157160). During the 9 yr of the study, there were 24,240 CHF hospital admissions for the 47 hospitals in Taipei. The analyses were stratified by temperature, either warm days (>20°C; n = 2325 days) or cool days (<20°C; n = 963 days). The number of CHF admissions was associated with concentrations of PM_{10}, NO_2, CO and O_3 on warm days, however on cool days, the positive effects on increased CHF admissions remained positive, although the effects were diminished for NO_2 and CO, and disappeared completely for PM_{10} and O_3 concentrations. In two-pollutant models, CO remained statistically significant after the inclusion of PM_{10}, SO_2 or O_3 on warm days. On cool days, the effects associated with CO remained positive, but

were no longer statistically significant after the inclusion of PM_{10}, SO_2, or NO_2, but became statistically significant and negative after the inclusion of O_3 in the model (Figure 5-6).

Figure 5-4 shows the effect estimates for associations between CO and daily admissions for CHF from selected studies; Table 5-9 summarizes the CHF hospital admission studies that examined CO exposures.

In summary, many of the studies that examined associations between ambient CO concentrations and daily hospital admissions for CHF reported positive associations at lags of 0-3 days.

Table 5-9. Summary of CHF hospital admission studies.

Study	Location	Endpoints Examined	Copollutants	Lags Examined	Upper CO Concentrations from AQS[a] in ppm	CO Concentrations Reported by Study Authors in ppm
STUDIES THAT FOCUSED SOLELY ON HF						
Wellenius et al. (2005, 087483)	Pittsburgh, PA (1987-1999)	CHF	PM_{10}, NO_2, SO_2, O_3	0,1,2,3	98th%: 1.4-3.4 99th%: 1.6-3.9 (24 h)	Mean: 1.03 (24 h)
Symons et al.(2006, 091258)	Baltimore, MD (2002)	CHF	$PM_{2.5}$, NO_2, O_3	0,1,2,3	98th%: 1.9-2.1 99th%: 2.3 (8 h)	Mean: 0.4 (8 h)
Lee et al. (2007, 090707)	Kaohsiung, Taiwan (1996-2004)	CHF	PM_{10}, NO_2, SO_2, O_3	0-2	NA	Mean: 0.76 (24 h)
Yang (2008, 157160)	Taipei, Taiwan (1996-2004)	CHF	PM_{10}, NO_2, SO_2, O_3	0-2	NA	Mean: 1.26 (24 h)
STUDIES THAT EXAMINED HF AMONG OTHER CVDS						
Linn et al. (2000, 002839)	Los Angeles, CA (1992-1995)	CHF, MI, All CVD, CA, OS	PM_{10}, NO_2, O_3	0	98th%: 1.0-7.8 99th%: 1.1-8.3 (24 h)	Mean: (24 h) Winter 1.7; Spring 1.0 Summer 1.2; Fall 2.1
Koken et al. (2003, 049466)	Denver, CO (1993-1997)	CHF, MI, CAth, PHD, CD	PM_{10}, NO_2, SO_2, O_3	0,1,2,3	98th%: 1.2-2.0 99th%: 1.3-2.0 (24 h)	Mean: 0.9 (24 h)
Metzger et al. (2004, 044222)	Atlanta, GA (1993-2000)	CHF, IHD, All CVD, CD, PVCD	PM_{10}, NO_2, SO_2, O_3	0-2ma	98th%: 5.0-5.1 99th%: 5.5-5.9 (1 h)	Mean 1.8 (1 h)
Peel et al. (2007, 090442)	Atlanta, GA (1993-2000)	CHF, IHD, All CVD, CD, PVCD	PM_{10}, NO_2, SO_2, O_3	0-2ma	98th%: 5.0-5.1 99th%: 5.5-5.9 (1 h)	Mean 1.8 (1 h)

Cardiac = AMI, angina, dysrhythmia, or HF; CA = Cardiac arrhythmia; CAth = Cardiac atherosclerosis; CD = cardiac dysrhythmias; CHF = Congestive heart failure; PHD = Pulmonary heart disease; OS = Occlusive stroke; PVCD = peripheral vascular and cerebrovascular disease, ma = moving average.
NA: Not Available
[a] Includes range across individual monitors in study site; AQS data available for U.S. studies only.

Cardiovascular Diseases

The following section reviews studies that have investigated the effect of CO on ED visits and hospital admissions for all CVD outcomes (e.g., nonspecific). Several of these studies also examined specific CVDs and were briefly discussed in previous sections.

A multicity time-series study was conducted to estimate the risk of CVD hospitalization associated with short-term CO exposure in 126 U.S. urban counties from 1999-2005 for over 9 million Medicare enrollees 65 yr old and older (Bell et al., 2009, 193780). The analyses yielded positive associations between same-day CO concentration and increased risk of hospitalization for total CVD outcomes, which remained positive and statistically significant but were attenuated with copollutant adjustment, especially with NO_2 (Figure 5-6). Overall, a 1 ppm increase in same-day 1-h max CO was associated with a 1.010 (95% PI: 1.008-1.011) increase in risk of CVD admissions.

After adjustment for NO_2, the estimate was attenuated to 1.005 (95% PI: 1.004-1.007). For most cause-specific CVD hospitalizations, associations were positive and statistically significant for same day CO concentration adjusted for same-day NO_2 (IHD 1.004 [95% PI: 1.001-1.007], heart rhythm 1.006 [95% PI: 1.001-1.011], HF 1.009 [95% PI: 1.005-1.012], and cerebrovascular 1.005 [95% PI: 1.002-1.009]). Cause-specific effect estimates were not presented for CO alone (without adjustment for NO_2).

As discussed earlier, a study was conducted in Atlanta, GA where over 4 million ED visits from 31 hospitals for the period 1993-2000 were analyzed (SOPHIA). Several articles have been published from this research, with three examining cardiovascular admissions in relation to CO exposures. The first of these used a time-series design and analyzed a 3-day ma over single-day lags 0-2 as the a priori lag structure (Metzger et al., 2004, 044222). Results showed that a 1 ppm increase in 1-h max CO concentration was associated with an increase in daily ED visits for all CVDs (RR: 1.017 [95% CI: 1.008-1.027]). This persisted in two-pollutant models that included NO_2 and $PM_{2.5}$.

The second of these publications examined the association of ambient air pollution levels and cardiovascular morbidity in visits with and without specific secondary conditions (Peel et al., 2007, 090442). Within a time-stratified case-crossover design, a 3-day ma over single-day lags 0-2 was used as the a priori lag structure. Results from the case-crossover analyses on all cardiovascular and peripheral vascular and cerebrovascular disease were similar to the time-series results presented earlier. Results from the various comorbidity analyses are presented in Table 5-10. Similar to the results from the earlier publication, CO was mostly associated with peripheral vascular and cerebrovascular disease (PVCD) among those with and without comorbidities, except among those with CHF. Overall, there is limited, if any, evidence of susceptibility to the effects of CO concentration for those with comorbid conditions.

Table 5-10. Association of ambient air pollution levels and cardiovascular morbidity in visits with and without specific secondary conditions.

Co-morbidity	IHD	Dysrhythmias	PVCD	CHF
HYPERTENSION				
- With	1.007 (0.978-1.037)	1.065 (1.015-1.118)	1.038 (1.004-1.074)	1.037 (0.997-1.079)
- Without	1.022 (1.000-1.043)	1.008 (0.988-1.029)	1.027 (1.002-1.054)	1.010 (0.985-1.037)
DIABETES				
- With	0.985 (0.945-1.027)	1.058 (0.976-1.146)	1.065 (1.012-1.121)	1.020 (0.975-1.067)
- Without	1.023 (1.004-1.042)	1.014 (0.995-1.034)	1.025 (1.003-1.048)	1.018 (0.993-1.044)
COPD				
- With	0.996 (0.938-1.057)	0.972 (0.878-1.077)	1.113 (1.027-1.205)	1.058 (1.003-1.115)
- Without	1.018 (1.000-1.036)	1.018 (0.999-1.038)	1.026 (1.004-1.047)	1.011 (0.987-1.036)
CHF				
- With	0.956 (0.907-1.007)	1.065 (0.968-1.173)	1.072 (0.981-1.172)	-
- Without	1.024 (1.006-1.042)	1.015 (0.996-1.034)	1.029 (1.008-1.051)	-
DYSRHYTHMIAS				
- With	1.028 (0.985-1.072)	-	1.072 (1.011-1.138)	1.004 (0.960-1.051)
- Without	1.014 (0.995-1.033)	-	1.026 (1.004-1.048)	1.023 (0.998-1.049)

PVCD - peripheral vascular and cerebrovascular disease, IHD = ischemic heart disease, CHF = congestive heart failure.

Source: Reprinted with Permission of Oxford Journals from Peel et al. (2007, 090442)

The third study utilizing the SOPHIA data extended the time period to include 1993 through 2004 (Tolbert et al., 2007, 090316) and focused on two large outcome groups: a respiratory diseases group and a cardiovascular diseases group. The combined cardiovascular case group included the

following groups of primary ICD-9 diagnostic codes: IHD (410-414), cardiac dysrhythmias (427), CHF (428), and peripheral vascular and cerebrovascular disease (433-437, 440, 443-445, 451-453). Results showed that a 1 ppm increase in 1-h max CO concentration was associated with an increase in daily ED visits for all CVDs (RR: 1.016 [95% CI: 1.008-1.024]). CO was the strongest predictor of CVD effects in models with two-pollutant combinations of NO_2, CO and total carbon, as well as in a model including all three pollutants.

Earlier research conducted in Los Angeles, CA, showed that a 0.5 ppm increase in same-day 24-h avg CO concentration was associated with a 1.6% increase in CVD hospital admissions among people >30 yr (Linn et al., 2000, 002839). When the analyses were stratified by season, the strongest CO effect occurred during the winter (1.9% increase) followed by the summer (1.8%) and fall (1.4%) with no effect in spring.

In contrast to other North American studies, a study in Spokane, WA, did not find an association between CO (lags of 1-3 days) and an increase in the number of daily cardiac hospital admissions (quantitative results not reported) (Slaughter et al., 2005, 073854). Similarly, a time-series study in Windsor, Ontario, did not find an association between ambient CO and daily hospital admissions for CVDs (defined as HF, IHD, or dysrhythmias) (Fung et al., 2005, 074322). A total of 11,632 cardiac admissions were analyzed for the period 1995-2000. The lag periods analyzed in this study were lag 0 (same-day), a 2-day avg (lag 0-1), and a 3-day avg (lag 0-2). For a 1 ppm increase in 1-h max CO concentration the mean percent change in daily admissions for the <65-yr age group (lag 0) was -2.6 (95% CI: -6.2 to 3.3); and for the 65+ yr age group, 0.4 (95% CI: -1.9 to 2.7). The authors reported moderate to low correlations with NO_2 (r = 0.38), PM_{10} (r = 0.21) and SO_2 (r = 0.16).

Two case-crossover studies in Taiwan reported an association between ambient CO and hospital admissions for CVDs. In Taipei, a total of 74,509 CVD admissions from 47 hospitals for the period 1997-2001 were analyzed (Chang et al., 2005, 080086). An increase of 0.5 ppm in 24-h avg CO concentration (average over lags 0-2) during warmer periods (≥ 20°C) was associated with an increase in daily hospital admissions (OR: 1.09 [95% CI: 1.065-1.121]) but not cooler periods (<20°C) (OR: 0.98 [95% CI: 0.93-1.004]). These results persisted after controlling for PM_{10}, SO_2, or O_3 in two-pollutant models. An identical study in Kaohsiung analyzed 29,661 CVD admissions for the period 1997-2000 (Yang et al., 2004, 094376). Results showed that a 0.5 ppm increase in 24-h avg CO concentration was associated with an increase in CVD hospital admissions during both the warmer periods (OR: 1.50 [95% CI: 1.38-1.63]) and cooler periods (OR: 1.89 [95% CI: 1.69-2.12]).

Similarly, two Australian studies also reported associations between ambient CO concentrations and increased CVD hospital admissions among older adults. The first of these studies analyzed data from five of the largest cities in Australia (Brisbane, Canberra, Melbourne, Perth, Sydney) and two New Zealand cities (Auckland, Christchurch) for the period 1998-2001 (Barnett et al., 2006, 089770). The combined estimates showed that an increase of 0.75 ppm in the average 8-h max CO concentration over the current and previous day (lag 0-1) was associated with a 1.8% (95% CI: 0.7-2.8) increase in all CVD admissions among those aged 65+ yr. Among those aged 15-64 yr there was a smaller increase in CVD admissions (1.0% [95% CI: 0.2-1.7]). The second of the Australian studies examined ED visits for CVDs in older adults (65+ yr) in Sydney for the period 1997-2001 (Jalaludin et al., 2006, 189416). A 0.75 ppm increase in 8-h max CO concentration for single-day lags 0 and 1 was associated with increases in admissions of 2.5% (95% CI: 1.6-3.5) and 1.4% (95% CI: 0.5-2.4), respectively. Based on an average over lags 0 and 1 (e.g., lag 0-1), there was an increase of 2.6% (95% CI: 1.5-3.6). There were positive increases of approximately 3% in CVD ED visits during the cool (May-October) period but not the warm period (November-April).

Very few studies investigating the association between CO and cardiovascular hospital admissions have been conducted in European cities. Ballester et al. (2001, 013257) analyzed emergency hospital admissions in Valencia, Spain, for the period 1994-1996. The mean daily number of CVD admissions was 7, and there was no association between CO and admissions for all CVDs (RR: 1.009 [95% CI: 0.99-1.016] per 1 ppm increase in 1-h max CO concentration), heart diseases (RR: 1.010 [95% CI: 0.993-1.028] per 1 ppm increase), and cerebrovascular diseases (RR: 0.985 [95% CI: 0.959-1.012] per 1 ppm increase). When the analyses were stratified by hot and cold seasons, only CO concentrations during the hot season were associated with an increase in all cardiovascular admissions (RR: 1.033 [95% CI: 1.006-1.064] per 1 ppm increase), heart disease admissions (RR: 1.033 [95% CI: 1.000-1.067] per 1 ppm increase), and cerebrovascular admissions (RR: 1.074 [95% CI: 1.007-1.113] per 1 ppm increase).

Ballester et al. (2006, 088746) extended this research to include data from 14 Spanish cities for the period 1995-1999. An average exposure period over lags 0-1 was analyzed and for the combined estimates a 0.75 ppm increase in 8-h max CO concentration was associated with a 1.77% (95% CI: 0.56-2.99) increase in all cardiovascular hospital admissions and a larger increase of 3.57% (95% CI: 1.12-6.08) for heart disease admissions. These results persisted in two-pollutant models that included NO_2, O_3 and SO_2.

A study was carried out to evaluate the association between air pollution cardiovascular ED visits in subjects with and without diabetes in Sao Paulo, Brazil (Pereira Filho et al., 2008, 190260). From January 2001 to July 2003, 45,000 ED visits were registered due to CVDs, of which 700 were registered due to CVDs in diabetic patients. SO_2 and NO_2 were positively and statistically significantly associated with CVD ED visits among diabetics and nondiabetics, while CO was only positive and statistically significant among non-diabetic patients. PM_{10} and O_3 were not positively associated with ED admissions among either group.

Table 5-11 summarizes the non-specific CVD hospital admission studies that examined CO exposures. Due to the heterogeneity of endpoints, these studies do not lend themselves to a quantitative meta-analysis, and a forest plot was used to summarize the results of the studies on all CVD outcomes. Figure 5-5 shows the effect estimates associated with daily admissions for nonspecific CVD hospital admissions from selected studies.

In summary, many of the studies that examined associations between ambient CO concentrations and ED visits and daily hospital admissions for CVD reported small yet precise positive associations at short (0-1 day) lags. Among studies that conducted stratified analyses, there were slightly stronger effects among older adults and possibly during warmer periods.

Study	Location	Lag	Group
Bell et al. (2009, 193780)	126 US counties	0	65+ yr
Tolbert et al. (2007, 090316)	Atlanta, GA	0-2	
Linn et al. (2000, 002839)	Los Angeles, CA	0	All Year
Linn et al. (2000, 002839)	Los Angeles, CA	0	Spring
Linn et al. (2000, 002839)	Los Angeles, CA	0	Summer
Linn et al. (2000, 002839)	Los Angeles, CA	0	Fall
Linn et al. (2000, 002839)	Los Angeles, CA	0	Winter
Fung et al. (2005, 074322)	Windsor, Can	0-2	<65 yr
Fung et al. (2005, 074322)	Windsor, Can	0-2	65+ yr
Barnett et al. (2006, 089770)	Australia, New Zealand	0-1	15-64 yr
Barnett et al. (2006, 089770)	Australia, New Zealand	0-1	65+ yr
Jalaludin et al. (2006, 189416)	Sydney, Australia	0-1	65+ yr
Ballester et al. (2006, 088746)	Multicity, Spain	0-1	
Pereira Filho et al. (2008, 190260)	Sao Paulo, Brazil	0	Diabetic
Pereira Filho et al. (2008, 190260)	Sao Paulo, Brazil	0	Nondiabetic
Chang et al. (2005, 080086)	Taipei, Taiwan	0-2	>20°C Temp
Chang et al. (2005, 080086)	Taipei, Taiwan	0-2	<20°C Temp
Yang et al. (2004, 094376)	Kaohsiung, Taiwan	0-2	<20°C Temp
Yang et al. (2004, 094376)	Kaohsiung, Taiwan	0-2	>20°C Temp

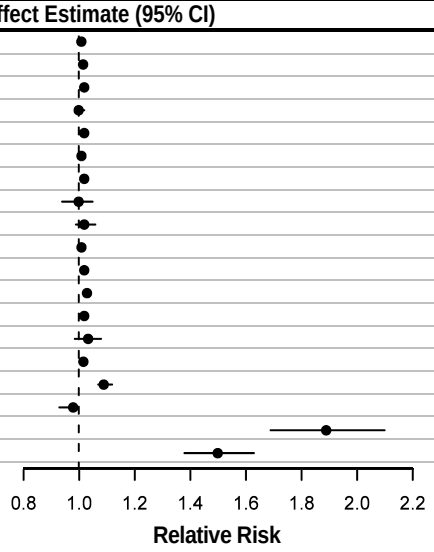


Figure 5-5. Summary of effect estimates (95% confidence intervals) associated with hospital admissions for CVD. Effect estimates have been standardized to a 1 ppm increase in ambient CO for 1-h max CO concentrations, 0.75 ppm for 8-h max CO concentrations, and 0.5 ppm for 24-h avg CO concentrations.

Table 5-11. Summary of nonspecific CVD hospital admission studies.

Study	Location	CVD Codes	Copollutants	Lags Examined	Upper CO Concentrations from AQS[b] in ppm	CO Concentrations Reported by Study Authors in ppm
Bell et al. (2009, 193780)	126 urban US counties (1999-2005)	Total CVD	$PM_{2.5}$, NO_2, EC	0, 1, 2	98th%: 1.1-19.1 99th%: 1.2-22.1 (1 h)	Median: 1.3 (1 h) Median: 0.5 (24 h)
Metzger et al. (2004, 044222)	Atlanta, GA (1993-2000)	All CVD	PM_{10}, NO_2, SO_2, O_3	0-2ma	98th%: 5.0-5.1 99th%: 5.5-5.9 (1 h)	Mean: 1.8 (1 h)
Peel et al. (2007, 090442)	Atlanta, GA (1993-2000)	All CVD	PM_{10}, NO_2, SO_2, O_3	0-2ma	98th%: 5.0-5.1 99th%: 5.5-5.9 (1 h)	Mean 1.8 (1 h)
Tolbert et al. (2007, 090316)	Atlanta, GA (1993-2004)	All CVD	PM_{10}, NO_2, SO_2, O_3	0-2ma	98th%: 4.7-4.9 99th%: 5.3-5.4 (1 h)	Mean 1.6 (1 h)
Linn et al. (2000, 002839)	Los Angeles, CA (1992-1995)	All CVD	PM_{10}, NO_2, O_3	0	98th%: 1.0-7.8 99th%: 1.1-8.3 (24 h)	Mean: (24 h) Winter 1.7; Spring 1.0; Summer 1.2; Fall 2.1
Slaughter et al. (2005, 073854)	Spokane, WA (1995-2001)	All CVD (ICD9: 390-459)	PM_{10}, $PM_{2.5}$, CO	1,2,3	98th%: 1.5-4.6 99th%: 1.7-5.0 (24 h)	Mean: range across 5 monitors 0.42-1.82 (24 h)
Fung et al. (2005, 074322)	Windsor, Can (1995-2000)	All CVD (HF, IHF, or Dysrhythmia)	PM_{10}, NO_2, SO_2, O_3	0, 0-1, 0-2	NA	Mean: 1.3 (1 h)
Chang et al. (2005, 080086)	Taipei, Taiwan (1997-2001)	All CVD (ICD9: 410-429)	PM_{10}, NO_2, SO_2, O_3	0-2	NA	Mean: 1.37 (24 h)
Yang et al. (2004, 094376)	Kaohsiung, Taiwan (1997-2000)	All CVD (ICD9: 410-429)	PM_{10}, NO_2, SO_2, O_3	0-2	NA	Mean: 0.79 (24 h)
Barnett et al. (2006, 089770)	Australia and New Zealand (1998-2001)	All CVD (ICD9: 390-459)	PM_{10}, NO_2, O_3	0-1	NA	Mean: (8h) 0.5-2.1
Jalaludin et al. (2006, 189416)	Sydney, Australia (1997-2001)	All CVD (ICD9: 390-459)	PM_{10}, NO_2, SO_2, O_3	0,1,2,3, 0-1	NA	Mean: 0.82 (8h)
Ballester et al. (2001, 013257)[a]	Valencia, Spain (1994-1996)	All CVD (ICD9: 390-459)	BS, NO_2, SO_2, O_3	1,2,3,4,5	NA	Mean: 0.54 (24 h)
Ballester et al. (2006, 088746)[a]	Multicity, Spain (1995-1999)	All CVD (ICD9: 390-459)	BS, PM_{10}, TSP, NO_2, SO_2, O_3	0-1	NA	Mean: range across 14 cities 0.12-0.24 (8h)
Pereira Filho et al. (2008, 190260)	Sao Paulo, Brazil (2001-2003)	All CVD	PM_{10}, NO_2, SO_2, O_3	0, 1, 2, 0-1, 0-2, 0-3	NA	Mean: 2.7 (8 h)

[a]These studies presented CO concentrations in the units mg/m^3. The concentrations were converted to ppm using the conversion factor 1 ppm = 1.15 mg/m^3, which assumes standard atmosphere and temperature.
[b] Includes range across individual monitors in study site; AQS data available for U.S. studies only.

Figure 5-6 and Figure 5-7 summarize the effects of CO concentration on ED visits and hospital admissions for all CVD outcomes other than stroke from studies that presented the results from two-pollutant models. Generally, the CO effect estimates from these studies are robust to the inclusion of copollutants, including PM_{10}, $PM_{2.5}$, NO_2, SO_2, and O_3. In all but two instances – Lee et al. (2007, 090707) (<25°C adjusted for NO_2) and Yang (2008, 157160) (<20°C adjusted for O_3) – when the single pollutant effect estimate was positive for CO, it remained positive after the addition of any of the copollutants investigated.

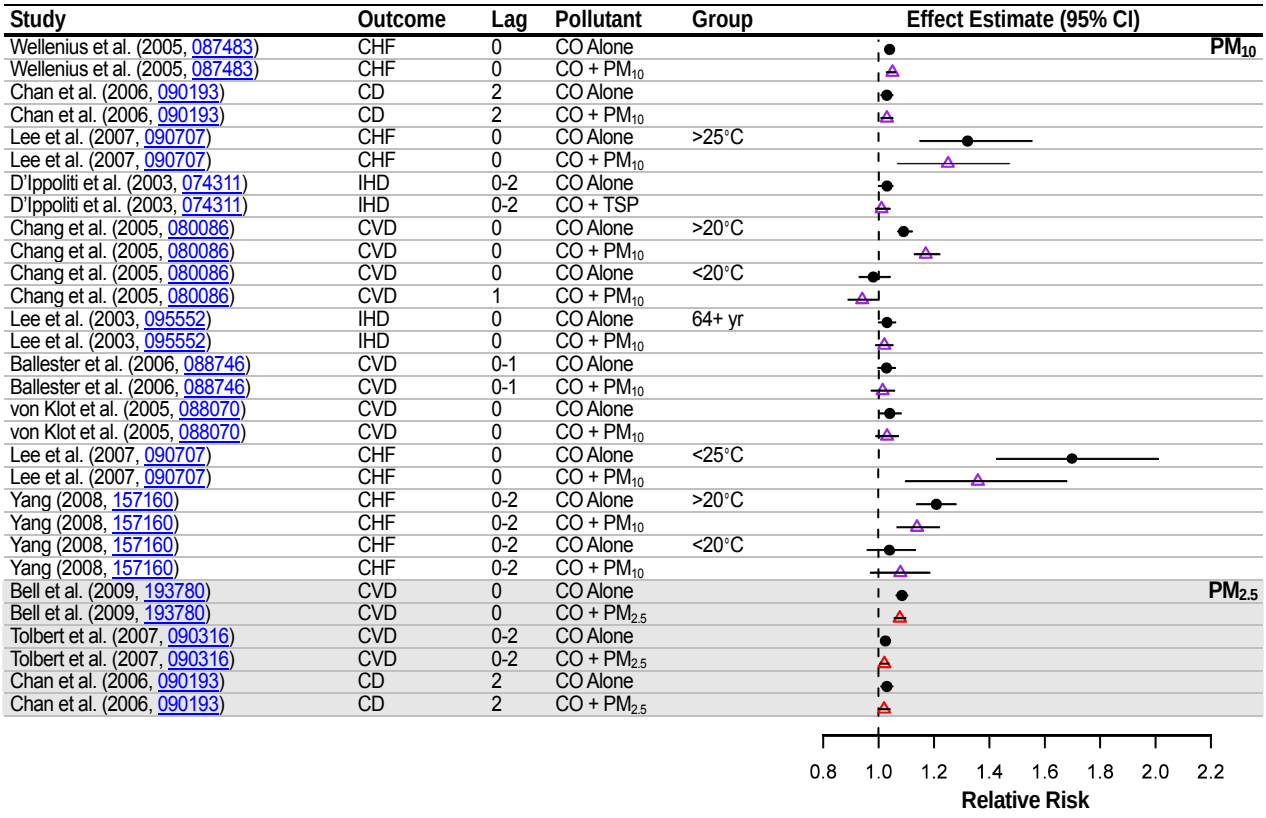


Figure 5-6. Effect estimates from studies of ED visits and hospital admissions for CVD outcomes other than stroke from single pollutant (CO only: black circles) and particulate copollutant (CO + $PM_{2.5}$: red triangles; CO + PM_{10} or TSP: purple triangles) models. Effect estimates have been standardized to a 1 ppm increase in ambient CO for 1-h max CO concentrations, 0.75 ppm for 8-h max CO concentrations, and 0.5 ppm for 24-h avg CO concentrations.

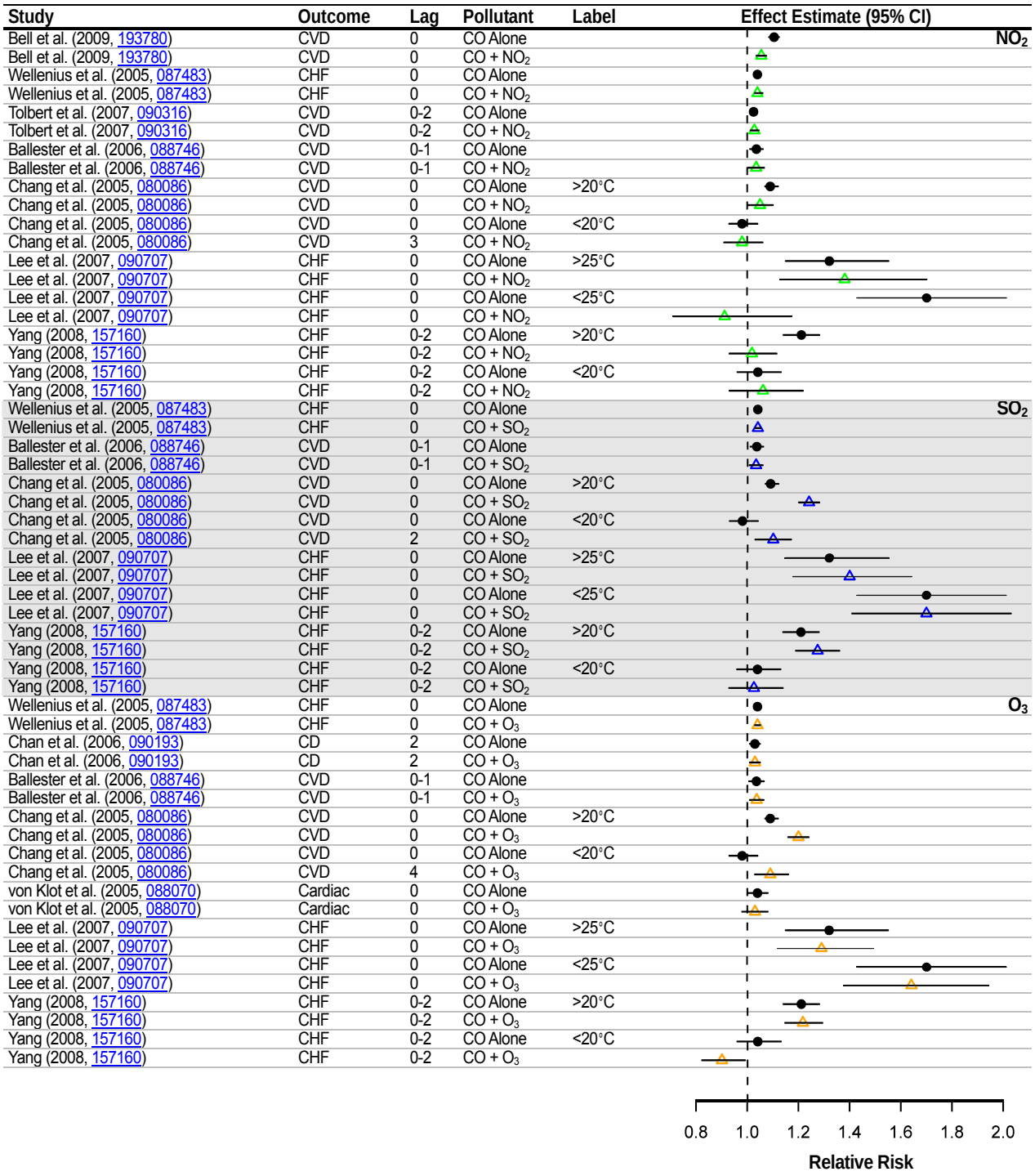


Figure 5-7. **Effect estimates from studies of ED visits and HAs for CVD outcomes other than stroke from single pollutant (CO only: black circles) and gaseous copollutant models (CO + NO_2, SO_2 and O_3= green, blue, and orange triangles, respectively). Effect estimates have been standardized to a 1 ppm increase in ambient CO for 1-h max CO concentrations, 0.75 ppm for 8-h max CO concentrations, and 0.5 ppm for 24-h avg CO concentrations.**

5.2.2. Epidemiologic Studies with Long-Term Exposure

Two studies examined CVD outcomes in association with long-term exposure to CO. Rosenlund et al. (2006, 089796) investigated long-term exposure (30 yr) to urban air pollution and the risk of MI in Sweden. The study included 2,246 cases and 3,206 controls aged 45-70 yr and residing in Stockholm County during 1992-1993. A detailed postal questionnaire was completed by 4,067 subjects, and all addresses inhabited during more than 2 yr since 1960 were geocoded. The exposures were then derived from dispersion calculations based on emissions data for each decade since 1960. These calculations were estimates of annual mean levels of traffic-generated NO_X, NO_2, CO, PM_{10}, and $PM_{2.5}$, with the addition of SO_2 from heating sources. The analyses were stratified by all cases, nonfatal cases, fatal cases, in-hospital death, and out-of-hospital death. Based on a 30-yr avg exposure all pollutants were not associated with overall MI incidence. However, increased CO was associated with out-of-hospital death from MI (OR: 1.81 [95% CI: 1.02-3.23] per 0.5 ppm increase in 30-yr avg CO concentration). Similar results were reported for NO_2. The correlation between the 30-yr NO_2 and CO exposures was reasonably strong (r = 0.74) and multipollutant models with both these pollutants included (NO_2, CO) were not examined. No other pollutants were significantly associated with all other MI outcomes. The study period was extended to include 43,275 cases of MI during 1985-1996 and 507,000 controls (Rosenlund et al., 2009, 190309). Five-year average exposures to NO_2, PM_{10} and CO were associated with incidence of MI, especially with fatal disease; when examining only nonfatal disease, no association was observed. The effect estimate for CO (OR: 1.03 [95%C CI: 1.02-1.04] per 0.5 ppm increase in 5-yr avg) was similar in magnitude to those for NO_2 and PM_{10}. When the analysis was restricted to the group that did not move between population censuses (the least expected misclassification of true individual exposure), the effect estimate for CO increased to 1.17 (95% CI: 1.11-1.24) per 0.5 ppm increase in 5-yr avg, and although the effect estimates for NO_2 and PM_{10} remained similar to the estimate for CO, in this analysis the effect estimate for CO was slightly greater in magnitude than the effect estimate for PM_{10}.

A small-area ecologic study analyzed mortality and hospital admissions for stroke across 1,030 census districts in Sheffield, U.K. (Maheswaran et al., 2005, 088683). Stroke counts within each census district were linked to modeled air pollution data which was then grouped into quintiles of exposure. For stroke hospital admissions, when the analyses were adjusted for only sex and age demographics, there was an exposure-response pattern exhibited across the quintiles of CO exposure with all levels reaching significance (RR: 1.37 [95% CI: 1.24-1.52] for the highest exposure group compared to the lowest group). However, this result did not persist when also adjusting for a deprivation index and smoking rates across the districts (RR: 1.11 [95% CI: 0.99-1.25]).

5.2.3. Summary of Epidemiologic Studies of Exposure to CO and Cardiovascular Effects

A substantial number of epidemiologic studies have examined the potential association between exposure to CO and various relevant cardiac endpoints or biomarkers. Overall, despite some mixed results reported among panel and retrospective cohort studies, there was evidence that exposure to CO has an effect on HR, various HRV parameters, and blood markers of coagulation and inflammation. Conversely, based on results from panel studies, there was little evidence of a link between CO and cardiac arrhythmia, cardiac arrest, the occurrence of MI, and increased BP.

Studies of ED visits and hospital admissions provide evidence that CO is associated with various forms of CVD, with lag periods ranging from 0 to 3 days. Nearly all of the studies include same day (lag 0) or next day (lag1) lag periods, which are consistent with the proposed mechanism and biological plausibility of these CVD outcomes. When categorized by specific cardiovascular outcome, the evidence is consistent. Studies of hospital admissions and ED visits for IHD provide the strongest evidence of ambient CO being associated with adverse CVD outcomes. The effect estimates for this outcome are nearly all positive, many are statistically significant, and the magnitude of effect is similar among the studies. Though not as consistent as the IHD effects, the effects for all CVD hospital admissions (which include IHD admissions) and CHF hospital admissions also provide evidence for an association with ambient CO concentrations. There is very limited evidence that ambient CO is associated with ischemic stroke. It is difficult to determine from this group of studies the extent to which CO is independently associated with CVD outcomes or if

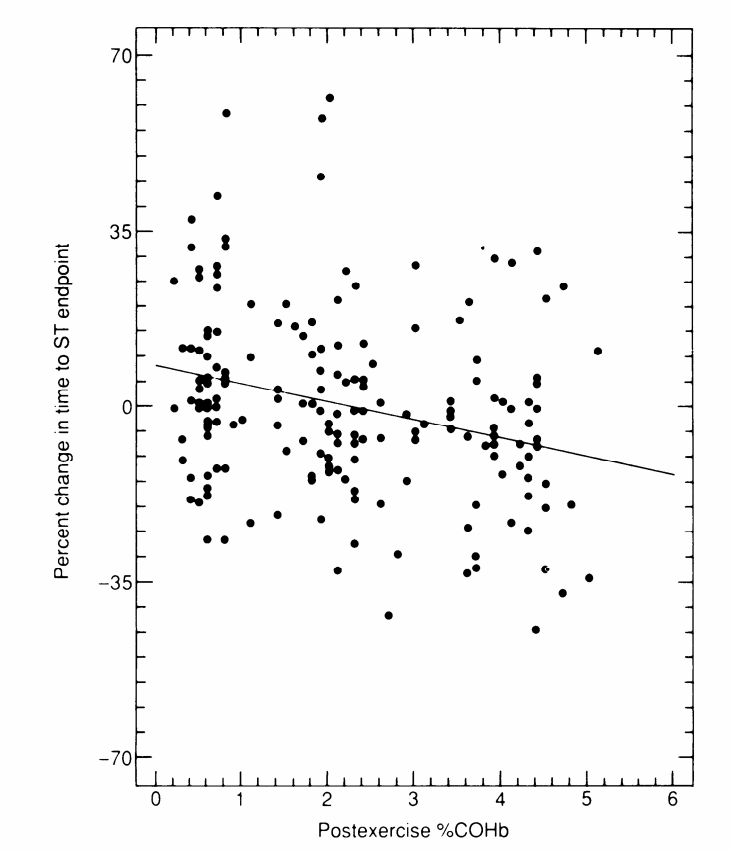
CO is a marker for the effects of another traffic-related pollutant or mix of pollutants. On-road vehicle exhaust emissions are a nearly ubiquitous source of combustion pollutant mixtures that include CO and can be an important contributor to CO in near-road locations. Although this complicates the efforts to disentangle specific CO-related health effects, the evidence indicates that CO associations generally remain robust in copollutant models and supports a direct effect of short-term ambient CO exposure on CVD morbidity.

5.2.4. Controlled Human Exposure Studies

Controlled human exposure studies provide valuable information related to the health effects of short-term exposure to air pollutants. Results of controlled human exposure studies can be used to provide coherence with the evidence from epidemiologic studies by expanding the understanding of potential mechanisms for the observed health outcomes. However, they may also provide information that can be used directly in quantitatively characterizing the exposure concentration-health response relationships at ambient or near-ambient concentrations.

Several human clinical studies cited in the 2000 CO AQCD (U.S. EPA, 2000, 000907) observed changes in measures of cardiovascular function among individuals with CAD, following short-term exposures to CO. Principal among these is a large multilaboratory study of men with stable angina (n = 63), designed to evaluate the effect of CO exposure resulting in COHb concentrations of 2% and 4% on exercise-induced angina and ST-segment changes indicative of myocardial ischemia (Allred et al., 1989, 013018; Allred et al., 1989, 012697; Allred et al., 1991, 011871). The majority of subjects were following an anti-ischemic medication regimen (e.g., beta blockers, nitrates, or calcium channel antagonists) which was maintained throughout the study. On three separate occasions, subjects underwent an initial graded exercise treadmill test, followed by 50- to 70-min exposures under resting conditions to average CO concentrations of 0.7 ppm (room air concentration range 0-2 ppm), 117 ppm (range 42-202 ppm) and 253 ppm (range 143-357 ppm). After the 50- to 70-min exposures, subjects underwent a second graded exercise treadmill test, and the percent change in time to onset of angina and time to ST endpoint between the first and second exercise tests was determined. The investigators conducted two exercise tests on exposure days (pre- versus postexposure) to control for day-to-day variability in the endpoints of interest. The effect of CO was evaluated by comparing the percent change in time to onset of angina or ST-segment change between the CO and clean air exposure days. The order of the three exposures was randomly determined and counterbalanced across subjects. For the CO exposure sessions, postexposure target COHb concentrations were set at values 10% greater than the post-exercise targets (i.e., 2.2% and 4.4%) to compensate for the elimination of CO during exercise testing in clean air following exposure. CO uptake constants were determined for each subject individually during a qualifying visit and were used to compute the inhaled concentration required to attain the target COHb concentrations. Although CO-oximetry was used at each center to rapidly provide approximate concentrations of COHb during the actual exposure, COHb concentrations determined by a gas chromatographic technique were used in the statistical analyses as this method is known to be more accurate than CO-oximetry and other spectrophotometric methods, particularly for samples containing COHb concentrations <5%. For the two CO exposures, the average postexposure COHb concentrations were reported as 2.4% and 4.7% (3.2% and 5.6% using CO-oximetry), and the average post-exercise COHb concentrations were reported as 2.0% and 3.9% (2.7% and 4.7% using CO-oximetry). While the average COHb concentrations during the exercise tests were clearly between the concentrations measured in postexposure and post-exercise blood samples, the study authors noted that the samples at the end of the exercise test represented the COHb concentrations at the approximate time of onset of myocardial ischemia as indicated by angina and ST segment changes. Relative to clean air exposure (COHb ≈ 0.6-0.7%), exposures to CO resulting in post-exercise COHb concentrations of 2.0% and 3.9% were shown to decrease the time required to induce ST-segment changes by 5.1% ($p = 0.01$) and 12.1% ($p < 0.001$), respectively. These changes were well correlated with the onset of exercise-induced angina. The observed dose-response relationship was further evaluated by regressing the percent change in time to ST-segment change or time to angina on actual post-exercise COHb concentration (0.2-5.1%) using the three exposures (air control and two CO exposures) for each subject. Regression analyses were conducted separately for each individual and the averages of the intercepts and slopes across subjects were reported. This analysis demonstrated significant decreases in time to angina and ST-segment change of approximately 1.9% and 3.9%, respectively, per 1% increase in COHb concentration, with no evidence of a measurable

threshold. The relationship between percent change in time to ST-segment endpoint and post-exercise COHb concentration is illustrated in Figure 5-8.



Source: Reprinted with Permission of HEI from Allred et al. (1989, 012697)

Figure 5-8. Regression of the percent change in time to ST endpoint between the pre- and postexposure exercise tests ([postexposure–pre-exposure]/pre-exposure) and the measured blood COHb levels at the end of exercise for the 63 subjects combined. The line represents the average of individual regressions.

In addition to the work of Allred et al. (1989, 013018; 1989, 012697; 1991, 011871) a number of other studies involving individuals with stable angina have also demonstrated a CO-induced decrease in time to onset of angina, as well as reduction in duration of exercise at COHb concentrations between 3 and 6%, measured using spectrophotometric methods (Adams et al., 1988, 012692; Anderson et al., 1973, 023134; Kleinman et al., 1989, 012696; Kleinman et al., 1998, 047186). However, Sheps et al. (1987, 012212) observed no change in time to onset of angina or maximal exercise time following a 1-h exposure to 100 ppm CO (targeted COHb of 4%) among a group of 30 patients with CAD. In a subsequent study conducted by the same laboratory, a significant increase in number of ventricular arrhythmias during exercise was observed relative to room air among individuals with CAD following a 1-h exposure to 200 ppm CO (targeted COHb of 6%) but not following a 1-h exposure to 100 ppm CO (targeted COHb of 4%) (Sheps et al., 1990, 013286).

While cardiovascular effects of CO have consistently been observed in studies of controlled human exposure among individuals with CAD at COHb concentrations between 2 and 6%, a quantitative meta-analysis of these studies is of limited value considering differences in the methods used. For example, variation in exercise protocols resulted in substantial differences between studies in total exercise time. More importantly, only Allred et al. (1989, 013018; 1989, 012697; 1991,

011871) analyzed COHb concentration using gas chromatography. Although all studies measured COHb using spectrophotometric methods, these methods are only accurate within approximately 1% COHb of the true value at COHb concentrations < 5% (U.S. EPA, 1991, 017643). Therefore, a quantitative evaluation of changes in cardiovascular response with small increases in COHb concentration (< 1%) as measured using CO-oximetry is neither appropriate nor informative, particularly at low COHb concentrations.

It should be noted that although the subjects evaluated in the studies described above are not necessarily representative of the most sensitive population, the level of disease in these individuals was moderate to severe, with the majority either having a history of MI or having ≥ 70% occlusion of one or more of the coronary arteries. The 2000 CO AQCD (U.S. EPA, 2000, 000907) presented very little evidence of CO-induced changes in cardiovascular function in healthy adults. Davies and Smith (1980, 011288) exposed healthy young adults continuously for 7 days to CO concentrations of 0, 15, or 50 ppm. In this study, a marked ST-segment depression was demonstrated in only 1 out of 16 subjects following exposure to 15 ppm CO (2.4% COHb) or 50 ppm CO (7.2% COHb).

Since the publication of the 2000 CO AQCD (U.S. EPA, 2000, 000907), no new human clinical studies have been published involving controlled CO exposures among subjects with CAD. However, a number of new studies have evaluated changes in various measures of cardiovascular and systemic responses following controlled exposures to CO in healthy adults. Adir et al. (1999, 001026) exposed 15 young healthy adult males to room air or CO for approximately 4 min, using a CO exposure concentration which had been shown to produce the targeted COHb level of 4-6%. Following each exposure, subjects performed an exercise treadmill test at their maximal capacity. Exposure to CO was not observed to cause arrhythmias, ST-segment changes, or changes in myocardial perfusion (thallium scintigraphy) during postexposure exercise. However, CO was demonstrated to decrease the postexposure duration of exercise by approximately 10% ($p = 0.0012$). In addition, the authors reported significant CO-induced decreases in metabolic equivalent units ($p < 0.001$), which is a relative measure of O_2 consumption. These results support the findings of several studies cited in the 2000 CO AQCD (U.S. EPA, 2000, 000907) which observed decreases in exercise duration and maximal aerobic capacity among healthy adults at COHb levels ≥ 3% (Drinkwater et al., 1974, 041332; Ekblom and Huot, 1972, 010886; Horvath et al., 1975, 010887; Raven et al., 1974, 041340). While these decreases in exercise duration were relatively small and only likely to be noticed by competing athletes, the findings are nonetheless important in providing coherence with the observed effects of CO on exercise-induced myocardial ischemia among patients with CAD.

Kizakevich et al.(2000, 052691) evaluated the cardiovascular effects of increasing CO concentration in healthy adults engaged in upper and lower body exercise. Subjects were initially exposed for 4-6 min to CO concentrations between 1,000 and 3,000 ppm, followed by continued exposure to 27, 55, 83, and 100 ppm to maintain COHb levels of 5, 10, 15, and 20%, respectively. Relative to room air control, CO exposure was not observed to cause ST-segment changes or affect cardiac rhythm at any concentration during either upper or lower body exercise. Compensation mechanisms for reduced O_2 carrying capacity during CO exposure were demonstrated, with statistically significant increases in heart rate occurring at COHb levels ≥ 5%, and statistically significant increases in cardiac output and cardiac contractility observed at COHb levels ≥ 10%. In a human clinical study designed to evaluate the contribution of CO to cardiovascular morbidity associated with cigarette smoking, Zevin et al. (2001, 021120) exposed 12 healthy male smokers for 7 consecutive days to clean air, CO, or cigarette smoke, with each subject serving as his own control. The COHb levels were similar between the exposures to cigarette smoke and CO, with average concentrations of 6% and 5%, respectively. Cigarette smoke, but not CO, was observed to significantly increase plasma levels of CRP and plasma platelet factor 4 relative to the air control arm of the study. Neither cigarette smoke nor CO was shown to affect BP. Hanada et al. (2003, 193915) observed an increase in leg muscle sympathetic nerve activity (MSNA) following controlled exposures to CO (COHb ≈ 20%) under normoxic or hyperoxic conditions. Although an increase in the magnitude of sympathetic activation is typically associated with regional vasoconstriction, no CO-induced changes in femoral venous blood flow were observed in this study. These findings are in agreement with those of Hausberg and Somers (1997, 083450) who observed no change in forearm blood flow or BP in a study of 10 healthy men and women following a controlled exposure to CO (COHb ≈ 8%). Interestingly, one recent study did observe an increase in retinal blood flow, retinal vessel diameter, and choroidal blood flow following controlled exposures to CO at a concentration of 500 ppm (Resch et al., 2005, 193853). This protocol resulted in COHb concentrations of 5.6% and 9.4% following exposures of 30 and 60 min, respectively, with

statistically significant increases in retinal and choroidal blood flow observed at both time points relative to synthetic air control. This CO-induced change in ocular hemodynamics may have been due to local tissue hypoxia; however, the clinical significance of this finding is unclear. Exposures to CO have also been shown to affect skeletal muscle function, with one recent human clinical study reporting a decrease in muscle fatigue resistance in healthy adult males, using both voluntary and electrically-induced contraction protocols following controlled exposures to CO resulting in an average COHb level of 6% (Morse et al., 2008, 097980).

In summary, controlled human exposures to CO among individuals with CAD have been shown to consistently increase markers of myocardial ischemia at COHb concentrations between 2 and 6%. No such effects have been observed in healthy adults following controlled exposures to CO. Although some studies have reported CO-induced hemodynamic changes among healthy adults at COHb concentrations as low as 5%, this effect has not been observed consistently across studies.

5.2.5. Toxicological Studies

While there was no toxicological research reported in the 2000 CO AQCD (U.S. EPA, 2000, 000907) that involved CO exposures at or below the NAAQS levels, adverse cardiovascular effects were reported for higher CO concentrations. The lowest observed effect levels for cardiovascular effects in experimental animals included 50 ppm (6-wk exposure, 2.6% COHb) for cardiac rhythm effects, 100 ppm (46 days, 9.3% COHb) for hematology effects, 150 ppm (30 min, 7.5% COHb) for hemodynamic effects, 200 ppm (30 days, 15.8% COHb) for cardiomegaly, and 250 ppm (10 wk, 20% COHb) for atherosclerosis and thrombosis (Table 6-11 in the 2000 CO AQCD) (U.S. EPA, 2000, 000907). Conflicting experimental data relating to the role of CO in promoting atherosclerotic vessel disease were discussed. While some animal studies have linked chronic CO exposure with atherosclerosis development resulting from increased fatty streaking and cellular lipid loading (Davies et al., 1976, 010660; Thomsen, 1974, 010704; Turner et al., 1979, 012328), other studies have failed to see this association (Penn et al., 1992, 013728; Stupfel and Bouley, 1970, 010557). Vascular insults due to acute exposure to CO concentrations of 50 ppm and higher were also reported (Ischiropoulos et al., 1996, 079491; Thom, 1993, 013895; Thom et al., 1998, 016750; Thom et al., 1999, 016757; Thom et al., 1999, 016753). In addition, chronic CO exposure has been shown to result in ventricular hypertrophy (Penney et al., 1984, 011567; Penney et al., 1988, 012521).

The following sections describe recent studies dealing with toxicity of low to moderate concentrations (35-250 ppm) of CO. There has been little new research with the overt purpose of examining environmentally-relevant levels of CO. For the most part, studies were designed to mimic exposures related to cigarette smoke, either side-stream or mainstream, accidental CO poisoning, or for the purposes of therapeutic application. Thus, few studies examined levels of CO within the current 1-h (35 ppm) or 8-h (9 ppm) NAAQS levels, and fewer still examined concentration response curves to delineate no-effects levels. However, it is apparent that CO, at low to moderate concentrations, has pathophysiologic effects on the cardiovascular system and on relatively ubiquitous cellular pathways. In evaluating these studies, it should be kept in mind that the traditional concept of CO pathophysiology resulting from reduced O_2 delivery is likely to be more relevant for higher concentrations of CO than are currently found in the ambient environment.

CO exposure at environmentally-relevant levels is unlikely to cause overt toxicity in a healthy cell; however, susceptibility may be rendered by disease or developmental stage. A common theme appears to be the vulnerability of vascular cells, especially the endothelium, which could be considered the first organ of contact once CO is taken up into the circulation. While relatively little research has been conducted since the 2000 CO AQCD (U.S. EPA, 2000, 000907), several key studies conducted at environmentally-relevant CO levels provide important clues to the potential public health implications of ambient CO exposure.

5.2.5.1. Endothelial Dysfunction

While the preferential binding to heme and effective displacement of O_2 by CO has been well established for over a century, new information from various fields of study are beginning to elucidate nonhypoxic mechanisms that may lead to cardiovascular abnormalities associated with CO exposure. Research by Thom, Ischiropoulos, and colleagues (Ischiropoulos et al., 1996, 079491; Thom and Ischiropoulos, 1997, 085644; Thom et al., 1994, 076459; Thom et al., 1997, 084337;

Thom et al., 1999, 016753; Thom et al., 1999, 016757), some of which was reported in the 2000 CO AQCD (U.S. EPA, 2000, 000907), has focused on CO-mediated displacement of NO from heme-binding sites. Some of this work demonstrates a specific pathway by which severe CO poisoning can lead to the release of NO from platelets with subsequent neutrophil activation and vascular injury (Ischiropoulos et al., 1996, 079491; Thom et al., 2006, 098418). The steps include: (1) peroxynitrite generation from the reaction of NO from platelets with neutrophil-derived superoxide; followed by (2) stimulation of intravascular neutrophil degranulation; that can result in (3) myeloperoxidase deposition along the vascular lining. Products from myeloperoxidase-mediated reactions can cause endothelial cell activation (Thom et al., 2006, 098418) and can lead to endothelial dysfunction. The concentrations used in these studies are greatly in excess of the NAAQS levels but certainly within the range of accidental or occupational exposures. Research by these same investigators at more environmentally-relevant CO levels was partially reviewed in the 2000 CO AQCD (U.S. EPA, 2000, 000907). The release of free NO was noted in isolated rat platelets exposed to 10-20 ppm CO (Thom and Ischiropoulos, 1997, 085644). Increased nitrotyrosine content of the aorta was observed in rats exposed to 50 ppm CO for 1 h (Thom et al., 1999, 016757; Thom et al., 1999, 016753). Furthermore, in this same study, a 1-h exposure to 100 ppm CO led to albumin efflux from skeletal muscle microvasculature at 3 h and leukocyte sequestration in the aorta at 18 h; LDL oxidation was also reported. These effects were dependent on NOS but not on neutrophils or platelets. A second study demonstrated NO-dependent effects of 50-100 ppm CO in lungs and is described in Section 5.5.4 (Thom et al., 1999, 016757). Studies in cultured endothelial cells were also conducted using buffer saturated with 10-100 ppm CO (Thom et al., 1997, 084337). These experiments were designed to mimic conditions where blood COHb levels were between 3.8 and 28%, resulting in exposure of endothelial cells to 11-110 nM CO. CO stimulated the release of NO from endothelial cells along with formation of peroxynitrite; delayed cell death was observed at CO concentrations of 22 nM and higher (Thom et al., 1997, 084337). A more recent study demonstrated adaptive responses in endothelial cells exposed to this same range of CO concentrations (Thom et al., 2000, 011574). Specifically, 1-h exposure to 11 nM CO resulted in MnSOD and HO-1 induction and resistance to the apoptotic effects of 110 nM CO. These protective effects of CO were mediated by NO, as demonstrated using an inhibitor of NOS and a scavenger of peroxynitrite. Collectively, these experiments demonstrated oxidative and nitrosative stress, the initiation of inflammation, increased microvascular permeability and altered cell signaling in animals and isolated cells following exposure to 10-100 ppm CO.

CO is an endogenous regulator of vasomotor tone through vasodilatory effects, mediated by activation of soluble guanylate cyclase and activation of large conductance Ca^{2+}-activated K^{+} channels. However, CO does not cause vasodilation in every vascular bed. For example, 5, 100, 500 and 2,500 ppm CO administered by inhalation to near-term fetal lambs did not induce pulmonary vasodilation, and the HO-inhibitor zinc protoporphyrin IX failed to affect baseline vascular tone (Grover et al., 2000, 097088). In some cases CO promotes vasoconstriction, which is thought to be mediated by inhibition of endothelial NOS (Johnson and Johnson, 2003, 053611; Thorup et al., 1999, 193782) or decreased NO bioavailability. An interesting series of studies has also suggested that endogenous CO derived from HO-1 which is induced in a variety of disease models (salt-sensitive forms of hypertension, metabolic syndrome in obese rats) is responsible for skeletal muscle arterial endothelial dysfunction (Johnson and Johnson, 2003, 053611; Johnson et al., 2006, 193874; Teran et al., 2005, 193770). Additional studies will be useful in determining whether environmentally-relevant concentrations of CO have detrimental effects on preexisting conditions such as hypertension, metabolic syndrome or pregnancy.

Several recent animal studies examined the vascular effects of controlled exposures to complex combustion mixtures containing CO. Vascular dilatation was decreased following exposure to diesel (4 h at 4 ppm) (Knuckles et al., 2008, 191987) and gasoline engine emissions (6 h/day for 1, 3, and 7 days at 80 ppm) (Lund et al., 2009, 180257). Furthermore, evidence of vascular ROS following gasoline emissions has been shown in certain animal models (6 h/day for 50 days at 8-80 ppm) (Lund et al., 2007, 125741). While none of these studies examined the potential independent role of CO, it is clearly a common factor in the various combustion atmospheres, and future work will be needed to reveal its importance on vascular health.

5.2.5.2. Cardiac Remodeling Effects

Cardiomyopathy, or abnormal growth of the cardiac muscle, can manifest in different ways, depending on the nature of the insult. The adverse effects of cardiac hypertrophy are due to reduction of ventricular chamber volume and a diminishing efficiency of the heart. Such concentric hypertrophy typically occurs in response to chronic increases in load, as occurs with hypertension. Ischemia of the cardiac tissue can also lead to cardiac remodeling and myopathy. During and after an acute infarction or obstruction of major coronary vessels, downstream tissues can suffer severe regional ischemia that leads to significant necrosis. Such regions will lose the ability to contract, and surrounding tissue will show deficits in contractility. Decreased contractility is often a result of structural thinning of the ventricular wall, as well as metabolic impairments. Chronic ischemia, such as may result from CAD, may similarly impair cardiomyocyte function and cause decreased contractility and remodeling. However, ultimately cardiomyopathies are of a complex origin involving mismanagement of fluid balance, abnormal hormonal influences (epinephrine, angiotensin), and insufficient perfusion/nutrition. Assessing the role of exogenous CO in altering pathways leading to cardiomyopathy is a relatively new endeavor, and several new findings are of great interest.

The heart is a known target for CO toxicity, potentially due to its high rate of O_2 consumption. Effects of CO on the healthy heart have only been observed at relatively high concentrations. For example, a recent study by Sorhaug et al. (2006, 180414) demonstrated cardiac hypertrophy in rats exposed for 72 wk to 200 ppm CO. COHb levels were reported to be 14.7%. Neither structural signs of hypertension in the pulmonary arteries nor atherosclerotic lesions in the systemic arteries were observed. A follow-up study by the same investigators (Bye et al., 2008, 193777) found reduced aerobic capacity and contractile function leading to pathologic cardiac hypertrophy in rats exposed for 18 mo to 200 ppm CO. Cardiac hypertrophy was also demonstrated in rats exposed to 100-200 ppm CO for 1-2 wk (Loennechen et al., 1999, 011549). This response was accompanied by an increase in endothelin-1 expression. COHb levels were reported to be 12-23% in this latter study.

Effects of CO on the healthy heart have also been demonstrated following short-term exposures. In a study by Favory et al. (2006, 184462) rats were exposed to 90 min of 250 ppm CO, which led to peak COHb values of roughly 11%; recovery of 96 h was needed for COHb levels to return to baseline. The authors noted that within the first 24 h of recovery, while COHb values decreased from 11% to 5%, the coronary vascular perfusion pressure and the left ventricular developed pressure were significantly increased compared to baseline. Concomitantly, the ratio of cGMP to cAMP decreased, and the sensitivity of the coronary vascular bed to both acetylcholine and a NO donor was reduced by CO exposure. The authors concluded that the discordant alterations in contractility (increased) and perfusion (decreased) may place the heart at risk of O_2 limitations following this exposure to CO.

Several studies examined the impact of lower levels (50 ppm) on preexisting or concurrent cardiac pathologies. In one such study, CO exacerbated the effects of a hypoxia-based model of right ventricular remodeling and failure (Gautier et al., 2007, 096471). In controlled laboratory settings, chronic hypobaric hypoxia (HH) caused right ventricular hypertrophy as a result of pulmonary arterial vasoconstriction and increased pulmonary resistance. Using such a model (Wistar rats exposed for 3 wk to hypoxia), CO (50 ppm during the last week of hypoxia, continuous) only increased COHb from 0.5% to 2.4% in the hypoxia model, yet had significant effects on blocking compensatory functional responses to hypoxia, such as increased fractional shortening and contractility. Also, while right ventricular weight was increased by hypoxia alone, significant pathology related to necrosis was observed in the hypoxia + CO-exposed rats. The reduced coronary perfusion of the right ventricle in hypoxia + CO-exposed rats may help explain the histopathologic findings. The authors cited previous work demonstrating that exogenous CO can inhibit NOS (Thorup et al., 1999, 193782), which is essential for coronary dilation and angiogenesis. Thus, this study provided evidence that exogenous CO may interrupt or downregulate pathways that endogenous CO may activate.

In two studies by Melin et al. (2002, 037502; 2005, 193833), Dark Agouti rats were exposed for 10 wk to either HH, 50 ppm CO or HH plus 50 ppm CO. CO exposure amplified the right ventricular cardiac hypertrophy and decreased the right ventricular diastolic function which occurred in response to HH. In addition, the combined exposure led to effects on left ventricular morphology and function which were not seen with either exposure alone. Changes in HRV were also reported. Results from both of these studies combined with results of Gautier and colleagues (Gautier et al., 2007, 096471) indicated that CO may interfere with normal homeostatic responses to hypoxia. This

could occur by blocking HIF-1α-responsive elements (vascular endothelial growth factor, erythropoietin) or other cell signaling pathways.

In a similar study, Carraway et al. (2002, 026018) exposed rats to HH (380 torr) with or without co-exposure to CO (50 ppm). These exposures were continuous for up to 21 days and focused on pulmonary vascular remodeling. While the addition of CO to HH did not alter the thickness or diameter of vessels in the lung, there was a significant increase in the number of small (<50 μm) diameter vessels compared to control, HH-only, and CO-only exposures. Despite the greater number of vessels, the overall pulmonary vascular resistance was increased in the combined CO + hypoxic exposure, which the authors attributed to enhancement of muscular arterioles and β-actin. Results of this study, taken together with results from the studies of Gautier et al. (2007, 096471) and Melin et al. (2002, 037502; 2005, 193833), suggested that the combined effect of low levels of CO with hypoxia is an enhanced right ventricle workload and an exacerbated cardiomyopathy related to pulmonary hypertension. The population at risk of primary pulmonary hypertension is low, but secondary pulmonary hypertension is a frequent complication of COPD and certain forms of heart failure.

5.2.5.3. Electrocardiographic Effects

In two related studies, Wellenius et al. (2004, 087874; 2006, 156152) examined the effects of CO in an animal model of post-infarction myocardial sensitivity (Wellenius et al., 2002, 025405). In a previous study, ECG changes were observed during exposure to residual oil fly ash (ROFA) particles in anesthetized post-MI Sprague Dawley rats (Wellenius et al., 2002, 025405). Using this model, Wellenius and colleagues tested the effects of 35 ppm CO (1-h exposure) on the induction of spontaneous arrhythmias (Wellenius et al., 2004, 087874). CO exposure caused a statistically significant decrease (60.4%) in ventricular premature beat (VPB) frequency during the exposure period in rats with a high number of pre-exposure VPB. No interaction was observed with co-exposure to carbon concentrated particles, which independently reduced VPB frequency during the postexposure period when administered alone. In a follow-up publication, results from the analysis of supraventricular ectopic beats (SVEB) were provided (Wellenius et al., 2006, 156152). A decrease in the number of SVEB was observed with CO (average concentration 37.9 ppm) compared to filtered air. While the authors concluded that CO exposure did not increase risk of SVEB in this particular rodent model of coronary occlusion, the fact that cardiac electrophysiological dynamics are significantly altered by short-term exposure to low-level CO may be of concern for other models of susceptibility.

5.2.5.4. Summary of Cardiovascular Toxicology

Experimental studies demonstrated that short-term exposure to 50-100 ppm CO resulted in aortic injury as measured by increased nitrotyrosine and the sequestration of activated leukocytes in healthy rats. In addition, skeletal muscle microvascular permeability was increased. Short-term exposure to 35 ppm CO altered cardiac electrophysiology in a rat model of arrhythmia. Furthermore, short-term exposure to 50 ppm CO exacerbated cardiac pathology and impaired function in an animal model of hypertrophic cardiomyopathy and enhanced vascular remodeling and increased pulmonary vascular resistance in an animal model of pulmonary hypertension. Ventricular hypertrophy was observed in healthy rats in response to chronic exposures of 100-200 ppm CO. These studies provide some support for the development of adverse health effects resulting from exposures to CO at environmentally-relevant concentrations.

5.2.6. Summary of Cardiovascular Effects

5.2.6.1. Short-Term Exposure to CO

The most compelling evidence of a CO-induced effect on the cardiovascular system at COHb levels relevant to the current NAAQS comes from a series of controlled human exposure studies among individuals with CAD. These studies, described in the 1991 (U.S. EPA, 1991, 017643) and

2000 (U.S. EPA, 2000, 000907) CO AQCDs, demonstrate consistent decreases in the time to onset of exercise-induced angina and ST-segment changes following CO exposures resulting in COHb levels of 2-6% (Section 5.2.4). No human clinical studies have been designed to evaluate the effect of controlled exposures to CO resulting in COHb concentrations lower than 2%. Human clinical studies published since the 2000 CO AQCD (U.S. EPA, 2000, 000907) have reported no association between CO and ST-segment changes or arrhythmia; however, none of these studies included individuals with diagnosed heart disease.

While the exact physiological significance of the observed ST-segment changes among individuals with CAD is unclear, ST-segment depression is a known indicator of myocardial ischemia. It is also important to note that the individuals with CAD who participated in these controlled exposure studies may not be representative of the most sensitive individuals in the population. It is conceivable that the most sensitive individuals respond to COHb concentrations lower than those evaluated in studies of controlled human exposures. Variability in activity patterns and severity of disease among individuals with CAD is likely to influence the critical level of COHb which leads to adverse cardiovascular effects.

The degree of ambient CO exposure which leads to attainment of critical levels of COHb will also vary between individuals. Although endogenous COHb is generally <1% in healthy individuals, higher endogenous COHb levels are observed in individuals with certain medical conditions. Nonambient exposures to CO, such as exposure to ETS, may increase COHb above endogenous levels, depending on the gradient of pCO. Ambient exposures may cause a further increase in COHb. Modeling results described in Chapter 4 indicate that increases of ~1% COHb are possible with exposures of several ppm CO, depending on exposure duration and exercise level.

Findings of epidemiologic studies conducted since the 2000 CO AQCD (U.S. EPA, 2000, 000907) are coherent with results of the controlled human exposure studies. These recent studies observed associations between ambient CO concentration and ED visits and hospital admissions for IHD, CHF and cardiovascular disease as a whole and were conducted in locations where the mean 24-h avg CO concentrations ranged from 0.5 ppm to 9.4 ppm (Table 5-7). All but one of these studies that evaluated CAD outcomes (IHD, MI, angina) reported positive associations (Figure 5-2). Although CO is often considered a marker for the effects of another traffic-related pollutant or mix of pollutants, evidence indicates that CO associations generally remain robust in copollutant models and supports a direct effect of short-term ambient CO exposure on CVD morbidity. These studies add to findings reported in the 2000 CO AQCD (U.S. EPA, 2000, 000907) that demonstrated associations between short-term variations in ambient CO concentrations and exacerbation of heart disease.

The known role of CO in limiting O_2 availability lends biological plausibility to ischemia-related health outcomes following CO exposure. However, it is not clear whether the small changes in COHb associated with ambient CO exposures results in substantially reduced O_2 delivery to tissues. Recent toxicological studies suggest that CO may also act through other mechanisms by initiating or disrupting cellular signaling. Studies in healthy animals demonstrated oxidative injury and inflammation in response to 50-100 ppm CO, while studies in animal models of disease demonstrated exacerbation of cardiomyopathy and increased vascular remodeling in response to 50 ppm CO. Further investigations will be useful in determining whether altered cell signaling contributes to adverse health effects following ambient CO exposure.

Given the consistent and coherent evidence from epidemiologic and human clinical studies, along with biological plausibility provided by CO's role in limiting O_2 availability, it is concluded that **a causal relationship is likely to exist between relevant short-term exposures to CO and cardiovascular morbidity.**

5.2.6.2. Long-Term Exposure to CO

Only two epidemiologic studies were identified that investigated the relationship between long-term exposure to CO and cardiovascular effects, and the results of these studies provide very limited evidence of an association. Considering the lack of evidence from controlled human exposure studies and the very limited evidence from toxicological studies on cardiovascular effects following long-term exposure to CO, the available evidence is **inadequate to conclude that a causal relationship exists between relevant long-term exposures to CO and cardiovascular morbidity.**

5.3. Central Nervous System Effects

5.3.1. Controlled Human Exposure Studies

The behavioral effects of controlled human exposures to CO have been examined by several laboratories, and these studies were summarized in the 2000 CO AQCD (U.S. EPA, 2000, 000907). Briefly, decreases in visual tracking as well as visual and auditory vigilance were observed following exposures to CO resulting in COHb levels between 5% and 20% (Benignus et al., 1987, 012250; Fodor and Winneke, 1972, 011041; Horvath et al., 1971, 011075; Putz et al., 1979, 023137). One study reported similar behavioral effects (time discrimination) among a group of healthy volunteers with COHb levels <3% (Beard and Wertheim, 1967, 011015), though subsequent studies were unable to replicate these findings at such low exposure concentrations (Otto et al., 1979, 010863; Stewart et al., 1973, 093412). These outcomes represent a potentially important adverse effect of CO exposure resulting in COHb levels ≥ 5%, although it is important to note that these findings have not been consistent across studies. Similarly, some studies demonstrated decreases in reaction time as well as decrements in cognitive function and fine motor skills following controlled exposures to CO; however, these studies were not typically conducted using double-blind procedures, which may significantly affect the outcome of behavioral studies (Benignus, 1993, 013645). It should be noted that all behavioral studies of controlled CO exposure were conducted in normal, healthy adults. No new human clinical studies have evaluated CNS or behavioral effects of exposure to CO.

5.3.2. Toxicological Studies

The evidence for toxicological effects of CO exposure in laboratory animal models comes from in utero or perinatal exposure involving relatively low to relatively high concentrations of CO (12.5-750 ppm). Affected endpoints from this early, developmental CO exposure include behavior, memory, learning, locomotor ability, peripheral nervous system myelination, auditory decrements, and neurotransmitter changes. These data are addressed in detail in the Birth Outcomes and Developmental Effects section of the ISA (Section 5.4.2). Further, a group of studies have found that exposure to high concentrations of CO (500-1,200 ppm) can result in CO-dependent ototoxicity, specifically loss of threshold of cochlear compound action potentials (CAP) and potentiation of noise-induced hearing loss (NIHL) (Chen et al., 2001, 193985; Fechter et al., 1997, 081322; Fechter et al., 2002, 193926; Liu and Fechter, 1995, 076524). Proposed mechanisms for these effects include ROS generation and glutamate release.

5.3.3. Summary of Central Nervous System Effects

Exposure to high levels of CO has long been known to adversely affect CNS function, with symptoms following acute CO poisoning including headache, dizziness, cognitive difficulties, disorientation, and coma. However, the relationship between ambient levels of CO and neurological function is less clear and has not been evaluated in epidemiologic studies. Studies of controlled human exposures to CO discussed in the 2000 CO AQCD (U.S. EPA, 2000, 000907) reported inconsistent neural and behavioral effects following exposures resulting in COHb levels of 5-20%. No new human clinical studies have evaluated central nervous system or behavioral effects of exposure to CO. At ambient-level exposures, healthy adults may be protected against CO-induced neurological impairment owing to compensatory responses including increased cardiac output and cerebral blood flow. However, these compensatory mechanisms are likely impaired among certain potentially susceptible groups, including individuals with reduced cardiovascular function.

Toxicological studies that were not discussed in the 2000 CO AQCD (U.S. EPA, 2000, 000907) employed rodent models to show that low to moderate CO exposure during the in utero or perinatal period can adversely affect adult outcomes, including behavior, neuronal myelination, neurotransmitter levels or function, and the auditory system (discussed in Section 5.4). In utero CO exposure, including both intermittent and continuous exposure, has been shown to impair multiple behavioral outcomes in offspring including active avoidance behavior (150 ppm CO), nonspatial memory (75 and 150 ppm CO), spatial learning (endogenous CO inhibition), homing behavior

(150 ppm CO), locomotor movement (150 ppm CO), and negative geotaxis (125 and 150 ppm). In two separate studies, in utero CO exposure (75 and 150 ppm) was associated with significant myelination decrements without associated changes in motor activity in adult animals. Multiple studies demonstrated that in utero CO exposure affected glutamatergic, cholinergic, catecholaminergic, and dopaminergic neurotransmitter levels or transmission. Possible or demonstrated adverse outcomes from the CO-mediated aberrant neurotransmitter levels or transmission include respiratory dysfunction (200 ppm CO), impaired sexual behavior (150 ppm CO), and an adverse response to hyperthermic insults resulting in neuronal damage (200 ppm). Finally, perinatal CO exposure has been shown to affect the developing auditory system of rodents, inducing permanent changes into adulthood. This is manifested by atrophy of cochlear cells innervating the inner hair cells (25 ppm CO), decreased immunostaining associated with impaired neuronal activation (12.5 ppm CO), impaired myelination of auditory associated nerves (25 ppm CO), decreased energy production in the sensory cell organ of the inner ear or the organ of corti (25 ppm CO). Some of these changes have been proposed to be mediated by ROS. Functional tests of the auditory system of rodents exposed neonatally to CO using OAE testing (50 ppm) and action potential amplitude measurements of the 8th cranial nerve (12, 25, 50, 100 ppm), revealed decrements in auditory function at PND22 and permanent changes into adulthood using action potential (AP) testing (50 ppm). Additionally, exposure to high concentrations of CO has been shown to result in CO-dependent ototoxicity in adult animals, possibly through glutamate and ROS-dependent mechanisms. Together, these animal studies demonstrated that in utero or perinatal exposure to CO can adversely affect adult behavior, neuronal myelination, neurotransmission, and the auditory system in adult rodents. Considering the combined evidence from controlled human exposure and toxicological studies, the evidence is **suggestive of a causal relationship between relevant short- and long-term exposures to CO and central nervous system effects.**

5.4. Birth Outcomes and Developmental Effects

5.4.1. Epidemiologic Studies

Although the body of literature is growing, the research focusing on adverse birth outcomes is limited when compared to the numerous studies that have examined the more well-established health effects of air pollution. Among this small number of studies, various dichotomized measures of birth weight, such as low birth weight (LBW), small for gestational age (SGA), and intrauterine growth restriction (IUGR), have received more attention in air pollution research while preterm birth (<37 wk gestation; [PTB]), congenital malformations, and infant mortality are less studied.

In the 2000 CO AQCD (U.S. EPA, 2000, 000907), only two studies were cited that examined the effect of ambient air pollution on adverse birth outcomes, and both of these studies investigated LBW as an endpoint (Alderman et al., 1987, 012243; Ritz and Yu, 1999, 086976). At that time this area of research was in its infancy; however, there has since been increasing interest.

5.4.1.1. Preterm Birth

A small number of air pollution-birth outcome studies have investigated the possible association between PTB and maternal exposure to CO, with the majority of U.S. studies conducted in southern California. The earliest of these studies examined exposures to ambient CO during the first month of pregnancy and the last 6 wk prior to birth among a cohort of 97,158 births in southern California between 1989 and 1993 (Ritz et al., 2000, 012068). The exposure assessment within this study was based on data from fixed-site monitors that fell within a 2-mi radius of the mother's ZIP code area. The crude relative risks for PTB associated with a 1 ppm increase in 3-h avg CO concentration (6:00-9:00 a.m.) during the last 6 wk prior to birth and the first month of pregnancy were 1.04 (95% CI: 1.03-1.5) and 1.01 (95% CI: 1.00-1.03), respectively. However, when the authors controlled for other risk factors, only the effect associated with CO during the last 6 wk prior to birth persisted (RR: 1.02 [95% CI: 1.01-1.03]). Furthermore, when the analyses included variables

for either season or other pollutants, the CO effect estimates generally were reduced such that they remained positive but were no longer statistically significant.

Expanding on this research, Wilhelm and Ritz (2005, 088668) examined PTB among a cohort of 106,483 births in Los Angeles County, CA, between 1994 and 2000. Based on data recorded at monitoring stations of varying proximities to the mother's residence, the main exposure windows examined were the first trimester and the last 6 wk prior to birth. Among women living within a 1-mi radius of a CO monitoring station, a 0.5 ppm increase in 24-h avg CO concentration during the first trimester was associated with a 3% (RR: 1.03 [95% CI: 1.00-1.06]) increased risk of PTB. This result persisted after simultaneously adjusting for NO_2 and O_3 (RR: 1.05 [95% CI: 1.00-1.10]) but not with the inclusion of PM_{10} into the regression model (RR: 0.99 [95% CI: 0.91-1.09]). The result from the single pollutant model for CO exposures averaged over the 6 wk prior to birth was similar in magnitude but failed to reach statistical significance (RR: 1.02 [95% CI: 0.99-1.04]).

A limitation of many air pollution-birth outcome studies is the limited availability of detailed information on maternal lifestyle factors and time-activity patterns during pregnancy. To assess possible residual confounding due to these factors, Ritz and colleagues (2007, 096146) were able to analyze detailed maternal information from a survey of 2,543 from a cohort of 58,316 eligible births in 2003 in Los Angeles County. Based on data from the closest monitor to the mother's ZIP code area, exposures to CO, NO_2, O_3, and $PM_{2.5}$ during the first trimester and last 6 wk prior to delivery were examined, and results from the overall cohort (n = 58,316) with limited maternal information were compared to the more detailed nested case-control cohort (n = 2,543). Within the overall cohort, 24-h avg CO during the first trimester was associated with an increased risk of 25% (OR: 1.25 [95% CI: 1.12-1.38]; highest exposure group >1.25 ppm versus lowest ≤ 0.58 ppm). This result persisted within the nested case-control cohort (OR: 1.21 [95% CI: 0.88-1.65]) where factors such as passive smoking and alcohol use during pregnancy were included in the model; however, the confidence intervals were wider due to the smaller sample. Any possible association between CO and PTB was less evident during the last 6 wk prior to birth. A strength of this study was that it also highlighted how there was little change in the air pollution effect estimates when controlling for more detailed maternal information (e.g., smoking, alcohol use), as opposed to only controlling for more limited maternal information that is routinely collected on birth registry forms.

In contrast to the Los Angeles studies, a case-control study of PTB across California for the period 1999 through 2000 found a positive association with 24-h CO concentration during the entire pregnancy (OR: 1.03 [95% CI: 0.98-1.09] per 0.5 ppm increase) and the first month of gestation (OR: 1.05 [95% CI: 0.99-1.10] per 0.5 ppm increase), but no association during the last 2 wk of gestation (OR: 1.00 [95% CI: 0.96-1.04] per 0.5 ppm increase) (Huynh et al., 2006, 091240). Although there was an indication of an effect during early pregnancy, the small sample size (when compared to other studies) may not have provided sufficient power to detect statistical significance. Furthermore, exposures within this study were assigned based on a county-level average which may explain the lack of effect, given the poor level of exposure assessment.

Studies outside of the U.S. have been conducted in Canada, Australia, and Korea, with mixed results reported. In Vancouver, Canada, based on a city-wide average across available monitoring sites, 24-h avg CO concentration during the last month of pregnancy was associated with a 4% (OR: 1.04 [95% CI: 1.00-1.07]) increased risk of PTB per 0.5 ppm increase, while there was no association found during the first month of pregnancy (OR: 0.98 [95% CI: 0.94-1.00]) (Liu et al., 2003, 089548). This study investigated maternal exposures to ambient gaseous pollutants (CO, NO_2, SO_2, O_3) averaged over the first and last month of pregnancy among a cohort of 229,085 births between 1985 and 1998.

In a cohort of 52,113 births in Incheon, Korea, between 2001 and 2002, a kriging technique was used to assign the maternal exposures to CO. Kriging is a statistical mapping technique that allows the prediction of an average concentration over a spatial region from data collected at specific points. The spatial average CO concentrations were then linked to each study subject's residential address. CO concentrations during the first trimester were associated with a 26% (RR: 1.26 [95% CI: 1.11-1.44]) increased risk of PTB for the highest quartile of exposure when compared to the lowest quartile (Leem et al., 2006, 089828). There was also a strong significant trend exhibited across the quartiles. A similar result was found for 24-h avg CO concentration during the last trimester, although the effect was less pronounced (RR: 1.16 [95% CI: 1.01-1.24]).

Conversely, a study in Sydney, Australia, examined maternal exposure to ambient air pollution during the first and last month and the first and last trimester of pregnancy among a cohort of 123,840 births between 1998 and 2000 and found no association between PTB and CO (Jalaludin et

al., 2007, 156601). Maternal exposure estimates in this study were based on a city-wide average of available monitoring sites and also based on data from fixed sites within 5 km of the mother's postcode area. The odds ratios for PTB associated with 8-h avg CO concentrations during the first trimester and last 3 mo of gestation were 1.18 (95% CI: 0.85-1.63) and 1.08 (95% CI: 0.95-1.22), respectively, when including births within 5 km of a monitor. Interestingly, when all births were included in the analyses and the exposure was based on a city-wide average, these effects had become protective for the first trimester (OR: 0.82 [95% CI: 0.77-0.87]) and null for the last 3 mo of gestation (OR: 0.99 [95% CI: 0.92-1.07]). This suggests that exposures based on data from fixed sites closer to the mother's address are more likely to detect an effect than a city-wide average.

Figure 5-9 shows the odds for the risk of delivering a preterm infant from the reviewed studies; Table 5-12 provides a brief overview of the PTB studies. In summary, there are mixed results across the studies. Although these studies are difficult to compare directly due to the different exposure assessment methods employed, there is some evidence that CO during early pregnancy (e.g., first month and trimester) is associated with an increased risk of PTB. The most consistency is exhibited within the studies conducted around Los Angeles, CA, and surrounding areas, whereby all studies reported a significant association with CO exposure during early pregnancy, and exposures were assigned from monitors within close proximity of the mother's residential address (Ritz et al., 2000, 012068; Ritz et al., 2007, 096146; Wilhelm and Ritz, 2005, 088668). It should also be noted that the mixed results when analyzing different cohorts that resided within varying proximities to a monitor may be attributable to analyzing different populations.

Study	Location	Exposure Period	Exposure Indicator
Ritz et al. (2000, 012068)	California, US	First month	<2 mi of monitor
Ritz et al. (2000, 012068)	California, US	Last 6 weeks	<2 mi of monitor
Wilhelm & Ritz (2005, 088668)	Los Angeles, CA	First trimester	ZIP code level
Wilhelm & Ritz (2005, 088668)	Los Angeles, CA	Last 6 weeks	ZIP code level
Huynh et al. (2006, 091240)	California, US	First month	County level
Huynh et al. (2006, 091240)	California, US	Last 2 weeks	County level
Huynh et al. (2006, 091240)	California, US	Entire pregnancy	County level
Liu et al. (2003, 089548)	Vancouver, Can	First month	City wide
Liu et al. (2003, 089548)	Vancouver, Can	Last month	City wide
Jalaludin et al. (2007, 156601)	Sydney, Australia	First month	City wide
Jalaludin et al. (2007, 156601)	Sydney, Australia	First trimester	City wide
Jalaludin et al. (2007, 156601)	Sydney, Australia	Last month	City wide

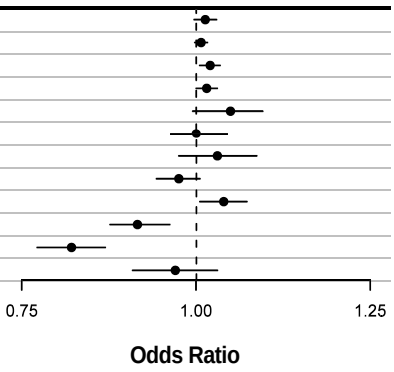


Figure 5-9. Summary of effect estimates (95% confidence intervals) for PTB associated with maternal exposure to ambient CO. Effect estimates have been standardized to a 1 ppm increase in ambient CO for 1-h max CO concentrations, 0.75 ppm for 8-h max CO concentrations, and 0.5 ppm for 24-h avg CO concentrations.

Table 5-12. Brief summary of PTB studies.

Study	Location Sample Size	Mean CO (ppm)	Exposure Assessment	Exposure Window
Ritz et al. (2000, 012068)	California, US (n = 97,158)	2.7 (6-9 a.m.)	<2 mi of monitor	First mo Last 6 wk
Wilhelm and Ritz (2005, 088668)	Los Angeles, CA (n = 106,483)	1.4 (24 h)	Varying distances to monitor	Last 6 wk
Ritz et al.(2007, 096146)	Los Angeles, CA (n = 58,316)	0.87 (24 h)	Nearest monitor to ZIP code	Entire pregnancy First Trimester Last 6 wk
Huynh et al. (2006, 091240)	California, US (n = 42,692)	0.8 (24 h)	County level	Entire pregnancy First mo Last 2 wk
Liu et al. (2003, 089548)	Vancouver, Can (n = 229,085)	1.0 (24 h)	City-wide avg	First mo Last mo
Leem et al. (2006, 089828)	Incheon, Korea (n = 52,113)	0.9 (24 h)	Residential address within Dong-based on kriging	First trimester Last trimester
Jalaludin et al. (2007, 156601)	Sydney, Australia (n = 123,840)	0.9 (8 h)	City-wide avg and <5 km from monitor	First mo First trimester Last trimester Last mo

5.4.1.2. Birth Weight, Low Birth Weight, and Intrauterine Growth Restriction/Small for Gestational Age

With birth weight routinely collected in vital statistics and being a powerful predictor of infant mortality, it is the most studied outcome within air pollution-birth outcome research. Air pollution researchers have analyzed birth weight as a continuous variable and/or as a dichotomized variable in the forms of LBW (<2,500 g [5 lbs, 8 oz]) and SGA.

It should be noted that the terms SGA, which is defined as a birth weight <10th percentile for gestational age (and often sex), and IUGR are used interchangeably. However, this definition of SGA does have limitations. For example, using it for IUGR may overestimate the percentage of "growth-restricted" neonates as it is unlikely that 10% of neonates have growth restriction (Wollmann, 1998, 193812). On the other hand, when the 10th percentile is based on the distribution of live births at a population level, the percentage of SGA among preterm births is most likely underestimated (Hutcheon and Platt, 2008, 193795). Nevertheless, it should be noted that SGA represents a statistical description of a small neonate, whereas the term IUGR is reserved for those with clinical evidence of abnormal growth. Thus, all IUGR neonates will be SGA, but not all SGA neonates will be IUGR (Wollmann, 1998, 193812). In the following sections the terms SGA and IUGR are referred to as each cited study used the terms.

Over the past decade a number of studies examined various metrics of birth weight in relation to maternal exposure to CO with the majority conducted in the U.S. Given that most studies examined multiple birth weight metrics, the following section focuses on each study only once and presents results for each metric within that study.

Most of the U.S. studies have been conducted in southern California, with inconsistent results reported with regard to gestational timing of the CO effects. The first of these studies was reviewed in the 2000 CO AQCD (U.S. EPA, 2000, 000907) and is briefly summarized here. Ritz and Yu (1999, 086976) examined the effect of ambient CO during the last trimester on LBW among 125,573 births in Los Angeles between 1989 and 1993. When compared to neonates born to women in the lowest CO exposure group (<2.2 ppm), neonates born to women in the highest exposure group (5.5 ppm-95th percentile) had a 22% (OR: 1.22 [95% CI: 1.03-1.44]) increased risk of being born as LBW.

Building upon this research, Wilhelm and Ritz (2005, 088668) reported similar results when extending this study to include 136,134 births for the period 1994–2000. Exposure to ambient CO

during each trimester was based on data recorded at monitoring stations of varying proximities to the mother's residence. For women residing within 1 mi of a station, there was 36% (OR: 1.36 [95% CI: 1.04-1.76]) increased risk of having a term LBW baby for women with third-trimester exposure above the 75th percentile when compared to women below the 75th percentile. There was also an increased risk of term LBW (OR: 1.28 [95% CI: 1.12-1.47]) among women in the highest exposure group when the analyses included women within a 5-mi radius of a station. However, when the analyses included women within a 1- to 2-mi or 2- to 4-mi radius of a station, the CO effects failed to reach statistical significance, and there was no evidence of an exposure-response pattern exhibited across the varying distances to a station. Furthermore, none of the significant CO results persisted after controlling for other pollutants. Although standard errors were certainly increased after controlling for the other pollutants, leading to non-significant results, some of the effect sizes were similar, providing some consistency. It is interesting to note, however, that maternal exposure to CO during trimesters one and two was not associated with LBW (quantitative results not reported by authors).

Further validation in association with exposure times was observed in an analysis using a subset of participants in the Children's Health Study. Salam and colleagues (2005, 087885) found that CO only during the first trimester was associated with reduced fetal growth. Their research examined birth weight, LBW, and IUGR among a subset of participants in the Children's Health Study (Peters et al., 1999, 087243) who were born in California between 1975 and 1987 (n = 3,901). The study examined term births with a gestational age between 37 and 44 wk. Exposures in this study were based on CO data from up to the 3 nearest monitoring sites within 50 km of the centroid of the mother's ZIP code. Exposures for the entire pregnancy and each trimester were analyzed, and a 0.5 ppm increase in 24-h CO concentration during the first trimester was associated with a 7.8 g (95% CI: 15.1-0.4) decrease in birth weight, which also translated to a 6.7% (OR: 1.07 [95% CI: 1.00-1.13]) increased risk of IUGR; however, there was no association with LBW (OR: 1.00 [95% CI: 0.88-1.16]).

In contrast to the previous studies, another California study of 18,247 singleton births born at 40-wk gestation during 2000 found no association between ambient 24-h CO concentration and reduced birth weight or SGA, where the highest quartile of exposure was 0.98 ppm. Based on data from fixed sites within 5 mi of the mother's residence, exposures to CO and $PM_{2.5}$ during the entire pregnancy and each trimester were analyzed. Although CO during the entire pregnancy was associated with a 20 g (95% CI: 40.1-0.8) reduction in birth weight, this did not persist after controlling for $PM_{2.5}$. $PM_{2.5}$ was found to have a strong effect on birth weight within each trimester (Parker et al., 2005, 087462).

Two similar studies were conducted in the northeastern U.S. with inconsistent results. A study of 89,557 singleton term births in Boston, MA, Hartford, CT, Philadelphia, PA, Pittsburgh, PA, and Washington, DC, between 1994 and 1996 found that exposure to ambient 24-h avg CO during the third trimester was associated with an increased risk of LBW (OR: 1.14 [95% CI: 1.03-1.27] per 0.5 ppm increase) (Maisonet et al., 2001, 016624). When stratified by race this effect was only significant among African-Americans for the first and third trimesters (first OR: 1.32 [95% CI: 1.22-1.43]; third OR: 1.20 [95% CI: 1.09-1.32]). Exposures to PM_{10} and SO_2 were examined, and there was no strong evidence that these pollutants were associated with LBW. Exposures for this study were based on a city-wide average of monitors within the mother's city of residence. The second study examined 358,504 births at 32- to 44-wk gestation between 1999 and 2002 in Connecticut and Massachusetts (Bell et al., 2007, 091059), and 24-h CO exposures were estimated from fixed sites within each mother's county of residence (e.g., county level). CO averaged over the entire pregnancy was associated with a reduction in birth weight of 27.0 g (95% CI: 21.0-32.8). This result persisted after controlling for each additional pollutant (PM_{10}, $PM_{2.5}$, NO_2, and SO_2) in two-pollutant models. However, this reduction in birth weight did not translate to an increased risk of LBW (OR: 1.05 [95% CI: 0.97-1.12] per 0.5 ppm increase in CO). When controlling for exposure during each trimester, the reduction in birth weight associated with a 0.5 ppm increase in 24-h CO concentration during the first trimester ranged from 18.8 to 16.5 g, while the reductions associated with third trimester exposure ranged between 27.2 and 23.3 g. It is interesting to note that, although the exposures were based on data averaged at the county level, CO was associated with a reduction in birth weight. In contrast, in a previously cited California study by Huynh and colleagues (2006, 091240) exposures were also at the county level yet there was no association with PTB. This difference may be due to the counties being smaller in New England than in California, resulting in more precise exposure estimates.

Two studies in Canada investigated the effects of ambient air pollution on fetal growth with exposures derived from a city-wide average across the available monitoring sites. The first of these studies was among a cohort of 229,085 singleton term births (37- and 42-wk gestation) in Vancouver, BC, with monthly and trimester exposures to CO investigated in relation to LBW and IUGR (Liu et al., 2003, 089548). For a 0.5 ppm increase in 24-h CO concentration during the first month of pregnancy, there was an increased risk of IUGR (OR: 1.03 [95% CI: 1.00-1.05]), and this was of borderline significance when CO was averaged over the first trimester (OR: 1.02 [95% CI: 1.00-1.05]). This result persisted after controlling for other gaseous pollutants. Conversely, maternal exposure to CO was not associated with LBW. The more recent of these two studies examined 386,202 singleton term births (37- to 42-wk gestation) in Calgary, Edmonton, and Montreal, between 1986 and 2000 (Liu et al., 2007, 090429). The study examined monthly and trimester exposures to CO with IUGR being the only endpoint. A 0.5 ppm increase in 24-h CO concentration was associated with an increased risk of IUGR in the first (OR: 1.09 [95% CI: 1.07-1.11]), second (OR: 1.07 [95% CI: 1.05-1.09]), and third trimesters (OR: 1.09 [95% CI: 1.07-1.11]) of pregnancy. This result translated to CO exposure having a positive effect on IUGR within each individual month of pregnancy with the highest effect during the first and last months. This result persisted after controlling for concurrent NO_2 and $PM_{2.5}$.

Two studies in Sao Paulo, Brazil, a city with notably high levels of air pollution (mean CO 3.7 ppm) investigated associations between maternal exposures to CO in relation to reduced birth weight and LBW within two consecutive time periods and found similar results. In both studies the exposures were derived from a city-wide average across the available monitoring sites. The first study examined 179,460 singleton term births during 1997 and found that a 0.75 ppm increase in 8-h CO concentration averaged over the first trimester was associated with a 17.3 g (95% CI: 31.0-3.7) reduction in birth weight (Gouveia et al., 2004, 055613). The second of these studies examined 311,735 singleton births (37- to 41-wk gestation) between 1998 and 2000 and reported a 6.0 g (95 % CI: 7.75-4.1) reduction in birth weight associated with a 0.5 ppm increase in 24-h CO concentration averaged over the first trimester (Medeiros and Gouveia, 2005, 089824). It is important to note that neither of these studies found an association between CO exposure and an increased risk of LBW. Therefore, despite CO during the first trimester being associated with reduced birth weight, it was not associated with LBW.

Similar to the two studies in Sao Paulo, Brazil, researchers in Seoul, South Korea, conducted two studies using data from two consecutive time periods. Both of these studies based the exposure estimates on a city-wide average from all available fixed sites and as would be expected, the results pertaining to CO were similar for both studies. Ha and colleagues (2001, 019390) examined maternal exposures to CO during the first and third trimesters among 276,763 singleton term births in Seoul between 1996 and 1997. Exposure to CO during the first trimester was associated with a decrease in birth weight of 13.3 g, which also translated into an increased risk of LBW (RR: 1.10 [95% CI: 1.05-1.14] per 0.5 ppm increase in 24-h CO concentration). When Lee and colleagues (2003, 043202) extended this study to include singleton term births for the period 1996-1998, with 24-h CO concentrations averaged over each month of pregnancy and trimester, CO exposure during the first trimester was associated with an increased risk of LBW (OR: 1.04 [95% CI: 1.01-1.07] per 0.5 ppm increase). No associations were found in the third trimester for any of the pollutants. Monthly-specific exposures showed that the risk of LBW tended to increase with CO exposure between months two through five of pregnancy.

In contrast to other studies reporting that early and late pregnancy are the critical periods for CO exposure, a Sydney, Australia study of 138,056 singleton births between 1998 and 2000 reported a reduction in birth weight of 21.7 g (95% CI: 38.2-5.1) and 17.2 g (95% CI: 33.4-0.9) associated with a 0.75 ppm increase in maternal exposure to 8-h CO averaged over the second and third trimesters, respectively (Mannes et al., 2005, 087895). However, this result did not persist after controlling for other pollutants (PM_{10}, NO_2) and was only statistically significant when including births where the mother resided within 5 km of a monitor. Furthermore, this result did not translate to an increased risk of SGA, which was defined as a birth weight two standard deviations below the mean. The odds ratios for SGA for CO exposures during the first, second and third trimesters were 0.96 (95% CI: 0.91-1.03), 0.99 (95% CI: 0.92-1.07), and 1.01 (95% CI: 0.93-1.08) per 0.75 ppm increase in 8-h CO, respectively. While the majority of studies restrict the analyses to term births as a method of controlling for gestational age, it is important to note that the Sydney study used all births and controlled for gestational age in the birth weight analyses and SGA was derived for each gestational age group.

Of all studies reviewed, only two did not find an association between maternal exposure to CO and birth weight variables. In northern Nevada, Chen and colleagues (2002, 024945) examined CO, PM_{10}, and O_3 exposures among a cohort of 39,338 term births (37- to 44-wk gestation) between 1991 and 1999 and found no association between CO exposure during the entire pregnancy (and each trimester) and a reduction in birth weigh or an increased risk of LBW. For a 0.75 ppm increase in 8-h CO concentration averaged over the entire pregnancy, there was a reduction in birth weight of 6 g; however it failed to reach statistical significance. Exposures for this study were based on data from all monitoring sites across Washoe County, Nevada.

In a retrospective cohort study among 92,288 singleton term births (37- to 44-wk gestation) in Taipei and Kaoshiung, Taiwan, between 1995 and 1997, maternal exposures to CO, SO_2, O_3, NO_2, and PM_{10} in each trimester of pregnancy were examined, and only SO_2 during the third trimester showed evidence of contributing to LBW. Exposure assessment was based on data from the monitor closest to the centroid of the mother's residential district, and the final analyses included only those mothers whose district centroid was within 3 km of a monitor. CO exposures were grouped into low (~1.1 ppm), medium (~1.2-15.0 ppm), and high (>15.0 ppm) and when compared to the lowest exposure group, the odds ratio for LBW in the highest exposure group was 0.90 (95% CI: 0.75-1.09) for the first trimester, 1.00 (95% CI: 0.82-1.22) for the second trimester, and 0.86 (95% CI: 0.71-1.03) for the third trimester (Lin et al., 2004, 089827).

Table 5-13 provides a brief overview of the birth weight studies. In summary, there is evidence of ambient CO during pregnancy having a negative effect on fetal growth. From the reviewed studies Figure 5-10 shows the change in birth weight (grams), Figure 5-11 shows the effect estimates for LBW, and Figure 5-12 shows the effect estimates for SGA. In general the reported reductions in birth weight are small (~10-20g). It is difficult to conclude whether CO is related to a small change in birth weight in all births across the population or a marked effect in some subset of births. Furthermore, there is a large degree of inconsistency across these studies. This may be due to several factors such as inconsistent exposure assessment and statistical methods employed, different CO concentrations, and/or different demographics of the birth cohorts analyzed. The main inconsistency among these findings is the gestational timing of the CO effect. Although the majority of studies reported significant effects during either the first or third trimester, other studies failed to find a significant effect during these periods. Several studies found an association with exposure during the entire pregnancy, providing evidence for a possible accumulative effect; however, these results are inconclusive and may be the result of correlated exposure periods.

Several studies examined various combinations of birth weight, LBW, and SGA/IUGR, and inconsistent results are reported across these metrics. For example, several studies reported an association between maternal exposure to CO and decreased birth weight, yet no increase in risk of LBW or SGA. However, a measurable change, even if only a small one, at the population level is different than an effect observed for a subset of susceptible births which may increase the risk of IUGR/LBW/SGA. It is difficult to conclude if CO is related to a small change in birth weight in all births across the population or a marked effect in some subset of births.

Study	Location	Exposure Period	Exposure Indicator
Bell et al. (2007, 091059)	CT & MA, US	Entire pregnancy	County wide
Salam et al. (2005, 087885)	California, US	First trimester	ZIP code level
Salam et al. (2005, 087885)	California, US	Second trimester	ZIP code level
Salam et al. (2005, 087885)	California, US	Third trimester	ZIP code level
Salam et al. (2005, 087885)	California, US	Entire pregnancy	ZIP code level
Chen et al. (2002, 024945)	Northern NV, US	First trimester	County level
Chen et al. (2002, 024945)	Northern NV, US	Second trimester	County level
Chen et al. (2002, 024945)	Northern NV, US	Third trimester	County level
Chen et al. (2002, 024945)	Northern NV, US	Entire pregnancy	County level
Mannes et al. (2005, 087895)	Sydney, Australia	First trimester	City level
Mannes et al. (2005, 087895)	Sydney, Australia	Second trimester	City level
Mannes et al. (2005, 087895)	Sydney, Australia	Third trimester	City level
Mannes et al. (2005, 087895)	Sydney, Australia	Last month	City level
Gouveia et al. (2004, 055613)	Sao Paulo, Brazil	First trimester	City level
Gouveia et al. (2004, 055613)	Sao Paulo, Brazil	Second trimester	City level
Gouveia et al. (2004, 055613)	Sao Paulo, Brazil	Third trimester	City level
Medeiros and Gouveia (2005, 089824)	Sao Paulo, Brazil	First trimester	City level
Medeiros and Gouveia (2005, 089824)	Sao Paulo, Brazil	Second trimester	City level
Medeiros and Gouveia (2005, 089824)	Sao Paulo, Brazil	Third trimester	City level

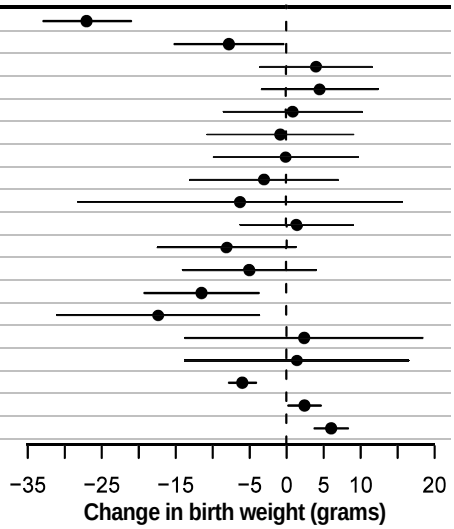


Figure 5-10. Summary of change in birth weight (95% confidence intervals) associated with maternal exposure to ambient CO. Effect estimates have been standardized to a 1 ppm increase in ambient CO for 1-h max CO concentrations, 0.75 ppm for 8-h max CO concentrations, and 0.5 ppm for 24-h avg CO concentrations.

Study	Location	Exposure Period	Exposure Indicator
Bell et al. (2007, 091059)	CT & MA, US	Entire pregnancy	County level
Maisonet et al. (2001, 016624)	Northeastern US	First trimester	City level
Maisonet et al. (2001, 016624)	Northeastern US	Second trimester	City level
Maisonet et al. (2001, 016624)	Northeastern US	Third trimester	City level
Wilhelm & Ritz (2005, 088668)	LA County, CA	Third trimester	ZIP code level
Salam et al. (2005, 087885)	California, US	First trimester	ZIP code level
Salam et al. (2005, 087885)	California, US	Second trimester	ZIP code level
Salam et al. (2005, 087885)	California, US	Third trimester	ZIP code level
Salam et al. (2005, 087885)	California, US	Entire pregnancy	ZIP code level
Liu et al. (2003, 089548)	Vancouver, Can	First month	City level
Liu et al. (2003, 089548)	Vancouver, Can	Second month	City level
Ha et al. (2001, 019390)	Seoul, Korea	First trimester	City level
Ha et al. (2001, 019390)	Seoul, Korea	Third trimester	City level
Lee et al. (2003, 043202)	Seoul, Korea	First trimester	City level
Lee et al. (2003, 043202)	Seoul, Korea	Second trimester	City level
Lee et al. (2003, 043202)	Seoul, Korea	Third trimester	City level
Lee et al. (2003, 043202)	Seoul, Korea	Entire pregnancy	City level

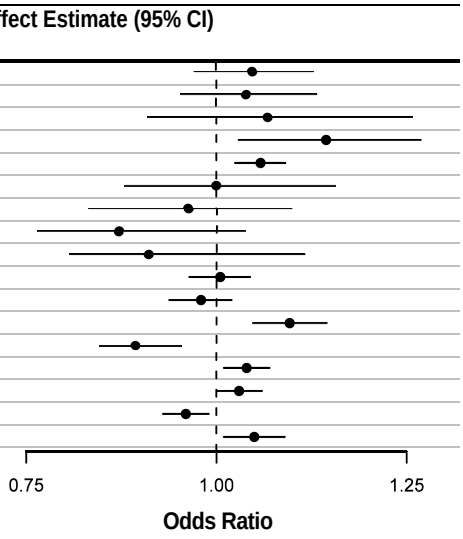


Figure 5-11. Summary of effect estimates (95% confidence intervals) for LBW associated with maternal exposure to ambient CO. Effect estimates have been standardized to a 1 ppm increase in ambient CO for 1-h max CO concentrations, 0.75 ppm for 8-h max CO concentrations, and 0.5 ppm for 24-h avg CO concentrations.

Study	Location	Exposure Period	Exposure Indicator	Effect Estimate (95% CI)
Salam et al. (2005, 087885)	California, US	First trimester	ZIP code level	
Salam et al. (2005, 087885)	California, US	Second trimester	ZIP code level	
Salam et al. (2005, 087885)	California, US	Third trimester	ZIP code level	
Salam et al. (2005, 087885)	California, US	Entire pregnancy	ZIP code level	
Liu et al. (2003, 089548)	Vancouver, Can	First month	City level	
Liu et al. (2003, 089548)	Vancouver, Can	First trimester	City level	
Liu et al. (2003, 089548)	Vancouver, Can	Second trimester	City level	
Liu et al. (2003, 089548)	Vancouver, Can	Third trimester	City level	
Liu et al. (2003, 089548)	Vancouver, Can	Last month	City level	
Liu et al. (2007, 090429)	Multicity, Can	First trimester	City level	
Liu et al. (2007, 090429)	Multicity, Can	Second trimester	City level	
Liu et al. (2007, 090429)	Multicity, Can	Third trimester	City level	
Mannes et al. (2005, 087895)	Sydney, Australia	First trimester	City level	
Mannes et al. (2005, 087895)	Sydney, Australia	Second trimester	City level	
Mannes et al. (2005, 087895)	Sydney, Australia	Third trimester	City level	
Mannes et al. (2005, 087895)	Sydney, Australia	Last month	City level	

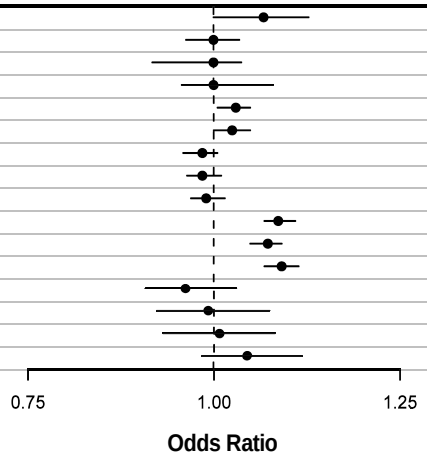


Figure 5-12. Summary of effect estimates (95% confidence intervals) for SGA associated with maternal exposure to ambient CO. Effect estimates have been standardized to a 1 ppm increase in ambient CO for 1-h max CO concentrations, 0.75 ppm for 8-h max CO concentrations, and 0.5 ppm for 24-h avg CO concentrations.

The possibility exists that the small reductions in birth weight associated with maternal CO exposures are the result of residual confounding associated with other factors (e.g., other pollutants, temperature, and spatial/temporal variation in maternal factors) or other correlated pollutants. For example, in some studies the CO effect did not persist after controlling for other pollutants (Mannes et al., 2005, 087895; Parker et al., 2005, 087462; Wilhelm and Ritz, 2005, 088668), while in some studies it did persist (Bell et al., 2007, 091059; Gouveia et al., 2004, 055613; Liu et al., 2003, 089548), and other studies did not report results from multipollutant models (Ha et al., 2001, 019390; Lee et al., 2003, 043202; Maisonet et al., 2001, 016624; Medeiros and Gouveia, 2005, 089824). In addition, various methods have been employed to control for seasonality and trends (e.g., month of birth, season of birth, year of birth, smoothed function of time), which may explain some of the mixed results.

The two U.S. studies conducted in the Northeast compared results from analyses stratified by race. The earlier of these studies found an association between CO and LBW among African-Americans but not among whites and Hispanics (Maisonet et al., 2001, 016624). In contrast, despite reporting an 11g reduction in birth weight among African-Americans and a 17 g reduction among whites, the more recent of the two studies found no significant difference between these reductions by race (Bell et al., 2007, 091059). Parker and colleagues (2005, 087462) also tested for interactions between race and found no significant association.

Table 5-13. Brief summary of birth weight studies.

Study	Outcomes Examined	Location Sample Size	Mean CO (ppm)	Exposure Assessment	Exposure Windows
UNITED STATES					
Ritz and Yu (1999, 086976)	LBW	Los Angeles, CA (n = 125, 573)	2.6 (6-9 a.m.)	<2 mi of monitor	Trimester 3
Wilhelm and Ritz (2005, 088668)	LBW	Los Angeles County, CA (n = 136, 134)	1.4 (24 h)	Varying distances from monitor	Trimesters 1, 2, 3
Salam et al. (2005, 087885)	Birth weight LBW IUGR	California, US (n = 3901)	1.8 (24 h)	ZIP code level	Entire pregnancy Trimesters 1, 2, 3
Parker et al. (2005, 087462)	Birth weight SGA	California, US (n = 18,247)	0.75 (8 h)	<5 mi from monitor	Entire pregnancy Trimesters 1, 2, 3
Maisonet et al. (2001, 016624)	LBW	Boston, MA Hartford, CT Philadelphia & Pittsburg, PA Washington DC (n = 103,465)	1.1 (24 h)	City-wide avg	Trimesters 1, 2, 3
Bell et al. (2007, 091059)	Birth weight LBW	CT & MA, US (n = 358,504)	0.6 (24 h)	County-level avg	Entire pregnancy Trimesters 1, 3
Chen et al. (2002, 024945)	Birth weight LBW	Northern Nevada, US (n = 36,305)	0.9 (8 h)	County level	Trimesters 1, 2, 3
CANADA					
Liu et al. (2003, 089548)	LBW IUGR	Vancouver, Can (n = 229,085)	1.0 (24 h)	City-wide avg	Trimester 1
Liu et al. (2007, 090429)	IUGR	Calgary, Edmonton, & Montreal, Can (n = 386,202)	1.1 (24 h)	City-wide avg	Trimesters 1, 2, 3
SOUTH AMERICA					
Gouveia et al. (2004, 055613)	Birth weight LBW	Sao Paulo, Brazil (n = 179,460)	3.7 (8 h)	City-wide avg	Trimesters 1, 2, 3
Medeiros and Gouveia (2005, 089824)	Birth weight LBW	Sao Paulo, Brazil (n = 311,735)	3.0 (24 h) (Presented in graph)	City-wide avg	Trimesters 1, 2, 3
AUSTRALIA/ASIA					
Ha et al. (2001, 019390)	Birth weight LBW	Seoul, Korea (n = 276,763)	1.2 (24 h)	City-wide avg	Trimesters 1 and 3
Lee et al. (2003, 043202)	LBW	Seoul, Korea (n = 388,105)	1.2 (24 h)	City-wide avg	Entire pregnancy Trimesters 1, 2, 3
Mannes et al. (2005, 087895)	Birth weight SGA	Sydney, Australia (n = 138,056)	0.8 (8 h)	City-wide avg and <5 km from monitor	Trimesters 1, 2, 3 Last 30 days
Lin et al. (2004, 089827)	LBW	Taipei, Kaoshiung, Taiwan (n = 92,288)	Taipei 1.1, Kaoshiung 8.1	<3 km of monitor	Entire pregnancy Trimesters 1, 2, 3

5.4.1.3. Congenital Anomalies

Despite the growing evidence of an association between ambient air pollution and various adverse birth outcomes, few studies have investigated the effect of temporal variations in ambient air pollution on congenital anomalies. Heart defects have been the focus of the majority of these recent air pollution studies, given the higher prevalence than other congenital anomalies and associated mortality. Another study's focus was cleft lip/palate.

The earliest of these studies was conducted in southern California (Ritz et al., 2002, 023227). Exposure to ambient CO, NO_2, O_3 and PM_{10} during each of the first 3 mo of pregnancy was examined among births during 1987-1993. Maternal exposure estimates were based on data from the fixed site closest to the mother's ZIP code area. When using a case-control design where cases were matched to 10 randomly selected controls, results showed that CO during the second month of pregnancy was associated with cardiac ventricular septal defects. The CO exposures were grouped by quartiles (25th = 1.14, 50th = 1.57, 75th = 2.39 ppm), and when compared to those in the lowest quartile exposure group (<1.14 ppm), the odds ratios for ventricular septal defects across the 3 higher exposure groups were 1.62 (95% CI: 1.05-2.48), 2.09 (95% CI: 1.19-3.67), and 2.95 (95% CI: 1.44-6.05), respectively. In a multipollutant model a similar exposure-response pattern was exhibited across the quartiles with the highest quartile of exposure reaching statistical significance (OR: 2.84 [95% CI: 1.15-6.99]). The only other pollutant associated with a defect was O_3 during the second month of pregnancy, which was associated with aortic artery and valve defects.

Another study was conducted in Texas (Gilboa et al., 2005, 087892), where exposure to ambient CO, NO_2, SO_2, O_3 and PM_{10} during the 3rd-8th week of gestation was examined among births between 1997 and 2000. Maternal exposure estimates were calculated by assigning the data from the closest monitor to the mother's residential address. If data were missing on a particular day then data from the next closest site were used. The median distances from a monitor ranged from 8.6 to 14.2 km, with maximum distances ranging from 35.5 to 54.5 km. The main results showed that CO was associated with multiple conotruncal defects and Tetralogy of Fallot. CO exposures were grouped into quartiles of much lower concentrations (25th = 0.4, 50th = 0.5, 75th = 0.7 ppm) than the California study (Ritz et al., 2002, 023227), and when compared to the lowest quartile, the odds ratios for conotruncal defects across the 3 CO exposure groups were 1.38 (95% CI: 0.97-1.97), 1.17 (95% CI: 0.81-1.70), and 1.46 (1.03-2.08), respectively, without a significant test for trend (p for trend = 0.0870). A strong exposure-response pattern was exhibited across the quartiles of CO exposure for Tetralogy of Fallot (25th OR: 0.82 [95% CI: 0.52-1.62]; 50th OR: 1.27 [95% CI: 0.75-2.14]; 75th OR: 2.04 [95% CI: 1.26-3.29]; p for trend = 0.0017). The only significant associations found with other pollutants were between PM_{10} and isolated atrial septal defects, and SO_2 and ventricular septal defects.

A study conducted in Atlanta, GA, investigated the associations between ambient air pollution concentrations during weeks 3-7 of pregnancy and risks of cardiovascular malformations among a cohort of pregnancies conceived during 1986-2003 (Strickland et al., 2009, 190324). The mean 24-h CO concentration during this period was 0.75 ppm. The authors did not report any statistically significant associations with ambient CO concentrations and cardiac malformations, though there were elevated risk ratios for ambient CO concentration and patent ductus arteriosus, Tetralogy of Fallot, and right ventricular outflow tract defect. These results remained consistently positive in five sensitivity analyses conducted and were closer to achieving statistical significance in these sensitivity analyses. The only statistically significant results were for the association between PM_{10} and patent ductus arteriosus.

The last of these studies was a case-control study that examined maternal exposure to various air pollutants during the first 3 mo of pregnancy and the risk of delivering an infant with an oral cleft, namely cleft lip with or without palate (CL/P). Birth data from the Taiwanese birth registry from 2001 to 2003 was linked to air pollutant data that were spatially interpolated from all fixed monitoring sites across Taiwan. Based on data at the center of the townships or districts, exposure estimates for PM_{10}, SO_2, NO_X, O_3, and CO were averaged over each of the first 3 mo of pregnancy. The mean 8-h avg CO concentration was 0.69 ppm. Interestingly, of all the pollutants examined, only O_3 during the first 2 mo of pregnancy was significantly associated with an increased risk of CL/P. In multipollutant models CO was not associated with CL/P (Hwang and Jaakkola, 2008, 193794).

The main results from the southern California study showed that CO was associated with an increased risk of ventricular septal defects, and this was exhibited by an exposure-response pattern across the quartiles of exposure; yet there was no indication that ambient CO concentration in Texas

was associated with ventricular septal defects. Conversely, ambient CO concentration in Texas was associated with an increased risk of conotruncal defects; yet there was no indication that CO in southern California was associated with conotruncal defects. The Atlanta study (Strickland et al., 2009, 190324) found positive, though not statistically significant associations for patent ductus arteriosus, Tetralogy of Fallot, and right ventricular outflow tract defect. The elevated risk ratio for Tetralogy of Fallot is consistent with the result observed in Texas (Gilboa et al., 2005, 087892).

Interestingly, similar inconsistencies were also found for PM_{10} between these studies. For example, PM_{10} in Texas was associated with an increased risk of atrial septal defects and with patent ductus arteriosus in Atlanta, GA; yet there was no indication of such an effect in southern California where PM_{10} concentrations were markedly higher.

The authors of the Texas study (Gilboa et al., 2005, 087892) provided little discussion toward the inconsistent results with the southern California study. One suggestion was the different CO concentrations across the studies with the 75th quartile in southern California being 2.39 ppm while in Texas it was much lower at 0.7 ppm. However, this suggests that different defects are associated with different concentrations of CO; yet it still does not explain why particular associations were reported in Texas and not southern California where concentrations were higher. Similarly, the authors of the Texas study (Gilboa et al., 2005, 087892) also suggested the inconsistency was due to different exposure periods. In Texas the exposures were averaged over the 3rd-8th wk while in southern California the exposures were averaged over the second month of pregnancy. However, there was no reason provided as to why this small difference in the examined exposure period would explain the inconsistent results.

Overall, there is some evidence that maternal exposure to CO is associated with an increased risk of congenital anomalies, namely heart defects and cleft lip and palate. Further research is required to corroborate these findings.

5.4.1.4. Neonatal and Postneonatal Mortality

A handful of studies examined the effect of ambient air pollution on neonatal and postneonatal mortality, with the former the least studied. These studies varied somewhat with regard to the outcomes and exposure periods examined and study designs employed.

Neonatal

In Sao Paulo, Brazil, a time-series study examined daily counts of neonatal (up to 28 days after birth) deaths for the period 1998-2000 in association with concurrent-day exposure to SO_2, CO, O_3, and PM_{10}. Moving averages from 27 days were examined. The mean city-wide CO concentration was 2.8 ppm, and there was no association between daily ambient CO and neonatal deaths. Despite CO being correlated with PM_{10} ($r = 0.71$) and SO_2 ($r = 0.55$), only PM_{10} and SO_2 were associated with an increase in the daily rate of neonatal deaths (Lin et al., 2004, 095787).

In another study of neonatal death, Hajat et al. (2007, 093276) created a daily time-series of air pollution and all infant deaths between 1990 and 2000 in 10 major cities in England. The mean daily CO concentration across the 10 cites was 0.57 ppm. This study provided no evidence for an association between ambient CO concentration and neonatal deaths.

Postneonatal

Two studies in the U.S. examined the potential association between ambient CO and postneonatal (from 28 days to 1 yr after birth) mortality and inconsistent results were reported. These studies, however, varied somewhat in study design.

The first of these studies employed a case-control design and examined all infant deaths during the first year of life among infants born alive during 1989-2000 within 16 km of a monitoring site within the South Coast Air Basin of California. Exposures for 2-wk, 1-mo, 2-mo, and 6-mo periods before death were linked to each individual death. Extensive analyses were conducted for all-cause infant deaths, respiratory causes of death, and sudden infant death syndrome (SIDS). Given the long time period of the data analyzed, in order to alleviate the confounding trends in infant mortality and CO levels, this study was able to match by year (Ritz et al., 2006, 089819). Ambient

1-h max CO concentrations averaged over the 2 mo before death were associated with an 11% (OR: 1.11 [95% CI: 1.06-1.16]) increase in risk of all-cause post-neonatal death (per 1 ppm increase) and a 19% (OR: 1.19 [95% CI: 1.10-1.28]) increase in risk of SIDS. In the multipollutant models (including PM_{10}, NO_2, O_3) the positive CO mortality effect decreased by around 50% and was not statistically significant. Based on exposure from 2 wk before death, CO was associated with an increased risk of respiratory related postneonatal deaths occurring 28 days to 1 yr after birth (OR: 1.14 [95% CI: 1.03-1.25] per 1 ppm increase) and 28 days to 3 mo after birth (OR: 1.20 [95% CI: 1.02-1.40]); but no effect was observed for respiratory related deaths occurring 4-12 mo after birth. These results persisted in the multipollutant models, and exposure-response patterns were exhibited across the exposures groupings of 1.02 to <2.08, and ≥ 2.08 ppm. To control for gestational age and birth weight the analyses were stratified by "term/normal-weight infants" and "preterm and/or LBW infants." When these two strata were analyzed, CO was associated with an increased risk of all-cause death and SIDS within both strata (ORs ranged from 1.12 to 1.46). However, these effects did not persist in multipollutant models (Ritz et al., 2006, 089819).

Another study examined 3,583,495 births, including 6,639 postneonatal deaths occurring in 96 counties throughout the U.S. (in counties with >250,000 residents) between 1989 and 2000 (Woodruff et al., 2008, 098386). Only exposure during the first 2 mo of life was examined, and this was based on an average of CO concentrations recorded across all available monitors within the mother's county of residence. In contrast to the other postnatal mortality study in California, CO averaged over the first 2 mo of life was not associated with all-cause death (OR: 1.01 [95% CI: 0.94-1.09] per 0.5 ppm increase in 24-h CO concentration), or with respiratory related deaths (OR: 1.08 [95% CI: 0.91-1.54] per 0.5 ppm increase in 24-h CO concentration), SIDS (OR 0.85 [95% CI: 0.70-1.04] per 0.5 ppm increase in 24-h CO concentration), or other causes of postneonatal mortality (OR: 1.03 [95% CI: 0.96-1.09] per 0.5 ppm increase in 24-h CO concentration). These null findings may be due to higher error of the exposure assessment at the county level as opposed to using data from monitors within close proximity to the residence.

In a study that included 10 major cities in England, Hajat et al. (2007, 093276) created a daily time-series of air pollution and all infant deaths between 1990 and 2000. While there was no evidence for an association with neonatal deaths and ambient CO concentrations, there was a strong adverse effect of CO in postneonatal deaths, although the confidence intervals were wide due to a small sample size (RR 1.09, 95% CI: 0.94-1.25).

The only other postnatal mortality studies have been conducted throughout Asia. Two identical studies in Taiwan failed to find an association between daily counts of postneonatal deaths and ambient air pollutants, including CO. The data analyzed were from the cities of Taipei (Yang et al., 2006, 090760) and Kaohsiung (Tsai et al., 2006, 090709), with ambient CO concentrations being 1.6 ppm and 0.8 ppm, respectively. Both studies examined deaths for the period 1994-2000 and employed a case-crossover design that compared air pollution levels 1 wk before and after each infant's death.

Similarly, another study in South Korea examined postneonatal mortality for the period 1995-1999, using a time-series design. Same-day CO was not associated with all-cause death (RR: 1.02 [95% CI: 0.97-1.06] per 0.5 ppm increase). However, same-day CO was associated with postneonatal mortality when the analyses were restricted to respiratory mortality (RR: 1.33 [95% CI: 1.01-1.76] per 0.5 ppm increase) (Ha et al., 2003, 042552). An additional study examined the relationship between air pollution and postneonatal mortality for all causes in Seoul, Korea. This study used both case-crossover and time-series analyses for all firstborn infants during 1999-2003. The mean 8-h max CO concentration during this time period was 1.01 ppm. The association between ambient CO concentration and postneonatal mortality was the strongest in magnitude for CO when compared to the other criteria pollutants, though the confidence intervals were wide (RR: 1.02 [95% CI: 0.87-1.20] for case-crossover analysis; RR: 1.23 [1.06-1.44] for time-series analysis per 0.75 ppm increase in 8-h max CO concentration).

In general, the inconsistent exposure periods examined among these studies restricts direct comparison and interpretation. Nevertheless, there is limited evidence that CO is associated with an increased risk of infant mortality during the postneonatal period. The exposure periods examined varied from the same-day CO to lag periods up to a 6-mo period prior to birth, with one study alternatively exploring exposures averaged over the first 2 mo of life. Furthermore, given that birth weight and gestational age are strong predictors of infant mortality, in all of the reviewed studies these factors have not been considered at either the design or analysis stage. Hence, the link between fetal, neonatal, and postneonatal exposures, and the possible interaction that birth weight and

gestational age may have on the results yielded from these examined exposure periods needs further attention within this field of research.

5.4.1.5. Summary of Epidemiologic Studies of Birth Outcomes and Developmental Effects

There is some evidence that CO during early pregnancy (e.g., first month and first trimester) is associated with an increased risk of PTB. Additionally, there is evidence of ambient CO during pregnancy having a negative effect on fetal growth. In general, the reviewed studies (Figure 5-10 through Figure 5-12) reported small reductions in birth weight (~10-20 g). Although the majority of studies reported significant effects during either the first or third trimester, other studies failed to find a significant effect during these periods. Several studies examined various combinations of birth weight, LBW, and SGA/IUGR, and inconsistent results are reported across these metrics. For example, six studies reported an association between maternal exposure to CO and decreased birth weight, yet the decrease in birth weight did not translate to an increased risk of LBW or SGA. It should be noted that having a measurable, even if small, change in a population is different than having an effect on a subset of susceptible births, which may increase the risk of IUGR/LBW/SGA. It is difficult to conclude if CO is related to a small change in birth weight in all births across the population or a marked effect in some subset of births.

Three studies examined the effects of CO on cardiac birth defects and found maternal exposure to CO to be associated with an increased risk of cardiac birth defects. Human clinical studies also demonstrated the heart as a target for CO effects (Section 5.2). In general, there is limited evidence that CO is associated with an increased risk of infant mortality during the postneonatal period.

5.4.2. Toxicological Studies of Birth Outcomes and Developmental Effects

The brief overview of the reproductive and development toxicology of CO that follows is not limited to the past 10 yr as are other areas discussed in this document. This is because reproductive and developmental toxicology endpoints have not been covered in previous CO AQCDs. Effects of both exogenous CO exposure and endogenous production of CO are discussed since exposure to exogenous CO could possibly alter pathways normally regulated by endogenous CO production. This document details how in utero or perinatal CO exposure in pregnant dams or pups affects outcomes in the offspring, including postnatal mortality, skeletal development, the ability of the developing fetus to tolerate maternal dietary manipulation, behavioral outcomes, neurotransmitters, brain development, the auditory system, myocardial development, and immune system development. Similarly, endogenous CO is discussed in relation to pregnancy maintenance, vascular tone during gestation, the placenta, the ovaries, the anterior pituitary axis, and lactation. Together, this toxicological summary documents the importance of CO in reproductive and developmental toxicology in laboratory animal models.

5.4.2.1. Birth Outcomes

Decreased Birth Weight

Multiple reports have been published associating CO exposure in laboratory animals and decrements in birth weight (90-600 ppm); some of these studies also noted reduced growth evident in the prenatal period (65-500 ppm CO). Significant decreases in fetal body weight at GD21 after 21 days of continuous CO exposure (125, 250, or 500 ppm) in pregnant Wistar rats have been reported (Prigge and Hochrainer, 1977, 012326). This decrease was not found in rats exposed to 60 ppm CO. Penney et al. (1983, 011385) exposed pregnant rats to CO (200 ppm) for the final 17 days of prenatal development and also found significant decreases in near-term fetal rat weight at GD20-GD21; gestation in rats is ~ 22 days. Penney et al.(1982, 011387) continued to find decreased

body weight to PND210 after postnatal CO exposure (500 ppm, PND1-PND32) and to a larger extent in male pups when compared to female pups. Singh et al. (1984, 011409; 1993, 013892) found significant decreases in fetal weight in gestationally CO-exposed mouse pups (65, 125, 250 or 500 ppm) in two studies. Near-term fetal body weight was decreased at GD18 in mice exposed from GD7-GD18 to 125, 250, and 500 ppm CO but not 65 ppm CO (Singh and Scott, 1984, 011409). However, a second study found decreased fetal weight at GD18 with all CO exposures (65-500 ppm) from GD8-GD18 (Singh et al., 1993, 013892).

A number of studies have found decreases in birth weight after CO exposure. A decrease in body weight at birth was seen in neonates of pregnant rats exposed to 157, 166, and 200 ppm CO over GD6-GD19 (Penney et al., 1983, 011385). Singh (2006, 190512) showed decreases in birth weight of mouse pups gestationally exposed for 6 h/day for the first 2 wk of pregnancy to 125 ppm but not 65 ppm CO. Carmines and Rajendran (2008, 188440) exposed Sprague Dawley rats to ~600 ppm CO (dam COHb 30%) via nose-only inhalation (levels similar to those seen in cigarette smoke) during GD6-GD19 of gestation for 2 h/day and found significant decreases in birth weight (0.5 g or 13%) of exposed pups versus controls. Maternal body weight was unchanged through gestation, but corrected terminal body weight (body weight minus uterine weight) was significantly elevated in CO-exposed dams at term, indicating a decrease in uterine weight. Other studies have not found decreases in birth weight after gestational CO exposure (Carratu et al., 2000, 015839; Mereu et al., 2000, 193838).

Other animal models have been used to examine decreased birth weight resulting from CO exposure. Astrup et al. (1972, 011121) found significant decreases (11 and 20%, respectively) in birth weight of rabbits exposed to either 90 or 180 ppm CO continuously over the duration of gestation. Tolcos et al. (2000, 015997) found significant decreases in body, brain, and liver weights, and crown-to-rump length in guinea pig fetuses after exposure to 200 ppm CO for 10h/day from GD23-GD25 until GD61-GD63, at which time the fetuses were collected (term ranges from GD68 to GD72). In other studies, there was no significant differences in birth weight of guinea pig pups after a similar exposure (200 ppm from GD23-GD25 to term, fetal and maternal COHb levels of 13% and 8.5%, respectively) (McGregor et al., 1998, 085342; Tolcos et al., 2000, 010468) or in Long Evans rats (150 ppm CO continuous exposure over all of gestation) (Fechter and Annau, 1977, 010688). Fetal mouse weight was significantly greater than control in the 7 h/day exposures and significantly less than control animals in the 24 h/day (250 ppm CO, GD6-GD15) exposure groups, with corresponding significant differences in crown-to-rump length in the two groups (Schwetz et al., 1979, 011855). However, animals that showed no decrement in birth weight were significantly smaller at PND4 compared to control guinea pigs (McGregor et al., 1998, 085342), with dam and fetal COHb levels of 13% and 8.5%, respectively, during pregnancy.

Pregnancy Loss and Perinatal Death

Two studies have provided evidence for CO-induced pregnancy loss and perinatal death at CO concentrations between 90 and 250 ppm. Schwetz et al. (1979, 011855) exposed CF-1 mice and New Zealand rabbits to 250 ppm CO over GD6-GD15 (mice) or GD6-GD18 (rabbits) for either 7 h/day or 24 h/day, yielding 4 exposure paradigms. The fetuses were then collected at the termination of exposure, near term. Maternal COHb in the 7 h/day exposure groups was approximately 10-15% COHb in rabbits and mice; COHb was not followed in the 24-h exposure groups. The mice exposed to CO for 7 h/day but not 24 h/day had a significant increase in the number of resorbed pups. Rabbits were less affected by CO exposure, manifesting no significant perinatal death or pregnancy loss. Astrup et al. (1972, 011121) studied the effect of CO on fetal development after continuous CO exposure (90 or 180 ppm CO, COHb 8-9% and 16-18%, respectively) over the duration of gestation in rabbits. In the immediate neonatal period, 24 h postpartum, 35% (180 ppm) and 9.9% (90 ppm) of CO-exposed animals died. In the postpartum period after the first 24 h and extending out to PND21, 90 ppm CO-exposed pups experienced 25% mortality versus 13% in controls; there was no difference from control at the 80 ppm CO exposure level. Gestation length was unchanged with CO exposure. Conversely, Fechter and Annau (1977, 010688) exposed Long Evans rats in utero to 150 ppm CO continuously through gestation (dam COHb 15%) and saw no effects of CO on litter mortality at PND1.

Effect of Maternal Diet

As mentioned above, CO induced offspring mortality after prenatal exposure. Alterations in maternal dietary protein and zinc further altered offspring mortality and teratogenicity caused by CO (65-500 ppm).

Maternal Protein Intake and Neonatal Mouse Mortality and Teratogenicity

Pregnant CD-1 mice were exposed intermittently (6 h/day for first 2 wk of pregnancy) to CO (0, 65, or 125 ppm) in combination with protein modified diets (27% [supplemental protein], 16% [control], 8% [low], or 4% [very low protein]) to assess the role of dietary protein in modulating CO effects on neonatal mortality at 1 wk of age (Singh, 2006, 190512). Litter size was not affected by CO exposure. Pup weight was inversely related to CO exposure and directly related to dam diet protein content during pregnancy. Pup mortality at birth was directly related to CO exposure in certain protein groups (supplemental, and 4% protein) and inversely related to the dam's dietary protein content. At 1 wk of age, pup mortality was significantly increased by CO exposure as well as dietary protein restriction; all pups in the 4% protein diet died by 1 wk of age. CO exposure (65 ppm only) combined with a normal protein diet (16%) and CO exposure (65 and 125 ppm) with a supplemental protein diet (27%) significantly increased pup mortality at 1 wk versus control air pups (0 ppm CO). Contrary to other findings, low protein diet (8%) combined with CO (125 ppm) led to a slight yet significant decrease in pup mortality at 1 wk of age versus control (0 ppm CO). In summary, these data show that in utero CO exposure induced increased neonatal mouse deaths at 1 wk in supplemental protein and normal protein diet exposure groups and increased perinatal mortality when combined with supplemental or restricted protein.

The role of diet as a contributor to teratogenicity of CO (0, 65, 125, or 250 ppm CO) in CD-1 mice given various protein diets (4, 8, 16, or 27% protein) during pregnancy was explored by Singh et al. (1993, 013892). Timed-pregnant CD-1 mice were exposed continuously to CO from GD8-GD18, at which point animals were sacrificed and fetuses collected. Work by this group has shown that low protein diets plus CO exposure act in an additive fashion to increase placental COHb in mice (Singh, 2003, 053624; Singh et al., 1992, 013759). As expected, all levels of CO and the lowest protein diet (4 or 8% protein) given to the dams during gestation resulted in significantly decreased near-term weight of normal fetuses at GD18. CO exposure did not produce maternal toxicity except for a significant decrease in maternal weight at GD18 with 4 and 8% protein diets versus control diet in non-CO-exposed animals. Dam dietary protein levels were inversely related to gross fetal malformations including jaw changes. All concentrations of CO exposure within each maternal dietary protein level significantly increased the percentage of litters with malformations in a dose-dependent manner. Skeletal malformations were present in offspring, with the percent of litters affected inversely related to dietary protein levels. CO exposure concomitant with a low protein diet increased the percent of skeletal malformations in offspring. The percent of dead, resorbed, or grossly malformed fetuses was directly related to CO concentration and inversely related to maternal dietary protein levels. CO and maternal dietary protein restriction had a synergistic effect on mouse offspring mortality and an additive effect on malformations.

Maternal Zinc and Protein Intake and Neonatal Mortality and Teratogenicity

Singh (2003, 053624) explored how teratogenicity and fetal mortality were affected by zinc (Zn) modulation in CO-exposed (500 ppm from GD8-GD18) pregnant dams (CD-1 mouse) given protein-insufficient diets. CO exposure in low-protein conditions (9% protein) decreased the mean implants per litter as compared to air exposure. CO exposure also increased the near-term fetal mortality over all groups, and to a larger extent in the low-protein groups, both Zn normal (57% versus 6% mortality) and Zn deficient groups (86.6% versus 70.9% mortality). Under low-protein conditions, CO exposure increased the incidence of malformations (9.4% versus 0%) when Zn levels were normal and increased the incidence of gastroschisis (5% versus 0%) when Zn levels were low. Joint protein and Zn deficiency led to 60% of litters with gastroschisis. Conversely, CO exposure under Zn deficiency decreased the incidence of other malformations such as exencephaly, jaw, syndactyly, and tail malformations.

Further studies by Neggers and Singh (2006, 193964) only partially confirmed these findings. As before, diets deficient in both Zn and protein had significant detrimental influence on both fetal malformations and mortality. Exposure to 500 ppm CO increased fetal mortality and malformation

rates under deficient protein (9%) and supplemental Zn (3.3 g/kg diet) conditions; however, CO had a negligible effect on these endpoints under deficient protein and deficient or normal Zn conditions.

Role of Endogenous CO

CO is produced endogenously from heme protein catabolism by heme oxygenases, HO-1, HO-2, and HO-3. CO has recently been recognized as a second messenger signaling molecule, similar to NO, with a number of normal physiological roles in the body. Some of these roles are played in maintaining pregnancy, controlling vascular tone, regulating hormone balance, and sustaining normal ovarian follicular maturation. These areas could be potential areas of interaction of exogenous CO.

Pregnancy Maintenance

HO-1 is known to protect organs from rejection (Kotsch et al., 2006, 193899) and thus, HO may also protect the developing fetus from rejection by the non-self maternal immune system. Idiopathic spontaneous abortions are more frequent in women with HO-1 polymorphisms (GT)n microsatellite polymorphisms associated with altered HO-1 transcription in their genome (Denschlag et al., 2004, 193894). Similarly, administering HO-inhibitors to pregnant rodents induced total litter loss, possibly due to vasoconstriction and associated ischemia of the placental vascular bed (Alexandreanu and Lawson, 2002, 192373). Also, mice overexpressing HO-1 had a significantly decreased rate of spontaneous abortion (Zenclussen et al., 2006, 193873). Various pathologies of pregnancy, including IUGR and pre-eclampsia, are associated with significant decreases in placental HO activity (Denschlag et al., 2004, 193894; McLaughlin et al., 2003, 193827). Oxygenation is important in early pregnancy and triggers trophoblast invasion of the spiral arteries (Kingdom and Kaufmann, 1997, 193897). Women living at high altitude have an increased risk of adverse pregnancy outcomes versus women living at lower altitudes (Zamudio et al., 1995, 193908). Also, women living at high altitude, women with pre-eclampsia, or women who had pregnancies with fetal growth restrictions (FGR) produced term placenta with significant decreases in HO-2 versus women living at lower altitude with uncomplicated pregnancies (Barber et al., 2001, 193891; Lyall et al., 2000, 193902). Thus, the HO/CO system is crucial for the developing fetus, helps in maintaining pregnancy, and plays a role in spontaneous abortions.

Vascular Control

During pregnancy, there is increased blood volume without a concurrent increase in systemic BP, which is accomplished by a decrease in total peripheral vascular resistance (Zhao et al., 2008, 193883). CO through the production of soluble guanylate cyclase is able to stimulate the relaxation of vascular smooth muscle (Villamor et al., 2000, 015838) and relaxation of pregnant rat tail artery and aortic rings (Longo et al., 1999, 011548). Further, the administration of the HO inhibitor SnMP increased maternal BP (systolic, diastolic, and mean arterial pressure) and significantly increased uterine artery blood flow velocity during pregnancy in mice (Zhao et al., 2008, 193883). Zhao et al. also showed pregnancy induced increased total body CO exhalation and that this increased CO production could be significantly decreased by SnMP administration. Abdominal aortas (AA) of pregnant dams are significantly dilated with pregnancy, and SnMP treatment leads to AA vasoconstriction to levels similar to nonpregnant mice. Isolated human placenta exposed to solutions containing CO demonstrated a concentration-dependent decrease in perfusion pressure (Bainbridge et al., 2002, 043161), further demonstrating the role of CO in maintaining basal vasculature tone. However, the addition of exogenous CO to isolated human and rat uterine tissue during pregnancy failed to induce relaxation and quiet the spontaneous contractility of rat or human myometrium (uterine smooth muscle)(Longo et al., 1999, 011548). CO is not able to relax all types of vascular smooth muscle (Brian et al., 1994, 076283), and pregnancy appears to modulate the response of tissues to CO (Katoue et al., 2005, 193896). Thus, it appears that the increased CO production during pregnancy may partially account for the decreased peripheral vascular resistance seen in pregnancy that prevents the increased blood volume of pregnancy from affecting BP.

Hormone Regulation

Endogenous CO has been shown to regulate neuroendocrine functions. Disruption of normal CO signaling causes changes in the cycles of a number of hormones involved in pregnancy. HO inhibition in rats significantly decreased ovarian production of gonadotrophin-induced androstenedione and progesterone without affecting estradiol levels (Alexandreanu and Lawson, 2002, 192373). However, treatment with the HO-inducer, hemin, caused androstenedione and estradiol production from rat ovaries in vitro. CO also has been shown to have a stimulatory effect on gonadotropin-releasing hormone (GnRH) release from rat hypothalamic explants in vitro (Lamar et al., 1996, 078819), while in vivo CO appears not to influence GnRH secretion (Kohsaka et al., 1999, 191000). HO-1 induction and HO concentration have been shown to be regulated by estrogen in the rat uterus (Cella et al., 2006, 193240) during pregnancy and in nongravid rats. This agrees with work by Tschugguel et al. (2001, 193785) in which CO was generated by primary endothelial cells from human umbilical veins and uterine arteries after exogenous 17-β estradiol administration. HO inhibition by CrMP decreased time in estrous in a dose-dependent manner (Alexandreanu and Lawson, 2002, 192373).

HO-1 and HO-2 are expressed in rat anterior pituitary, and the secretion of gonadotropins and prolactin is affected by HO-inhibitor and HO-substrate administration (Alexandreanu and Lawson, 2003, 193871). The estrogen-induced afternoon surge of luteinizing hormone (LH) was advanced forward in time by HO inhibition, and this advance could be reversed by concomitant administration of hemin. The serum follicle stimulating hormone (FSH) surge was unaffected by HO inhibition or hemin, but in vitro treatment of GnRH-stimulated pituitaries with hemin led to a significant increase in FSH release. The estrogen-dependent afternoon prolactin surge was inhibited or delayed by HO inhibition and significantly decreased prolactin release. In vitro studies using pituitary explants showed that LH release was significantly increased by HO inhibition. HO inhibition also decreased litter weight gain during lactation, which the authors attributed to decreased maternal milk production or milk ejection problems as cross-fostered pups regained weight that was lost during nursing on HO-inhibited dams (Alexandreanu and Lawson, 2002, 192373). The lactational effects seen in this model may be explained by changes in prolactin (Alexandreanu and Lawson, 2003, 193871). It is possible that HO inhibition by CrMP may also inhibit NO production, a mechanism that is distinct from CO-dependent effects.

Ovarian Follicular Atresia

As a part of normal follicular maturation in the ovaries, the majority of follicles undergo atresia via apoptosis prior to ovulation. Harada et al. (2004, 193920) harvested porcine granulosa cells from ovaries and found that cells naturally undergoing atresia or cell death more strongly expressed HO-1 than did successful follicles. Addition of the HO-substrate hemin or the HO-inhibitor Zn protoporphyrin IX (ZnPP IX) significantly induced or inhibited granulosa cell apoptosis, respectively. In this porcine model, HO was able to augment granulosa cell apoptosis allowing for proper follicular maturation.

Summary of Toxicological Studies on Birth Outcomes

There is some evidence that CO exposure leads to altered birth outcomes, including decreased birth and near-term body weight, increased pregnancy loss and perinatal death, and increased malformations. These events occurred at levels as low as 65 ppm for fetal body weight decrements and 90 ppm for changes in birth weight and perinatal death. Pregnancy loss was seen after exposure to 250 ppm CO, whereas skeletal malformations were present after 180 ppm CO. Dietary protein and zinc modifications exacerbated these CO-induced effects on birth outcomes. Maternal protein restriction and CO had a synergistic effect on peri- and postnatal mortality and an additive effect on malformations. Dietary zinc alterations resulted in inconsistent changes to CO-induced malformations and fetal mortality.

Endogenous CO is recognized as a second messenger signaling molecule with normal physiological roles in maintaining pregnancy and for proper fetal and postnatal development. The endogenous HO/CO system is also involved in controlling vascular tone, follicular maturation, ovarian steroidogenesis, secretion of gonadotropin and prolactin by the anterior pituitary, lactation,

and estrous cyclicity in rodent studies. These areas could be potential points of interaction of exogenous CO with endogenous HO/CO.

5.4.2.2. Developmental Effects

Congenital Abnormalities

Studies by Schwetz et al. (1979, 011855) found that gestational CO exposure (250 ppm) in CF-1 mice for 7 or 24 h/day over GD6-GD15 resulted in minor fetal skeletal alterations in the form of extra lumbar ribs and spurs (dam gestational COHb 10-15% for 7h/day exposure, 24 h/day dam COHb not measured). Similarly exposed rabbits did not exhibit these changes.

Astrup et al. (1972, 011121) studied the effect of CO exposure on fetal rabbit development via continuous CO exposure (90 or 180 ppm with gestational dam COHb of 9 and 17%, respectively) over the duration of gestation. Three pups in the 180 ppm CO group (n = 123) had deformities in their extremities at birth, whereas no control and no 90 ppm CO-exposed animals manifested with this malformation.

Further skeletal malformations were seen after gestational CO exposure in mice as described above ("Effect of Maternal Diet") (Singh et al., 1993, 013892). Briefly, pregnant CD-1 mice were exposed intermittently to CO (65-250 ppm; GD8-GD18) in combination with protein modified diets (27% [supplemental protein], 16% [control], 8% [low], or 4% [very low protein]) to assess the role of dietary protein in modulating CO effects on neonates at 1 wk of age. Maternal dietary protein restriction additively compounded the CO-induced skeletal malformations. Further, dietary restriction in Zn and protein led to increased teratogenicity, specifically increased incidence of gastroschisis (Singh, 2003, 053624). Conversely, Carmines and Rajendran (2008, 188440) did not find evidence of external malformations (teratogenicity) in rats after exposure to ~600 ppm CO from GD6-GD19.

CNS Developmental Effects

Behavioral

Investigators have used animal models to study the effects of moderate CO exposure (65-150 ppm) during gestation on behavioral outcomes after birth, including active avoidance, learning and memory, homing, and motor activity. These studies generally found decrements in behavior in early life after in utero exposure to CO concentrations >125 ppm and in some cases as low as 65 ppm. Table 5-14 shows results of behavioral response studies with CO exposure $\leq$ 150 ppm.

Table 5-14. Behavioral responses.

Study	Model System	CO Exposure	Response	Notes
BEHAVIORAL RESPONSES				
De Salvia et al. (1995, 079441)	Rats	75 and 150 ppm continuous GD0-GD20	Impaired acquisition (3 and 18 mo) and reacquisition (18 mo) of avoidance behavior at 150 ppm, not 75 ppm	
Mactutus and Fechter (1985, 011536)	Rats	150 ppm continuous GD0-GD20	Delayed acquisition of active avoidance (PND120) and disrupted retention (PND360)	COHb 15.6 ± 1.1%
Di Giovanni et al. (1993, 013822)	Rats	75 and 150 ppm continuous GD0-GD20	CO (150 ppm) reduced the minimum frequency of ultrasonic calls as well as decreased responsiveness to a challenge dose of diazepam. There was no change in locomotion; however, CO impaired learning in a two-way active avoidance task.	
Mactutus and Fechter (1984, 011355)	Rats	150 ppm	Acquisition did not improve with age/maturation, failure to learn; impaired reacquisition (PND31), failure to retain	COHb 15%
Giustino et al. (1999, 011538)	Rats	75 and 150 ppm continuous GD0-GD20	Decreased exploration, habituation, nonspatial working memory	COHb: 1.6 ± 0.1% (0 ppm); 7.36 ± 0.2% (75 ppm); 16.1 ± 0.9% (150 ppm)
Zhuo et al. (1993, 013905)	Mouse hippocampal brain sections	ZnPPIX (HO inhibitor) and 0.1-1.0 µM CO	HO inhibition blocked long-term potentiation and CO evoked synaptic potentials and long-term enhancement	
Stevens and Wang (1993, 188458)	Mouse and rat hippocampal brain slices	ZnPPIX (5-15 µM)	HO inhibition blocked long-term potentiation but not long-term depression.	
Mereu (2000, 193838)	Rat hippocampal brain sections	150 ppm GD0-GD20	Impaired long-term potentiation maintenance	
Fechter and Annau (1980, 011295)	Rats	150 ppm continuous GD0-GD20	Delayed homing behavior and poor reflexive response	
Fechter and Annau (1977, 010688)	Rats	150 ppm continuous GD0-GD20	Decreased locomotor activity at PND1, PND4, and PND14, but not PND21	COHb 15%
Singh (1986, 012827)	Mice	65 and 125 ppm continuous GD7-GD18	Impaired aerial righting score at PND14 (65 and 125 ppm), impaired negative geotaxis at PND10 and righting reflex on PND1 (125 ppm)	

Active Avoidance Behavior. To assess behavioral changes after in utero exposure, pregnant Wistar rats were exposed to CO (0, 75, or 150 ppm) continuously over GD0-GD20 (De Salvia et al., 1995, 079441). Male pups from exposed dams were evaluated for active avoidance behavior (mild shock avoidance) during acquisition and reacquisition. This work was designed to expand on the studies of Mactutus and Fechter (1985, 011536), who showed delayed acquisition (120 days of age) of an active avoidance task and disruption of retention at a later test date (360 days) after continuous in utero CO exposure (150 ppm CO, dam COHb concentrations of 15.6 ± 1.1%), and to determine if these behavioral changes were permanent. De Salvia et al. (1995, 079441) found there were no significant behavioral impairments following exposure to 75 ppm CO. However, animals exposed to the 150 ppm in utero had significantly impaired acquisition (at 3 and 18 mo of age) and reacquisition (at 18 mo of age) of conditioned avoidance behavior. This impaired learning was also seen in gestationally CO (150 ppm, trend seen at 75 ppm) exposed rats at PND90 (Di Giovanni et al., 1993, 013822). The authors speculated that this CO-dependent behavioral change may be mediated through neurotransmitter signaling, specifically changes in dopamine in the neostriatum or nucleus accumbens. These studies demonstrate that moderate CO exposure in utero can lead to permanent behavioral changes in male offspring.

Mactutus and Fechter (1984, 011355) also found that acquisition in a two-way conditioned avoidance test (flashing light warnings followed by mild footshock) failed to improve with age of in

utero CO-exposed (150 ppm, dam COHb 15%) Long Evans rats (male and female offspring) in contrast to air-exposed controls who improved with age/maturation, indicating a failure in the associative process of learning. They also found impairments in reacquisition performance, an index of retention, in PND31 rats that had received continuous in utero CO exposure. Overall, prenatal CO exposure (150 ppm, not 75 ppm) induced learning and memory deficits in male and female offspring.

Habituation, Memory, and Learning. Giustino et al. (1999, 011538) exposed primiparious pregnant Wistar rats to CO (0, 75 or 150 ppm) by inhalation from GD0-GD20. Blood COHb concentrations (mean % ± SEM) on GD20 were reported (0 ppm: 1.6 ± 0.1; CO 75 ppm: 7.36 ± 0.2; CO 150 ppm: 16.1 ± 0.9). Male offspring at age 40 days were given two habituation trials. In the first trial (T1), two similar objects were presented. In the second trial (T2), one object from the first trial was presented as well as one novel object. Results were quantified three ways. Exploration activity was defined as the time exploring both objects during each trial. Global habituation was quantified as a comparison of the time spent exploring the two objects in T1 to the time spent exploring objects in T2. Discrimination between new and familiar objects was measured in T2 by contrasting the time spent exploring the familiar object to the time spent exploring the new object. These recognition sessions test for the preference that rats have for investigating novel objects in lieu of familiar objects and are a measurement of nonspatial working memory. The results of this study showed 40 day old animals that were gestationally exposed to CO (both 75 and 150 ppm) spent less time exploring novel objects when compared to control animals. Control rabbits habituated or learned after a second exposure to a previously explored object (T2<T1), but T2 and T1 were not significantly different with CO exposure (150 ppm). Results for rats exposed to 75 ppm were inconsistent in that significantly different exploratory times were found using one statistical method (Wilcoxon paired signed-rank test) and not found using another method (Kruskal-Wallis ANOVA). Finally, the decreased time spent with a familiar object by control rats was not seen in CO-exposed animals (75 or 150 ppm). The authors speculated that the mesolimbic dopaminergic system may be responsible for these changes, possibly involving the nucleus accumbens. The human literature shows a possible connection with these CO-dependent rodent effects; infants whose mothers smoked during pregnancy manifest with habituation defects (Fried et al., 1998, 190210; Fried et al., 2003, 190209). Nonetheless, CO is just one of many constituents of cigarette smoke. The results from these animal toxicology studies showed that in utero exposure to CO affects nonspatial working memory in young adult male rats.

Studies have shown that endogenous and exogenous CO may be involved in the generation of the hippocampal long-term potentiation (LTP), which is believed to correlate with learning and memory (Hawkins et al., 1994, 076503; Mereu et al., 2000, 193838; Stevens and Wang, 1993, 188458; Zhuo et al., 1993, 013905). It is possible that CO can act as a retrograde synaptic signaling messenger, allowing a signal to travel from a postsynaptic to presynaptic neuron. Treatment of mouse or rat hippocampal brain sections with ZnPPIX, an HO-inhibitor, blocked induction of the LTP but not long-term depression (Stevens and Wang, 1993, 188458; Zhuo et al., 1993, 013905). Exogenous CO exposure (0.1-1.0 µM) also evoked long-term enhancement and evoked synaptic potentials (Zhuo et al., 1993, 013905). Similarly, hippocampal slices from gestationally CO-exposed (150 ppm from GD0-20) Wistar rats exhibited an impaired ability to maintain LTP over time and a modest reduction in post-tetanic potentiation (Mereu et al., 2000, 193838). Conversely, other studies have found no correlation between CO and LTP using step-through, step-down, and water-maze tests (Bing et al., 1995, 079418; Toyoda et al., 1996, 079945). Thus, distinct types of learning may be differentially regulated by CO exposure, and endogenous CO, as modulated by HO-inhibitors, may manifest with different outcomes when compared to outcomes seen for exogenous CO.

Homing and Locomotor Effects. Fechter and Annau (1977, 010688; 1980, 011295) exposed Long Evans rats in utero to 150 ppm CO continuously through gestation (dam COHb 15%) and saw significant effects of CO on pup locomotor activity measured across 10-min intervals for a 1-h period. CO-exposed pups showed consistently less activity than air-exposed controls through the preweaning window, with significantly reduced activity seen at PND1 and PND4 (both after subcutaneous L-DOPA administration to induce movement) and at PND14 but not at PND21. However, the PND14 rats only showed decreased activity after 30 min of testing. Di Giovanni et al. (1993, 013822) found that prenatal CO (75 and 150 ppm) did not significantly affect locomotor activity or D-amphetamine induced hyperactivity at PND14 or PND21, but the rats were only subjected to a 30-min session. This study may have overlooked the later window of possible decreased activity.

Under analogous exposure conditions, Fechter and Annau (1980, 011295) found that the development of homing behavior, orientation by the rat toward its home cage, was significantly delayed in rats prenatally exposed to 150 ppm CO. Also, exposed offspring manifested with poorer than normal performance on the negative geotaxis test, a reflexive response that results in a directional movement with or against gravity. Similarly, continuous prenatal CO exposure (125 ppm, GD7-GD18) in CD-1 mice impaired negative geotaxis at PND10 (Singh, 1986, 012827). The standardization and use of geotaxis as a vestibular, motor, or postural metric in infant rodents has been debated in the literature (Kreider and Blumberg, 2005, 193944).

Prenatal exposure to CO (125 ppm, GD7-GD18) significantly affected the righting reflex (the turning of an animal from its supine position to its feet) in exposed CD-1 mice on PND1. Also, the aerial righting score, or turning 180° and landing on the feet when dropped from the supine position at a height, was significantly decreased in pups exposed to CO in utero (65 and 125 ppm) at PND14 (Singh, 1986, 012827). The same trend of impaired righting reflex was seen in gestationally CO (150 ppm) exposed rats (Fechter and Annau, 1980, 011295). These behavioral tests indicated neuromuscular, vestibular, or postural effects in the CO-exposed neonate.

Conversely, no gross impairment of motor activity was found as measured by infrared movement monitoring in Wistar rats treated in utero (GD0-GD20) with 0, 75 or 100 ppm CO (Carratu et al., 2000, 015839). Monitoring was done at PND40 and PND90 and may have been too late to detect CO-dependent changes. Earlier studies by Fechter and Annau (1977, 010688) identified an early window of sensitivity for CO-dependent motor activity deficits of PND1-PND14, with recovery by PND21.

Emotionality. In utero CO exposure caused subtle alterations in the ontogeny of emotionality measured by the ultrasonic vocalization emitted by rat pups removed from their nest. Prenatal CO exposure (150 ppm) caused a reduction in the minimum frequency of ultrasonic calls emitted by PND5 pups (Di Giovanni et al., 1993, 013822). The rate of calling, maximum frequency, and duration and sound pressure level were not affected by prenatal CO. However, the rate of calling and responsiveness to a challenge dose of diazepam was decreased by prenatal CO exposure. Pup vocalization is mediated by the GABAergic neuron function which is altered by CO exposure (see below).

Neuronal

Since behavioral changes have been caused by CO exposure, studies have investigated whether CO exposure results in changes to neuronal structures and electrical excitability. Moderate levels of CO (75 -150 ppm) decrease peripheral nervous system (PNS) myelination due to impaired sphingomyelin homeostasis and can reversibly delay the rate of ion channel development after gestational exposure. In utero CO exposure also results in irreversible changes in sodium equilibrium potential. Further details of these studies are given below in Table 5-15.

Table 5-15. Neuronal responses.

Study	Model System	CO Exposure	Response	Notes
NEURONAL RESPONSES				
Carratu et al. (2000, 015839)	Rats	75 and 150 ppm continuous GD0-GD20	Decreased peripheral nerve fiber myelin sheath thickness	COHb: 0 ppm (GD10: 0.97 ± 0.02; GD20: 1.62 ± 0.1.), 75 ppm (GD10: 7.20 ± 0.12; GD20: 7.43 ± 0.62), and 150 ppm (GD10: 14.42 ± 0.52; GD20: 16.08 ± 0.88)
Carratu et al. (2000, 015935)	Rats	150 ppm continuous GD0-GD20	Impaired sphingomyelin homeostasis by increasing sphingosine	
Carratu et al. (1993, 013812)	Rats	75 and 150 ppm continuous GD0-GD20	Produced partly reversible changes in membrane excitability through delayed inward current inactivation and decreased inward current reversal potential	COHb: 15% at 150 ppm
De Luca et al. (1996, 080911)	Rats	75 and 150 ppm continuous GD0-GD20	Delayed development of the ion channels responsible for passive and active membrane electrical properties of skeletal muscle	
Montagnani et al. (1996, 080902)	Rats	75 or 150 ppm GD0-GD20	CO (150 ppm) increased the tetrodotoxin-inhibition of PNS-evoked vasoconstriction at PND5-7. CO exposure caused the relaxant effect by ACh to appear earlier and the contractile response to disappear earlier (vasodilator effects).	
Dyer et al. (1979, 190994)	Rats	150 ppm GD0-GD21	Increased early components (P1-N1 and N1-P1) of the cortical flash evoked potential peak-to-peak amplitudes at PND65 in female rats	Maternal COHb: 15%

Peripheral Nerve Myelination. The effect of in utero exposure (GD0-GD20) to 0, 75 or 150 ppm CO on sciatic nerve myelination in male offspring was studied in Wistar rats (Carratu et al., 2000, 015839). The dam CO blood concentration, expressed as % COHb, was determined for 0 ppm (GD10: 0.97 ± 0.02; GD20: 1.62 ± 0.1.), 75 ppm (GD10: 7.20 ± 0.12; GD20: 7.43 ± 0.62), and 150 ppm (GD10: 14.42 ± 0.52; GD20: 16.08 ± 0.88). The myelin sheath thickness of the peripheral nerve fibers was significantly decreased in CO-exposed animals (75 and 150 ppm); however, axon diameter was not affected. As mentioned above, even though CO affected myelination, it did not significantly affect motor activity of CO-exposed mice at 40 and 90 days. It is possible that these deficits in PNS myelination are due to impaired sphingomyelin homeostasis. In utero exposure (GD0-GD20) of Wistar rats to CO (150 ppm) caused a twofold increase in sphingosine (SO) but not sphinganine (SA) in the sciatic nerve at 90 days of age (Carratu et al., 2000, 015935). SO is an intermediate in sphingolipid turnover and SA is an intermediate of de novo sphingolipid biosynthesis. Hypoxia has been shown to induce sphingomyelin changes which could lead to impaired myelination and motor activity decrements (Ueda et al., 1998, 195136; Yoshimura et al., 1999, 195135). Prenatal CO exposure had no effect on brain SA or SO levels in male offspring at 90 days of age. These results demonstrate prenatal CO exposure could interrupt sphingolipid homeostasis in the PNS but not CNS, causing a decrease in nerve myelination without changes in motor activity.

Electrophysiological Changes.

Gestational exposure of Wistar rats to continuous CO (75 or 150 ppm (15% COHb at 150 ppm) yielded electrophysiological changes in the PNS (Carratu et al., 1993, 013812). Changes were noticeable in voltage- and time-dependent properties of sodium channels in the sciatic nerve after in utero CO exposure. Changes in sodium channel inactivation kinetics were reversible (present at PND40 and absent at PND270) but changes in the sodium equilibrium potential were irreversible. In utero CO exposure (150 ppm) also delayed the development of the resting chloride conductance (GCl) and resting potassium conductance (GK), with levels matching the control by PND80 and PND60, respectively (De Luca et al., 1996, 080911). CO exposure (75 and 150 ppm) also altered the pharmacological properties of the chloride channel and excitability parameters of skeletal muscle fibers. These changes in the nerve electrophysiological properties could account for increased

tetrodotoxin-inhibition of the vasoconstriction evoked by the PNS in 5- to 7-day-old prenatally exposed pups (Montagnani et al., 1996, 080902). Finally, gestational CO exposure increased early components (P1-N1 and N1-P1) of the cortical flash evoked potential peak-to-peak amplitudes at 65 days postexposure (PND65) in female, not male, rats (Dyer et al., 1979, 190994). The early waves of the cortical evoked potential, an indicator of visual cortical functioning, generally indicate activity in the retinogeniculostriate system. These studies showed that in utero CO exposure had both reversible and irreversible effects on sodium and potassium channels, which are essential for proper electrophysiological function of the muscles and PNS.

Neurotransmitter Changes

The developing nervous system is extremely sensitive to decreased oxygen availability. Virtually all neurotransmitter systems are present at birth but require further maturation. The studies listed below in Table 5-16 have shown that prenatal exposure to CO alters a number of neurotransmitters and their pathways at concentrations ranging from 75 to 300 ppm, both transiently and permanently.

Medullar Neurotransmitters. SIDS is a complex syndrome that involves the aberrant development of brain stem nuclei controlling respiratory, cardiovascular, and arousal activity. To investigate changes in the structure and neurochemistry of the brain stem, Tolcos et al. (2000, 015997) exposed pregnant guinea pigs to CO (200 ppm) over the last 60% of gestation. Guinea pigs and humans both have the majority of CNS development in utero. CO-exposed pups were found to have significant decrements in body, brain, and liver weights, crown-to-rump length, and medullar volume when compared to control pups. Neurotransmitter systems were also affected after CO exposure. Specifically, the brain stem displayed significant decreases in protein and immunoreactivity for tyrosine hydroxylase (TH), an enzyme necessary for catecholamine production, which is likely due to decreased cell number in specific medullar regions responsible for cardiorespiratory control. This was consistent with earlier work showing that prenatal CO exposure leads to aberrant respiratory responses to asphyxia and CO_2 (McGregor et al., 1998, 085342). The cholinergic system was also affected by prenatal CO exposure with significant increases in choline acetyl-transferase (ChAT) immunoreactivity of the medulla; however, no changes in muscarinic acetylcholine receptor were seen. This is in contrast to human infants with SIDS who show decreased brain stem muscarinic receptor binding (Kinney et al., 1995, 193898). ChAT changes in this study (Tolcos et al., 2000, 015997) were from areas of the medulla associated with tongue innervation, which is crucial to swallowing, possibly in relation to breathing.

A second risk factor for SIDS is hyperthermia. To explore the interaction of hyperthermia and CO-induced hypoxia, pregnant guinea pigs were exposed to CO (0 or 200 ppm) for 10 h/day for the last 60% of gestation (Tolcos et al., 2000, 010468). At PND4 male pups were exposed to hyperthermia or ambient temperature as a control. Brains were then collected at 1 and 8 wk of age. In utero CO exposure sensitized some areas of the brain to future hyperthermic insults. Specifically, CO plus hyperthermia induced significant increases in serotonin in multiple brain regions (NTS, DMV, and hypoglossal nucleus) at 1 wk of age; this change was no longer evident at 8 wk of age. Hyperthermia exposure alone induced decreased met-enkephalin neurotransmitter immunoreactivity at 1 wk of age that was absent at 8 wk and absent in CO-plus-hyperthermia exposed animals. Brain stem neurotransmitter (met-enkephalin, serotonin, TH, substance P) immunohistochemical differences were not apparent with CO treatment alone. At 8 wk of age, CO-plus-hyperthermia exposure induced glial aggregations and gliosis surrounding infarct or necrotic areas in the brain and the medulla lesions stained positive for glial fibrillary acidic protein (GFAP). GFAP upregulation is classically seen with neuronal diseases or following neurodegeneration. Gross structural observations revealed no differences in the medulla or cerebellum following in utero CO exposure alone. Together, these data showed that CO exposure in utero sensitizes the brain to future hyperthermic insults, lea ding to generation of necrotic lesions in the brain and changes in neurotransmitter levels.

Table 5-16. Neurotransmitter changes.

Study	Model System	CO Exposure	Response	Notes
NEUROTRANSMITTER CHANGES				
Tolcos et al. (2000, 015997)	Guinea pigs	200 ppm 10h/day GD23-GD25 to GD61-GD63	CO affected catecholaminergic system in brain stem by reducing tyrosine hydroxylase. Affected cholinergic system by increasing choline acetyl-transferase.	Fetal COHb: 13% Maternal COHb: 8.5%
Tolcos et al. (2000, 010468)	Guinea pigs	200 ppm 10h/day GD23-GD25 to birth Hyperthermia on PND4	CO sensitizes the brain to the effects of a short period of hyperthermia on PND4. The exposure combination resulted in lesions in the brain, as well as increased serotonin and glial fibrillary acidic protein. The exposure also caused reactive astrogliosis.	Fetal COHb: 13% Maternal COHb: 8.5%
McGregor et al. (1998, 085342)	Guinea pigs	200 ppm 10h/day GD23-GD25 to birth	CO increased tidal volume during steady state hypercapnia and progressive asphyxia, due to increased ventilation.	Fetal COHb: 13% Maternal COHb: 8.5%
Cagiano et al. (1998, 087170)	Rats	75 and 150 ppm GD0-GD20	In utero CO (150 ppm) exposure increased mount/intromission latency , decreased mount/intromission frequency, and induced ejaculatory abnormalities. CO also blunted the amphetamine-induced increase in dopamine.	Maternal COHb: GD10: 1, 7, and 15%; GD20: 1.5, 7, and 16% (0, 75, and 150 ppm CO, respectively)
Hermans et al. (1993, 190510)	Rats	Hypoxia (10.5% O_2) GD15-GD21	Hypoxia caused delayed initiation latencies of male sexual behavior and decreased number of ejaculations.	
Fechter et al. (1987, 012259)	Rats	75, 150, and 300 ppm GD0-GD20 or PND10	Prenatal CO exposure continuing to PND10 leads to increased concentrations of dopamine but not dopamine metabolites in striatal tissue.	Maternal COHb: 2.5 ± 0.1%, 11.4 ± 0.3%, 18.5 ± 0.5%, 26.8 ± 1.1% (0, 75, 150, and 300 ppm, respectively)
Storm and Fechter (1985, 011653)	Rats	150 ppm GD0-GD20	Prenatal CO exposure increased mean and total cerebellar norepinephrine concentration from PND14 to PND42, but not in the cortex.	
Storm and Fechter (1985, 011652)	Rats	75, 150, and 300 ppm GD0-GD20	CO transiently decreased 5HT and NE in the pons/medulla. CO increased NE in the cortex and hippocampus at PND42. CO dose-dependently reduced cerebellum wet weight.	Maternal COHb: 2.5%, 11.5%, 18.5%, and 26.8% (0, 75, 150, and 300 ppm, respectively)
Storm et al. (1986, 012136)	Rats	75, 150, and 300 ppm GD0-PND10	CO decreased cerebellar weight (150-300 ppm at PND10, 75-300 ppm at PND21) and decreased total cerebellar GABA (150-300 ppm at PND10 and PND21). CO (300 ppm) exposed cerebella has fewer fissures.	Maternal COHb: 2.5%, 11.5%, 18.5%, and 26.8% (0, 75, 150, and 300 ppm, respectively)
Benagiano et al. (2005, 180445)	Rats	75 ppm GD0-GD20	CO reduced the number of GABA and GAD 65/67 positive neuronal bodies and axon terminals in the cerebellar cortex.	
Benagiano (2007, 193892)	Rats	75 ppm GD5-GD20	Adult offspring exposed prenatally to CO exhibited decreased GABA and GAD in the molecular layer and Purkinje neuron layers of the cerebellar cortex	
Antonelli (2006, 194960)	Rats	75 ppm GD5-GD20	CO decreased cortical glutamatergic transmission both at rest and after a chemical depolarizing stimulus.	

Dopaminergic Effects. Dopamine is a catecholamine neurotransmitter that plays an important role in the regulation of male rat sexual behavior. Experiments assessing sexual behavior and mesolimbic dopaminergic function were conducted on adult (5 and 10 mo of age) male offspring gestationally exposed to CO (0, 75 or 150 ppm) (Cagiano et al., 1998, 087170). Maternal COHb at GD10 was 1, 7, and 15% and 1.5, 7, and 16% at GD20 (0, 75, and 150 ppm CO, respectively). At 5 mo of age, CO-exposed male offspring showed decrements in sexual behavior, including an increase in mount-to-intromission latency, a decrease in mount-to-intromission frequency, and a decrease in ejaculation frequency. Further, administration of amphetamine, which stimulates copulatory activity, did not alter CO-induced changes in mount-to-intromission latency or frequency. Basal extracellular dopamine concentration in the nucleus accumbens was unchanged after CO exposure. However, when stimulated with amphetamine administration, control rats had increased release of dopamine that was absent with CO-exposed rats. Rats followed to 10 mo of age showed no significant changes in copulatory activity or neurochemical parameters after CO exposure,

indicating recovery from earlier decrements. This altered male sexual behavior in CO-exposed offspring paralleled earlier studies of mice exposed gestationally to hypoxia (Hermans et al., 1993, 190510). In summary, in utero exposure to CO delayed copulatory sexual behavior in male offspring with accompanying changes in the mesolimbic dopaminergic system.

A second study also found no change in dopamine metabolite levels after prenatal exposure to CO; however, it did find an elevation in dopamine concentration in rats exposed both pre- and postnatally to CO. Exposure of Long Evans rat dams and pups continuously to CO (75, 150, or 300 ppm) with maternal COHb of 11, 19, and 27%, respectively) from conception to PND10 induced significant elevations in dopamine in the striatum at PND21 in CO-exposed offspring versus air exposed controls (Fechter et al., 1987, 012259).

Noradrenergic and Serotonergic Changes. Other monoamine neurotransmitters, norepinephrine (NE) and serotonin (5HT), were tested for sensitivity to CO during development. Long Evans rats exposed to CO (75, 150, or 300 ppm) over the duration of gestation yielded a dose-dependent reduction in cerebellum wet weight (significant at 150 and 300 ppm) at PND21, with increases in NE concentration found in the cortex and hippocampus at PND42 but not PND21 (Storm and Fechter, 1985, 011652). In a separate experiment, CO-exposed (150 ppm) animals presented with increased mean and total NE concentrations in the cerebellum but not cortex when monitored from PND14 to PND42 (Storm and Fechter, 1985, 011653). Also, NE concentration in the pons/medulla decreased linearly with increasing CO exposure at PND21 but not at PND42. A transitory decrease in 5HT concentration was also shown in the pons/medulla after gestational CO exposure (Storm and Fechter, 1985, 011652). Thus, in these studies, it appeared that CO both transiently and permanently altered the pattern of postnatal neurotransmitter development in a region-specific manner and stunted postnatal growth of the cerebellum.

Glutamatergic System. Glutamate is an abundant excitatory neurotransmitter that serves as a precursor for the synthesis of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) catalyzed by glutamic acid decarboxylase (GAD). Primary cell cultures obtained from the cerebral cortex of offspring (PND1) gestationally (GD5-GD20) exposed to CO (75 ppm) had decreased extracellular glutamate (basal and K^+-evoked) levels versus air-exposed controls (Antonelli et al., 2006, 194960). Similarly, CO-exposed (300 ppm only) pups at PND21 had significant decreases in cerebellar GABA content, decreased uptake of exogenous radio-labeled GABA, decreased fissures in the cerebellum, and decreased cerebellum size (Storm et al., 1986, 012136). It is possible this decrease in GABA content is due to a diminished activity of GAD. Rats exposed to CO (75 ppm) in utero (GD0-GD20) exhibited decreased GABA and GAD in the molecular layer and Purkinje neuron layer of the vermian cerebellar cortex (Benagiano et al., 2005, 180445; Benagiano et al., 2007, 193892). This alteration may functionally impair cortical glutamatergic transmission in CO-exposed offspring, possibly affecting learning and memory.

The Developing Auditory System

The developing auditory system of rodents has recently been investigated as a target of CO exposure at levels as low as 12 ppm. The rat brain and auditory system go through extensive cell division and multicellular organization during a major growth spurt in the postnatal period (PND7-PND20), making it a probable target for CO-induced effects. These studies showed that exposure to low concentrations of CO during development can lead to permanent changes in the auditory system that persist into adulthood. Similarly, prenatal exposure to tobacco smoke can cause auditory system deficits as seen in animal tests for auditory responsiveness, habituation, and auditory arousal. Term human infants born to smoking mothers have impaired cochlear development, albeit mild, with decreased amplitudes of transient evoked otoacoustic emissions (OAE) at the highest test frequency (4 kHz) versus newborns born to nonsmokers (Korres et al., 2007, 190908); CO is one of many potential affective components of cigarette smoke.

Table 5-17. Developing auditory system.

Study	Model System	CO Exposure	Response	Notes
DEVELOPING AUDITORY SYSTEM				
Stockard-Sullivan et al. (2003, 190947)	Rats	12-100 ppm 22 h/day PND6 to PND21-PND23	CO (50 ppm) reduced otoacoustic emissions (preneural cochlear function) at 7.13 and 8.01 kHz. CO persistently attenuated the amplitude of the action potential of the eighth cranial nerve (12-50 ppm), persisting to PND73. No functional impairment in the Morris Water Maze after CO exposure.	COHb: 10.2% (100 ppm); 5.5% (AR); 4.1% (MR)
Lopez et al. (2003, 193901)	Rats	12 and 25 ppm PND8-PND22	CO (25 ppm) led to swelling and mild vacuolization of nerve terminals innervating inner hair cells and the fibers of the 8th cranial nerve. CO (25 ppm) decreased expression of neurofilament and myelin basic proteins, cytochrome oxidase, NADH-TR, and calcium ATPase.	
Webber et al. (2003, 190515)	Rats	12.5, 25, 50 ppm PND8 to PND20-PND22	CO decreased c-Fos immunoreactivity in the central inferior colliculus at both PND27 and PND75-PND77 over all dose groups (12.5, 25, or 50 ppm CO)	
Webber et al. (2005, 190514)	Rats	25 and 100 ppm PND9-PND24	CO exposure (25 and 100 ppm) decreased neurofilament proteins, decreased c-Fos expression in the central IC, and increased CuZnSOD in the spiral ganglion neurons. Iron deficiency ablated these responses.	
Lopez et al. (2008, 097343)	Rats	25 ppm 10-18 h/day GD5-20 or GD5-GD20 and PND5-PND20	Prenatal CO exposure led to increased oxidative stress in the cochlear vasculature (high HO-1, SOD-1, iNOS, and nitrotyrosine) and decreased neurofilament proteins and synapsin-1. CO caused morphological deterioration of putative afferent terminals and mild deterioration in the inner hair cells at the basal region of the cochlea.	

Studies on the developing auditory system have used an artificial feeding system where pups were removed from their respective dams and fed a milk substitute comparable to natural rat milk via intragastric cannulation. This allowed nursing pups to be exposed to CO without possible confounding by lactational and maternal CO co-exposure. However, this invasive rat model does cause decreased brain, cerebellum, and lung weight at PND16 in normal air controls. A summary of these studies and others are presented in the above table (Table 5-17).

Using this model, Stockard-Sullivan et al. (2003, 190947) examined Sprague Dawley rat pups receiving low-dose CO (12, 25, or 50 ppm) to determine how perinatal CO exposure (PND6 to PND21-PND23) functionally affected hearing in the developing rat. Rodent pups were either maternally reared (MR), nutritionally supported with the artificial feeding system (AR), or received AR plus CO exposure (ARCO). CO (50 ppm, not 25 ppm) exposure caused significant reductions in distortion product otoacoustic emissions (DPOAE) levels at certain frequencies (7.13 and 8.01 kHz), a measure of preneural cochlear function and thus not affected by eighth cranial nerve function. However, the frequency range where significant CO results were seen is very narrow and low compared to the normal rat audiogram. The eighth cranial nerve, or vestibulocochlear nerve, is responsible for transmitting sound from the inner ear to the brain. This study also found significant attenuation of the action potential (AP) of the eighth cranial nerve with ARCO exposure (12, 25, and 50 ppm CO) versus AR controls at PND22. This is complicated by the finding that AR control animals had significant attenuation of the eighth cranial nerve AP versus MR control animals, implying that artificial rearing contributes to AP changes before CO was introduced. Nonetheless, the CO-dependent attenuation of the eighth cranial nerve AP (versus AR control) was permanent, persisting until adulthood in the 50 ppm CO exposure group (the only CO group monitored). Auditory brain stem response (ABR) conduction time was not affected in CO-exposed animals (12, 25, 50, 100 ppm).These functional tests reported that neonatal exposure to low concentrations of CO can induce auditory functional changes in rodents.

Further studies have investigated physiological changes in cochlear development resulting from chronic CO inhalation. Sprague Dawley rats exposed to low concentrations of CO (12 or 25 ppm, ARCO) from PND6 to PND27 had no evidence of damage to the inner or outer hair cells (Lopez et al., 2003, 193901). However, CO (25 ppm) caused atrophy or vacuolization of the nerve cells that innervate the inner (not outer) hair cells. Also, fibers of the eighth cranial nerve at the level of the internal auditory canal had distorted myelination and vacuolization of the axoplasm after 25 ppm CO exposure. Energy production markers in the organ of corti and spiral ganglion neurons

including cytochrome oxidase (electron transport chain complex IV) and NADH-TR (marker of complex I reductase activity) were significantly decreased after inhalation of 25 ppm (not 12 ppm) CO versus control (AR and MR). Reduced energy production likely led to the decreased expression of the calcium-mediated myosin ATPase and neurofilament proteins in the organ of corti and spiral ganglion neurons (25 ppm CO). Since no changes in body weight were found after CO exposure in these experiments (Stockard-Sullivan et al., 2003, 190947), it is likely that the decreased electron transport chain enzymes are specific to vulnerable areas such as the cochlea.

Further analysis focused attention on CO-induced changes in the inferior colliculus (IC), an auditory integrative section of the midbrain. Low concentrations of CO (12.5, 25, or 50 ppm) inhaled over PND8-PND22 decreased c-Fos immunoreactivity in the central IC at both PND27 and PND75-PND77; immunostaining of other subregions of the IC were not affected by CO (Webber et al., 2003, 190515). c-Fos is an immediate early gene whose tonotopic expression corresponds to neuronal activation in the auditory system. The same decrease in c-Fos expression was seen in rats exposed to 25 or 100 ppm CO from PND9 to PND24 (Webber et al., 2005, 190514). These CO-exposed rats also exhibited decreased neurofilament proteins and increased Cu-Zn superoxide dismutase (SOD1) in the spiral ganglion neurons. This response could be ablated by dietary iron restriction, suggesting an ROS-dependent contribution to the auditory changes seen after CO exposure. These authors postulated that CO creates a persistent oxidative stress condition where ROS generated via the interaction of peroxide and iron (via the Fenton reaction or Haber Weiss chemistry) leads to impaired cochlear development; decreasing the available iron decreases the total pool available for ROS generation. Further, the attenuation of the elevated SOD levels with iron restriction post CO-exposure gives credence to this model.

A recent study has found comparable auditory system responses after prenatal (GD5-GD20) exposure to CO with postnatal exposure (GD5-PND20,) similar to the studies described above (Lopez et al., 2008, 097343). Prenatal CO (25 ppm) exposure led to high levels of the oxidative stress markers HO-1, SOD-1, iNOS, and nitrotyrosine in cochlea vasculature and stria vascularis at PND12; however, unlike postnatally exposed pups, HO-1 and SOD1 levels returned to normal at PND20. Both groups of CO-exposed rats exhibited spiral ganglion cytoplasmic vacuolization, a decrease in type I spiral ganglion neuron neurofilament proteins, thinning and damage in the cells of the stria vascularis, and mild deterioration of the innervation of the inner hair cells. These nerve terminals also had a persistent decrease in synapsin-1, a regulatory neuronal phosphoprotein. These studies suggest that mild chronic CO exposure disrupts the developing auditory system, more often at the IHC innervation and the eighth cranial nerve of the spiral ganglion, possibly by creating an oxidative stress that may be reflected as hearing impairment.

Summary of Toxicological Studies on Developmental Central Nervous System Effects

Toxicological studies employing rodent models have shown that exposure to low concentrations of CO during the in utero or perinatal period can adversely affect adult outcomes including behavior, neuronal myelination, neurotransmitter levels or function, and the auditory system. In utero CO exposure has been shown to impair active avoidance behavior (150 ppm), habituation (75 and 150 ppm), nonspatial memory (75 and 150 ppm), and emotionality (150 ppm). These behavioral changes could be due to neuronal changes or altered neurotransmitter signaling. In utero CO exposure (75 and 150 ppm) was associated with PNS myelination decrements from impaired sphingolipid homeostasis (150 ppm CO). These neuronal changes were also accompanied by electrophysiological changes such as reversible delays in ion channel development and irreversible changes in sodium equilibrium potential (150 ppm). Also, multiple studies demonstrated that in utero CO exposure affected cholinergic (200 ppm), catecholaminergic (200 ppm), noradrenergic (150 ppm), serotonergic (75 ppm), dopaminergic (75 ppm) and glutamatergic (75 ppm), neurotransmitter levels or transmission in exposed rodents. Possible or demonstrated adverse outcomes from the CO-mediated aberrant neurotransmitter levels or transmission include respiratory dysfunction (150 ppm), impaired sexual behavior (150 ppm), and an adverse response to hyperthermic insults resulting in neuronal damage (200 ppm). Finally, perinatal CO exposure has been shown to affect the developing auditory system of rodents, inducing permanent changes into adulthood at concentrations as low as 12 ppm. Together, these animal studies demonstrate that in utero or perinatal exposure to CO can adversely affect adult behavior, neuronal function, neurotransmission, and the auditory system in rodents.

Cardiovascular and Systemic Developmental Effects

In utero exposure to moderate to high concentrations of CO (60, 125, 150, 250, or 500 ppm) is able to induce transient changes in cardiac morphology, cardiac action potentials, and systemic immunity that may make a CO-exposed animal more susceptible to other outside stressors during the immediate neonatal period. Studies of cardiovascular and systemic developmental responses to CO levels of 500 ppm and less are presented below in Table 5-18.

Table 5-18. Cardiovascular and systemic developmental responses.

Study	Model System	CO Exposure	Response	Notes
CARDIOVASCULAR AND SYSTEMIC DEVELOPMENTAL RESPONSES				
Sartiani et al. (2004, 190898)	Rats	150 ppm GD0-GD20	CO delayed action potential duration shortening, decreased the density of I_{to} channels and increased the density of ICa,L channels.	
Prigge and Hochrainer (1977, 012326)	Rats	60, 125, 250, and 500 ppm GD0-GD21	CO depressed fetal hemoglobin (250 and 500 ppm), reduced fetal weight (125, 250, and 500 ppm), decreased hematocrit (250 and 500 ppm), and increased heart weight (60-500 ppm).	
Fechter et al. (1980, 011294)	Rats	150 ppm GD0-GD20	CO transiently increased wet heart weight. There was no increase in dry heart weight.	COHb: 15%
Penney et al. (1982, 011387)	Rats	500 ppm PND1-PND32	CO increased heart weight to body weight ratio, which remained high to PND107. Right ventricular weight was high through PND217. Hydroxyproline and cardiac cytochrome c was depressed but only during CO exposure. Neither lactate dehydrogenase nor myoglobin was altered by CO.	
Styka and Penney (1978, 011166)	Rats	400 or 500 ppm increased to 1,100 ppm Adult 6 wk	CO caused increased heart weight to body weight that regressed within a couple of months after CO exposure.	COHb: 400 ppm-35%; 1,100 ppm-58%
Giustino et al. (1993, 013833)	Rats	75 and 150 ppm GD0-GD20	CO decreased splenic macrophage killing (75 and 150 ppm), phagocytosis (150 ppm), and superoxide release (150 ppm). These alterations were reversible, not seen at PND60.	
Giustino et al. (1994, 076343)	Rats	75 and 150 ppm GD0-GD20	CO (150 ppm) decreased the frequency of splenic leukocyte common antigen (LCA+) cells at PND21 but not PND15 or PND540	COHb: 150 ppm-15%

Myocardial Electrophysiological Maturation

A rat model of in utero exposure was employed to study CO effects on the development of cardiac myocytes. Results demonstrated that in utero CO exposure (150 ppm) alters postnatal cellular electrophysiological maturation in the rat heart (Sartiani et al., 2004, 190898). Specifically, at 4 wk of age, the action potential duration (APD) of isolated cardiac myocytes from CO-exposed animals failed to shorten or mature as the APD of control animals did. Further, the two ion conduction channels I_{to} (transient outward current, K^+-mediated) and ICa,L (L-type Ca^{2+} current), which largely control the rat APD, were significantly different from control animals after in utero CO exposure at 4 wk of age. These CO-dependent changes were resolved by 8 wk of age, reflecting a delayed maturation. Further, these authors postulated that a CO-dependent delay in electrophysiological maturation of the cardiac myocyte (lack of APD shortening) could lead to arrhythmias and thus could be associated with SIDS deaths.

Heart Morphological Changes after In Utero or Perinatal CO Exposure

Multiple authors have reported cardiomegaly following in utero exposure to low concentrations of CO. Prigge and Hochrainer (1977, 012326) reported increased fetal Wistar rat heart wet weight or cardiomegaly following continuous in utero CO (60, 125, 250, and 500 ppm) exposure, with no decreases in near term fetal hematocrit or Hb levels seen at exposures below 250 ppm. Fechter et al. (1980, 011294) found that prenatal exposure to CO affected cardiac development in exposed offspring. Long Evans rats that were exposed to CO continuously

(150 ppm) during gestation manifested with significant elevations in wet heart weight, as well as heart weight in relation to body weight at PND1 but not at PND4, PND14, or PND21. Dry-to-wet weight ratios revealed that the increased heart weight of CO-exposed pups at birth was due to edema or water content. Penney et al. (1982, 011387) studied CO-dependent (500 ppm) cardiomegaly in neonates (continuous CO exposure for 32 days starting at PND1). Other studies of adult male Charles River-derived rats exposed to CO for 6 wk (at 400 or 500 to 1,100 ppm CO), as adults only, developed CO-dependent cardiomegaly during exposure that significantly regressed within a couple of months after termination of CO exposure (Styka and Penney, 1978, 011166).

Systemic Immune Toxicology after In Utero CO Exposure

In utero exposure (GD0-GD20) of male Wistar rats to moderate CO (0, 75, or 150 ppm) concentrations induced reversible changes in macrophage function (Giustino et al., 1993, 013833). The killing of *Candida albicans* (yeast) by splenic macrophages was significantly decreased at PND15 in gestationally CO-exposed male offspring (75 and 150 ppm) but recovered function by PND21. Macrophage phagocytosis of *C. albicans* was significantly reduced at PND15 and PND21 in CO-exposed males (150 ppm only), and recovery was seen at PND60. Superoxide production by the splenic macrophage respiratory burst was significantly decreased at PND15 and PND21 after in utero CO exposure (150 ppm only), with recovery to control levels at PND60. In summary, CO exposure in utero leads to a reversible and concentration-dependent loss of function of splenic macrophages, with decreased killing ability, decreased phagocytosis, and decreased ROS production during the macrophage respiratory burst.

Further studies by the same laboratory showed that in utero exposure of male rats to CO (150 ppm) induced a subtle decrease in the frequency of splenic immunocompetent cells (leukocyte common antigen [LCA+] cells) in a population of splenic immune cells at PND21 but not PND15 or PND540 (Giustino et al., 1994, 076343). Specific LCA+ cell subpopulations, including macrophages, Major Histocompatibility (MHC) II cells, T and B lymphocytes, showed a decreasing trend but were not significant with CO exposure.

Summary of Toxicological Studies of Cardiovascular and Systemic Development

In utero CO exposure is associated with various adverse, albeit nonpersistent, cardiac aberrations. Exposure to 150 ppm induced a delayed maturation of the cardiac action potential in CO-exposed offspring. In other studies, continuous in utero CO exposure (60-500 ppm) induced cardiomegaly at PND1, which was transient and regressed by PND4. CO (75 and 150 ppm) also affects nonspecific immunity, shown through a reversible and dose-dependent loss of function of splenic macrophages, with decreased killing ability, decreased phagocytosis, and decreased macrophage ROS production (150 ppm). Also, the distribution of splenic immunocompetent cells was slightly skewed because of a decrease in the number of LCA+ cells in PND21 male rats exposed during gestation to 150 ppm CO. In conclusion, in utero exposure to moderate doses of CO (60-500 ppm) is able to induce transient changes in cardiac morphology, cardiac action potentials, and systemic nonspecific immunity.

5.4.3. Summary of Birth Outcomes and Developmental Effects

The most compelling evidence for a CO-induced effect on birth and developmental outcomes is for PTB and cardiac birth defects. These outcomes were not addressed in the 2000 CO AQCD (U.S. EPA, 2000, 000907), which included only two studies that examined the effect of ambient CO on LBW. Since then, a number of studies have been conducted looking at varied outcomes, including PTB, birth defects, fetal growth (including LBW), and infant mortality.

There is limited epidemiologic evidence that CO during early pregnancy (e.g., first month and first trimester) is associated with an increased risk of PTB. The only U.S. studies to investigate the PTB outcome were conducted in California, and these reported consistent positive associations with CO exposure during early pregnancy when exposures were assigned from monitors within close proximity of the mother's residential address. Additional studies conducted outside of the U.S. provide supportive, though less consistent, evidence of an association between CO concentration and PTB.

Very few epidemiologic studies have examined the effects of CO on birth defects. Two of these studies found maternal exposure to CO to be associated with an increased risk of cardiac birth defects. Human clinical studies also demonstrated the heart as a target for CO effects (Section 5.2). Animal toxicological studies provided additional evidence for cardiac effects with reported transient cardiomegaly at birth after continuous in utero CO exposure (60, 125, 250 and 500 ppm CO) and delayed myocardial electrophysiological maturation (150 ppm CO). Toxicological studies have also shown that continuous in utero CO exposure (250 ppm) induced teratogenicity in rodent offspring in a dose-dependent manner that was further affected by dietary protein (65 ppm CO) or zinc manipulation (500 ppm CO). Toxicological studies of CO exposure over the duration of gestation have shown skeletal alterations (7 h/day, CO 250 ppm) or limb deformities (24 h/day, CO 180 ppm) in prenatally exposed offspring.

There is evidence of ambient CO exposure during pregnancy having a negative effect on fetal growth in epidemiologic studies. In general, the reviewed studies, summarized in Figure 5-10 through Figure 5-12, reported small reductions in birth weight (~5-20 g). Several studies examined various combinations of birth weight, LBW, and SGA/IUGR, and inconsistent results were reported across these metrics. It should be noted that having a measurable, even if small, change in a population is different than having an effect on a subset of susceptible births and increasing the risk of IUGR/LBW/SGA. It is difficult to conclude if CO is related to a small change in birth weight in all births across the population or a marked effect in some subset of births. Toxicology studies have found associations between CO exposure in laboratory animals and decrements in birth weight (90-600 ppm), as well as reduced prenatal growth (65-500 ppm CO).

In general, there is limited epidemiologic evidence that CO is associated with an increased risk of infant mortality during the neonatal or postneonatal periods. In support of this limited evidence, animal toxicological studies provided some evidence that exogenous CO exposure to pups in utero significantly increased postnatal mortality (7 h/day and 24 h/day, 250 ppm CO; 24 h/day, 90 or 180 ppm CO) and prenatal mortality (7 h/day, 250 ppm CO).

Evidence exists for additional developmental outcomes which have been examined in toxicological studies but not epidemiologic or human clinical studies, including behavioral abnormalities, learning and memory deficits, locomotor effects, neurotransmitter changes, and changes in the auditory system. Structural aberrations of the cochlea involving neuronal activation (12.5, 25 and 50 ppm CO) and auditory related nerves (25 ppm CO) were seen in pups after neonatal CO exposure. Auditory functional testing using otoacoustic emissions testing (OAE at 50 ppm CO) and 8th cranial nerve action potential (AP) amplitude measurements (12, 25, 50, 100 ppm CO) in rodents exposed perinatally to CO showed auditory decrements at PND22 (OAE and AP) and permanent changes in AP into adulthood (50 ppm CO). Furthermore, exogenous CO may interact with or disrupt the normal physiological roles that endogenous CO plays in the body. There is evidence that CO plays a role in maintaining pregnancy, controlling vascular tone, regulating hormone balance, and sustaining normal ovarian follicular maturation.

Overall, there is limited though positive epidemiologic evidence for a CO-induced effect on PTB and birth defects, and weak evidence for a decrease in birth weight, other measures of fetal growth, and infant mortality. Animal toxicological studies provide support and coherence for these effects. Both hypoxic and nonhypoxic mechanisms have been proposed in the toxicological literature (Section 5.1), though a clear understanding of the mechanisms underlying reproductive and developmental effects is still lacking. Taking into consideration the positive evidence for some birth and developmental outcomes from epidemiologic studies and the resulting coherence for these associations in animal toxicological studies, the evidence is **suggestive of a causal relationship between relevant long-term exposures to CO and developmental effects and birth outcomes**.

5.5. Respiratory Effects

5.5.1. Epidemiologic Studies with Short-Term Exposure

This section evaluates the key epidemiologic studies published since the 2000 CO AQCD (U.S. EPA, 2000, 000907) that further examine the association between short-term exposure to CO and respiratory morbidity. Although the number of studies that have specifically examined the CO-respiratory health relationship have increased, there are still considerably less than that for the other criteria air pollutants (e.g., PM and O_3). The epidemiologic studies discussed below represent those studies which (1) were conducted in locations with ambient CO concentrations similar to those in the U.S.; (2) determined to use a reasonable study design and analytical methods; and (3) adequately adjusted for confounding using accepted methods. If limitations in the design or analytical methods used in a study were identified, they were noted. It is recognized that each of the studies evaluated has a varying degree of exposure measurement error due to (1) the number of monitors used within the study, the geographic size of the study area; (2) the spatial variability of CO; and (3) differences in personal exposure distributions in the population; (Section 3.6.8) all of which could influence the associations observed. As a result, in some instances specific details of a study are mentioned to address any potential bias in the reported CO associations. Finally, the issue of confounding by measured or unmeasured copollutants was evaluated, if possible, for each study, through the interpretation of copollutant models. The results from copollutant models were used as an attempt to disentangle the effect of CO from other pollutants while recognizing the high correlation between CO and other combustion-related pollutants.

5.5.1.1. Pulmonary Function, Respiratory Symptoms, and Medication Use

The 2000 CO AQCD (U.S. EPA, 2000, 000907) briefly discussed the potential acute respiratory health effects associated with short-term exposure to CO. An evaluation of the epidemiologic literature at the time did not find any evidence of an association between short-term exposure to CO and lung function, respiratory symptoms, or respiratory disease. As a result, the 2000 CO AQCD (U.S. EPA, 2000, 000907) did not conclude that a causal association exists between short-term exposure to CO and respiratory health effects. Multiple uncertainties were identified in the epidemiologic literature that contributed to this conclusion, which are discussed in Section 5.2.1. The following section evaluates the current literature that examines the potential association between short-term exposure to CO and respiratory health effects. Table 5-19 lists the studies evaluated in this section along with the respiratory health outcomes examined and CO concentrations reported.

Table 5-19. Range of CO concentrations reported in key respiratory morbidity studies that examined effects associated with short-term exposure to CO.

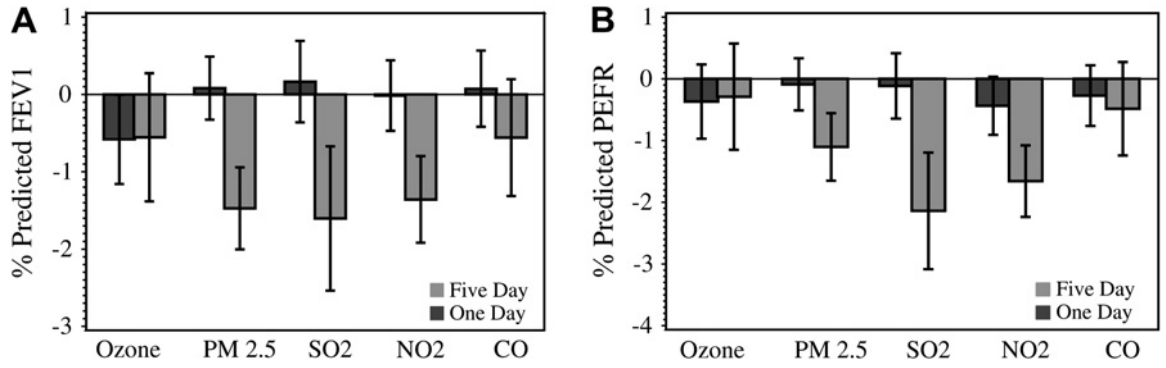
Study	Location Sample Size	Years	Health Outcome	Metric	Mean Concentration (ppm)	Middle/Upper Percentile Concentrations (ppm)
O'Connor et al. (2008, 156818)[b]	7 U.S. cities	8/1998-7/2001	Pulmonary function; Respiratory symptoms	8-h max 24-h avg	NR	8-h max: 50th: 1.2 75th 1.8 99th 3.8 24-h avg: 50th: 0.7 75th 0.9 99th: 1.8
Rabinovitch et al. (2004, 096753)	Denver, CO (Year 1: n = 41) (Year 2: n = 63) (Year 3: n = 43)	11/1999-3/2000; 11/2000-3/2001; 11/2001-3/2002	Pulmonary function; Medication use	24-h avg	1.0	50th: 0.9 75th: 1.2 Maximum: 3.5
Silkoff et al. (2005, 087471)	Denver, CO (Year 1: n = 16) (Year 2: n = 18)	1999-2000 (winter); 2000-2001 (winter)	Pulmonary function; Medication use	24-h avg	1999-2000: 1.2 2000-2001: 1.1	1999-2000 50th: 1.10 75th: 1.43 Maximum: 3.79 2000-2001 50th: 0.975 75th: 1.34 Maximum: 2.81
Fischer et al. (2002, 025731)[a]	The Netherlands (n = 68)	March - April[c]	Pulmonary function	24-h avg	0.80	Max: 1.34
Ranzi et al. (2004, 089500)[a]	Emilia-Romagna Region, Italy (n = 120)	2/1999-5/1999	Pulmonary function; Respiratory symptoms; Medication use	24-h avg	Urban: 1.34 Rural: 1.06	NR
Lagorio et al. (2006, 089800)[a]	Rome, Italy (n = 29)	5/1999-6/1999; 11/1999-12/1999	Pulmonary Function	24-h avg	Spring: 1.83 Winter: 10.7 Overall: 6.4	Overall Max: 25.1
Penttinen et al. (2001, 030335)[a]	Helsinki, Finland (n = 57)	11/1996-4/1997	Pulmonary function	24-h avg	NR	50th: 0.35 75th: 0.43 Maximum: 0.96
Timonen et al. (2002, 025653)[a]	Kuopio, Finland (n = 33)	2/1994-4/1994	Pulmonary function	24-h avg	0.52	Maximum: 2.43
Chen et al. (1999, 011149)	Taiwan (n = 941)	5/1995-1/1996	Pulmonary function	1-h max; 24-h avg	NR	1-h max Maximum: 3.6
Delfino et al. (2003, 050460)	Los Angeles, CA (n = 22)	11/1999-1/2000	Asthma symptoms	1-h max; 8-h max	1-h max: 7.7 8-h max: 5.0	1-h max 90th: 12.0 Maximum: 17 8-h max 90th: 7.9 Maximum: 10
Slaughter et al. (2003, 086294)	Seattle, WA (n = 133)	12/1993-8/1995	Asthma symptoms; Medication use	24-h avg	NR	50th: 1.47 75th: 1.87
Yu et al. (2000, 013254)	Seattle, WA (n = 133)	11/1993-8/1995	Asthma symptoms	24-h avg	1.6	50th: 1.47 Maximum: 4.18
Schildcrout et al. (2006, 089812)	8 North American cities (n = 990)	11/1993-9/1995	Asthma symptoms; Medication use	24-h avg	NR	50th: 0.63-1.49 75th: 0.77-1.90 90th: 0.95-2.40
von Klot et al. (2002, 034706)[a]	Erfurt, Germany (n = 53)	10/1996-3/1997	Asthma symptoms; Medication use	24-h avg	0.78	50th: 0.70 75th: 1.04 Maximum: 2.60

Study	Location Sample Size	Years	Health Outcome	Metric	Mean Concentration (ppm)	Middle/Upper Percentile Concentrations (ppm)
Park et al. (2005, 088673)	Incheon, Korea (n = 64)	3/2002-6/2002	Asthma symptoms; Medication use	24-h avg	Control days: 0.64 Dust days: 0.65	NR
Rodriguez et al. (2007, 092842)	Perth, Australia (n = 263)	6/1996-7/1998	Symptoms associated with respiratory illness	8-h max	1.41	Maximum: 8.03
de Hartog et al. (2003, 001061) [a]	Amsterdam, The Netherlands (n = 37) Erfurt, Germany (n = 47) Helsinki, Finland (n = 47)	1998-1999 (winter)	Respiratory symptoms	24-h avg	Amsterdam: 0.52 Erfurt: 0.35 Helsinki: 0.35	Maximum: Amsterdam: 1.39 Erfurt: 2.17 Helsinki: 0.87

[a]These studies presented CO concentrations in the units mg/m^3. The concentrations were converted to ppm using the conversion factor 1 ppm = 1.15 mg/m^3, which assumes standard atmosphere and ambient temperature.
[b]This study did not present air quality statistics quantitatively, as a result, the air quality statistics presented were estimated from a figure.
[c]This study did not provide the year(s) in which air quality data was collected.

Pulmonary Function

As part of the Inner-City Asthma Study (ICAS), O'Connor et al. (2008, 156818) examined the effect of air pollutants (i.e., $PM_{2.5}$, O_3, NO_2, CO, and SO_2) on lung function in a population of 861 children (5-12 yr old) with persistent asthma in 7 urban U.S. communities. Throughout the study, percent predicted forced expiratory volume in 1 s (FEV_1) and peak expiratory flow (PEF) were examined for each subject during 2-wk periods twice daily every 6 mo for 2 yr. Lung function was examined in single pollutant models using both same-day (lag 0) and 5-day (lag 0-4) ma pollutant concentrations (Figure 5-13). CO was not found to be associated with percent predicted FEV_1 at lag 0, but there was some evidence for a reduction in percent predicted FEV_1 when using the 5-day ma (-0.32 [95% CI: -0.75 to 0.11] per 0.5 ppm increase in 24-h avg CO concentrations). When examining percent predicted PEF, a small reduction was observed at lag 0 (not reported quantitatively), but the effect was found to be slightly larger at lag 0-4 (-0.28 [95% CI: -0.71 to 0.15]). In this study, CO was found to be moderately correlated with other combustion related pollutants (e.g., $PM_{2.5}$ [r = 0.44] and NO_2 [r = 0.54]); however, CO was not included in the multipollutant models examined, limiting the interpretation of the small reductions in lung function observed. Although the observed reductions in lung function did not reach statistical significance, the results do provide some evidence for a potential effect of CO on lung function at relatively low CO concentrations (99th percentile max 8-h avg concentrations: ~ 3.8 ppm).



Source: Reprinted with Permission of Elsevier Ltd. from O'Connor et al. (2008, 156818)

Figure 5-13. Estimated effect (95% confidence intervals) on pulmonary function due to a 10th to 90th percentile increment change in pollutant concentration in single-pollutant models. The estimates shown are from models that included either a 1-day or 5-day avg of pollutant concentration. Effect estimates were adjusted for site, month, site-by-month interaction, temperature, and intervention group in mixed models. Panel A: percent predicted FEV_1 as outcome variable; Panel B: percent predicted PEFR as outcome variable.

The remaining U.S.-based studies evaluated consisted of single-city studies conducted in Denver, CO. Rabinovitch et al. (2004, 096753) examined the association between exposure to ambient air pollutants and asthma exacerbation in a panel of urban minority children, 6-12 yr old, with moderate to severe asthma over three winters. The investigators examined pulmonary function by measuring FEV_1 and PEF in the morning on school days and also at night on weekends or other nonschool days. Using a 3-day ma (lag 0-2) for all pollutants, Rabinovitch et al. (2004, 096753) did not find an association between CO and either lung function parameter during the morning or at night. Silkoff et al. (2005, 087471) also examined lung function during the winter months, but in a panel of former smokers that were at least 40 yr old and had been diagnosed with COPD. In this study, CO concentrations were similar to those reported in Rabinovitch et al. (2004, 096753). The authors examined the association between exposure to air pollutants and lung function (i.e., FEV_1 and PEF) in both the morning and the evening. Silkoff et al. (2005, 087471) found contradictory results when examining the effects of CO for each of the winter periods (1999-2000 and 2000-2001) separately. During the analysis of the first winter (i.e., 1999-2000), CO was not found to be associated with lung function decrements in the morning at any lag, but there was some evidence for lung function decrements during the evening at lag 0. Of note is the increase in FEV_1 during the morning that was observed at lag 1 during this time period. For the second winter (i.e., 2000-2001) the authors found a significant negative association between CO exposure and FEV_1 in the evening at lag 2 and a moderate negative association with PEF at lag 0 in the morning and lag 2 in the evening. Silkoff et al. (2005, 087471) postulated that the difference in the FEV_1 results for the two study periods could be due to higher pollution concentrations along with somewhat lower temperatures and higher humidity in 2000-2001. However, mean CO levels remained relatively constant between the first and second winters, whereas, PM_{10}, $PM_{2.5}$, and NO_2 concentrations all increased. The decrements in FEV_1 observed in the second winter, therefore, may have been due to the slightly worse, although not significantly different, baseline lung function of the panel of subjects used during the second winter (Silkoff et al., 2005, 087471).

In the recent literature, the majority of studies that examined the association between short-term exposure to CO and lung function have been conducted in Europe and Asia. These studies provide some evidence for CO-induced changes in lung function. Negative associations between short-term exposure to CO and lung function were observed primarily in individuals with underlying respiratory conditions; however, some evidence also exists for effects in children that live in urban environments. Penttinen et al. (2001, 030335) examined the association between CO and lung function in a panel consisting of 57 nonsmoking adult asthmatics during the winter and spring in Helsinki, Finland. The authors observed negative associations with PEF (L/min) for a 0.5 ppm increase in 24-h avg CO concentrations in the morning at lag 1 (β = -0.54, SE = 0.084) and in the

afternoon (β = -1.52, SE = 0.29) and evening (β = -1.81, SE = 0.27) for a 5-day avg. In two-pollutant models with daily mean particle number concentration (PNC), CO effects on PEF in the morning were attenuated at lag 1 but remained negative. In addition, negative associations with PEF persisted in the afternoon and evening in the two-pollutant model at lag 0. In this study, moderate correlations between UFPs and other traffic-generated pollutants (e.g., CO [r = 0.44], NO [r = 0.60], and NO_2 [r = 0.44]) make it difficult to attribute the observed respiratory effects to a specific pollutant.

Lagorio et al. (2006, 089800) also conducted a study that examined the association between CO and lung function in adults. In this study, three panels of subjects with underlying asthma, COPD, or IHD, who resided in Rome, Italy, were selected. The ages of the subjects varied depending on the panel, but overall the subjects ranged from 18-80 yr old. In single-pollutant models with CO, a reduction in forced vital capacity (FVC) and FEV_1 was observed at most of the lags examined (i.e., 0, 0-1, and 0-2) for both the COPD and asthma panels. No association was observed between CO and FVC or FEV_1 in the IHD panel. Lagorio et al. (2006, 089800) did observe a relatively high correlation between CO and $PM_{2.5}$ but not NO_2 (r = 0.05). Copollutant models were not conducted in this analysis to identify whether the CO associations observed are potentially confounded by other pollutants.

Studies that focused on alterations in lung function in asthmatic children reported results consistent with those observed in adult asthmatics. Timonen et al. (2002, 025653) examined the effect of CO on bronchial responsiveness and pulmonary function (i.e., FVC, FEV_1, MMEF, and AEFV) at rest and after exercise in a panel of children, 7-12 yr old with chronic respiratory symptoms, during the winter in Kuopio, Finland. The authors found that CO was significantly associated with decrements in baseline lung function (i.e., lung function measured prior to exercise) for FVC (mL) at lags 2 (-17.5 mL), 3 (-24.8 mL), and 4-day avg (-52.5 mL), and for FEV_1 (mL) at lag 3 (-20.9 mL), for a 0.5 ppm increase in 24-h avg CO concentration. CO was not found to be associated with exercise-induced changes in lung function or bronchial responsiveness. Overall, Timonen et al. (2002, 025653) found that increased concentrations of combustion-related byproducts (i.e., BS, PM_{10}, particle numbers, NO_2, and CO) was associated with impairment in baseline lung function. These associations, along with the high correlation between CO and combustion-related pollutants (e.g., PM_{10} [r = 0.64]; NO_2 [r = 0.88]), contributed to the inability of the authors to conclude that the lung function effects observed were due to biological changes in lung pathology specific to CO exposure.

Chen et al. (1999, 011149) examined the effect of CO on lung function in 941 8- to 13-yr-old asthmatic children in Taiwan. The authors observed an association between short-term exposure to CO and decrements in FVC (mL) at a 2-day lag when using daytime average CO concentrations (from 8:00 a.m. to 6:00 p.m.) in a single-pollutant model. However, the authors found a high correlation between CO and NO_2 concentrations (r = 0.86-0.98), and did not conduct copollutant analyses.

An additional study, Fischer et al. (2002, 025731), examined the association between CO and respiratory health, specifically lung function in a cohort study of 68 children ages 10-11 yr who lived in an urban environment (Utrecht, The Netherlands). In this study, the authors examined whether eNO was a more sensitive measure of lung damage than the traditional pulmonary function measurements (i.e., FVC, FEV_1, PEF, and MMEF). Fischer et al. (2002, 025731) found negative associations between CO and FEV_1, PEF, and MMEF at both lags 1 and 2, as well as an association between CO and an increase in eNO at lag 1. However, the study did not provide pollutant correlations or examine copollutant models, limiting the interpretation of these results.

Respiratory Symptoms in Asthmatic Individuals

Upon evaluating the literature that examined the association between short-term exposure to CO and respiratory symptoms in asthmatic individuals, consistent, positive associations were observed across studies. The studies evaluated that included children enrolled in the Childhood Asthma Management Program (CAMP) study found that CO was positively associated with asthma symptoms. Yu et al. (2000, 013254) found a 1.14-fold increase in asthma symptoms ([95% CI: 1.05-1.23] per 0.5 ppm increase in 24-h avg CO) at lag 1 in a population of 5- to 13-yr-old asthmatic children (n = 133) in Seattle, WA. Similar effects were observed at lag 0 and lag 2. These effects persisted when controlling for previous day's asthma symptoms at all lags, with the largest effect at lag 1 (OR=1.12 [95% CI: 1.05-1.19]) and in multipollutant models with $PM_{1.0}$ and SO_2.

Using the same population of children, Slaughter et al. (2003, 086294) found an association between short-term exposure to CO at lag 1 and asthma severity both with and without controlling for the previous day's asthma severity, (RR = 1.04 [95% CI: 1.01-1.08] and RR = 1.03 [95% CI: 1.00-1.05] per 0.5 ppm increase in 24-h avg CO, respectively). However, this study only examined the effect of copollutant models on PM risk estimates, not CO. Schildcrout et al. (2006, 089812) examined the association between air pollutants and asthma symptoms in 990 children ages 5-12 yr in 8 North American cities. The authors found a positive association between short-term exposure to CO and asthma symptoms at lag 0 (OR = 1.04 [95% CI: 1.00-1.07] per 0.5 ppm increase in 24-h avg CO), but similar effects were also observed at lag 1, 2, and the 3-day moving sum. The CO effects observed persisted when NO_2, PM_{10}, and SO_2 where included in joint-pollutant models.

As previously mentioned, O'Connor et al. (2008, 156818) conducted an additional multicity study to examine the effect of air pollutants (i.e., $PM_{2.5}$, O_3, NO_2, CO, and SO_2) on respiratory health in a population of 861 children (5-12 yr) with persistent asthma in 7 U.S. urban communities. The authors collected information on asthma symptoms every 2 mo and examined the association between a 2-wk recall of the asthma symptoms and each air pollutant. O'Connor et al. (2008, 156818) used a 19-day lag, which encompassed the 14 days of the symptom recall period and the 5-day lag period proceeding the symptom recall period. In a single-pollutant model, CO was significantly associated with number of days with a wheeze-cough (14% [95% CI: 2-29]), number of nights with asthma symptoms (i.e., nighttime asthma) (19% [95% CI: 4-36]), and number of days a child slowed down or stopped play (15% [95% CI: 2-30]) per 0.5 ppm increase in 24-h avg CO concentrations during the 2-wk recall period. In this study, CO effects were not examined in a copollutant model.

U.S.-based single-city studies also found positive associations between CO and asthma symptoms (Delfino et al., 2003, 050460; Rabinovitch et al., 2004, 096753). Rabinovitch et al. (2004, 096753) found evidence for an increase in asthma exacerbations in response to 24-h avg CO concentrations for a 3-day ma (lag 0-2) (OR = 1.02 [95% CI: 0.89-1.16] per 0.5 ppm increase in 24-h avg CO) in a population of urban poor children with moderate to severe asthma in Denver, CO. Delfino et al. (2003, 050460) also reported evidence of a positive association between CO and asthma symptoms (based on symptoms that interfere with daily activities) using a population of Hispanic children with asthma in a Los Angeles, CA, community. However, Delfino et al. (2003, 050460) only found positive associations at 1-day lags when using either the 1-h max (OR=1.05 [95% CI: 0.88-1.26] per 1 ppm increase in 1-h max CO concentrations) or max 8-h avg (OR=1.09 [95% CI: 0.80-1.50] per 0.75 ppm increase in max 8-h avg CO concentrations) CO concentration as the exposure metric. It should be noted that in comparison to Rabinovitch et al. (2004, 096753) and the other respiratory symptoms studies discussed above, the mean ambient concentrations for 1-h max and max 8-h avg reported by Delfino et al. (2003, 050460) were 7.7 ppm and 5.0 ppm, respectively, both of which are approximately 3.5 times higher than the corresponding 24-h avg concentrations reported in the other studies.

In addition to the U.S.-based studies presented above, international studies were evaluated that examined the association between short-term exposure to CO and asthma symptoms in study populations that included adults. Figure 5-14 summarizes the results from studies that provided comparable quantitative results and examined the association between short-term exposure to CO and asthma or respiratory symptoms in asthmatic individuals. A panel study consisting of 53 adults with asthma or asthma symptoms in Germany (Von et al., 2002, 034706) observed a marginal association between CO concentration and the prevalence of wheezing at lag 0 (OR = 1.03 [95% CI: 0.97-1.08] per 0.5 ppm increase in 24-h avg CO), and a positive association for a 5-day mean concentration (OR = 1.12 [95% CI: 1.05-1.21] per 0.5 ppm increase in 24-h avg CO). However, the authors found CO to be highly correlated with UFPs (r = 0.66), complicating the interpretation of the associations observed. Additionally, Park et al. (2005, 088673) in a panel study of individuals 16-75 yr old in Incheon, Korea, with bronchial asthma, did not find an association between CO and nighttime asthma symptoms or cough.

To further examine the effect of CO on asthma and asthma symptoms, some studies also analyzed medication use in asthmatic individuals in response to an increase in air pollutant concentrations. The majority of U.S.-based studies (i.e., Rabinovitch et al., 2004, 096753; Schildcrout et al., 2006, 089812; Slaughter et al., 2003, 086294) focused on rescue inhaler use in children with ages ranging from 5 to13 yr. Rabinovitch et al. (2004, 096753) found a weak association (OR = 1.08 [95% CI: 1.00-1.17] per 0.5 ppm increase in 24-h avg CO) between rescue inhaler use in a population of 6- to 12-yr old urban minority children with moderate to severe asthma

in the winter in Denver, CO. In a population of 5- to 12-yr-old children with asthma in Seattle, WA, Slaughter et al. (2003, 086294) found a stronger association with rescue inhaler use both with and without taking into consideration the previous day's asthma severity, (RR: 1.04 [95% CI: 1.01-1.08] per 0.5 ppm increase in 24-h avg CO) and (RR: 1.03 [95% CI: 1.00-1.05] per 0.5 ppm increase in 24-h avg CO), respectively. Similar results were observed in a multicity study conducted by Schildcrout et al. (2006, 089812) which analyzed rescue inhaler use in 990 children ages 5-13 yr with asthma in 8 North American cities. Schildcrout et al. (2006, 089812) found that short-term exposure to CO was positively associated with rescue inhaler use at lags of 0, 2, and a 3-day moving sum, and that the association was fairly robust to a simultaneous increase in CO and other pollutants (i.e., NO_2, PM_{10}, and SO_2) in joint models. Overall, Slaughter et al. (2003, 086294) and Schildcrout et al. (2006, 089812) question the associations observed due to the lack of biological plausibility for CO-induced respiratory effects and the high correlation between CO and NO_2 (which suggests that other pollutants from mobile sources are driving the associations observed), respectively. Additional studies (Park et al., 2005, 088673; Silkoff et al., 2005, 087471; Von et al., 2002, 034706) conducted in Denver, CO; Erfurt, Germany; and Incheon, Korea, respectively, found associations between CO and medication use that are consistent with those previously reported, but in populations with combined ages ranging from 16 to 77 yr. Figure 5-14 presents the risk estimates from studies that examined the association between short-term exposure to CO and medication use in asthmatic individuals.

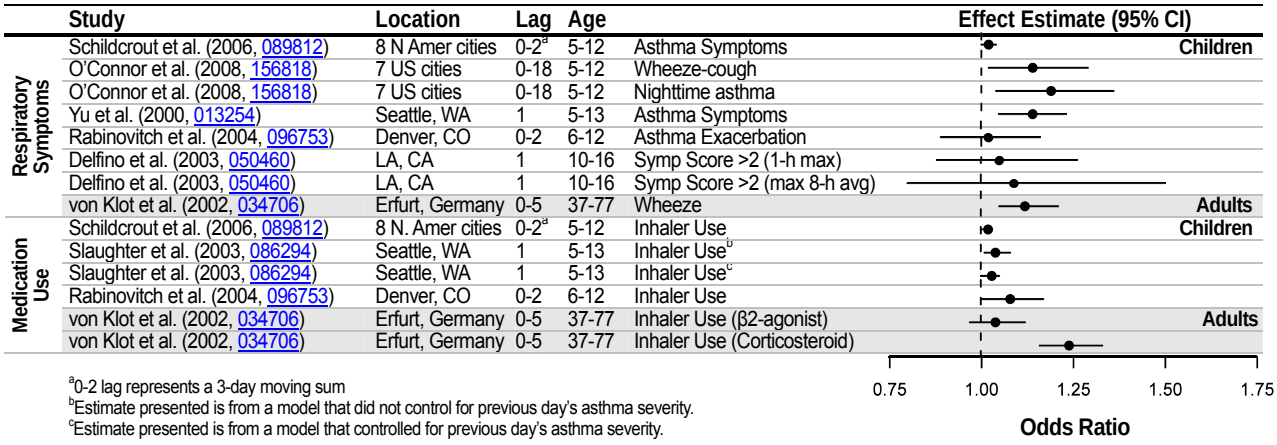


Figure 5-14. Summary of associations for short-term exposure to CO and asthma symptoms, respiratory symptoms and medication use in asthmatic individuals.[1] Effect estimates were standardized depending on the averaging time used in the study: 0.5 ppm for 24-h avg, 0.75 ppm for max 8-h avg, and 1.0 ppm for 1-h max.

Respiratory Symptoms in Nonasthmatic Individuals

In addition to examining the association between short-term exposure to CO and respiratory symptoms (e.g., cough, wheeze, shortness of breath) in asthmatic populations, some studies examined respiratory effects in individuals classified as nonasthmatics. Rodriguez et al. (2007, 092842) examined the effect of CO on respiratory symptoms in a panel of 263 children 0- to 5-yr old at high risk for developing asthma in Perth, Australia. Rodriguez et al. (2007, 092842) found CO concentrations to be positively associated with wheeze/rattle chest and runny/blocked nose at both a 5-day lag and a 0-5-day lag. In this study, copollutant models were not examined, CO correlations with other pollutants were not presented, and additional analyses were not conducted to further characterize the associations observed.

[1] Effect estimates from Park et al. (2005, 088673) were not included in this figure because the study did not provide the increment at which the effect estimates were calculated. Additionally, estimates for Silkoff et al. (2005, 087471) were not included in the figure because results were not presented quantitatively.

In a panel of individuals ≥ 50 yr of age with CHD in three European locations (Amsterdam, The Netherlands; Erfurt, Germany; and Helsinki, Finland) during the winter, de Hartog et al. (2003, 001061) observed some marginal associations, specifically between CO concentration and the incidence of the respiratory symptoms shortness of breath and phlegm at lag 3, OR=1.17 (95% CI: 0.96-1.40) and OR=1.22 (95% CI: 0.93-1.57), respectively, per 0.5 ppm increase in 24-h avg CO concentrations. However, the authors found that the associations between air-pollution exposure and respiratory symptoms were stronger for $PM_{2.5}$ than for gaseous air pollutants. Overall, the associations observed in this study should be viewed with caution because the panel consisted of individuals on a variety of daily medications (i.e., beta blockers, ACE inhibitor + AT blocker, calcium antagonist, aspirin, digitalis, inhaled beta-agonist, and nitroglycerin).

Summary of Associations between Short-Term Exposure to CO and Pulmonary Function, Respiratory Symptoms, and Medication Use

A limited body of evidence is available that examined the effect of short-term exposure to CO on various respiratory health endpoints. Specifically, among asthmatics, the studies reviewed generally found positive associations between short-term exposure to CO and respiratory-related health effects (i.e., decrements in lung function, respiratory symptoms, and medication use). On-road vehicle exhaust emissions are a nearly ubiquitous source of combustion pollutant mixtures that include CO and can be an important contributor to CO-related health effects in near-road locations, which is evident by the high correlations reported between CO and other combustion-related pollutants (i.e., NO_2 and PM). However, the limited number of copollutant analyses among this group of studies complicates the efforts to disentangle the health effects attributed to CO from the larger traffic-related pollutant mix. Additional uncertainty exists as to a biologically plausible mechanism that could explain the effect of CO on respiratory health.

5.5.1.2. Respiratory Hospital Admissions, ED Visits and Physician Visits

The 2000 CO AQCD (U.S. EPA, 2000, 000907) evaluated a limited amount of literature that examined the association between short-term exposure to CO and respiratory hospital admissions (HAs), ED visits, and physician visits in the U.S. (i.e., Seattle, WA; Reno, NV; and Anchorage, AK) and Europe (i.e., Barcelona, Spain). From these studies, the 2000 CO AQCD (U.S. EPA, 2000, 000907) concluded that positive associations were observed for short-term exposure to CO with several respiratory outcomes, including asthma and COPD. However, the lack of a biologically plausible mechanism for CO-induced respiratory morbidity at that time brought into question whether the results observed could be attributed to CO independently of other pollutants in the air pollutant mixture. Additional uncertainties were identified in the epidemiologic literature that contributed to this conclusion, which were discussed in Section 5.2.1.

This section evaluates those studies published since the 2000 CO AQCD (U.S. EPA, 2000, 000907) that examined the association between short-term exposure to CO at ambient concentrations similar to those found in the U.S. and respiratory-related HAs (Figure 5-15), ED visits (Figure 5-16), and physician visits. Unlike previous sections, which also evaluated studies conducted outside of North America, the expansive number of studies conducted in the U.S. and Canada provide adequate evidence to examine the association between short-term exposure to CO and respiratory HAs and ED visits. Although not discussed in this section, collectively, the studies conducted outside of the U.S. observed associations that are consistent with those observed in the U.S.- and Canadian-based studies evaluated below (see Annex C for results from the international studies evaluated).

Overall, this section focuses on respiratory-related HAs because the majority of the literature examines HAs as opposed to ED visits or physician visits (Table 5-20 presents the studies evaluated in this section along with the range of CO concentrations measured in each study). It must be noted that when examining the association between short-term exposure to CO and health outcomes that require medical attention, it is important to distinguish between HAs, ED visits, and physician visits for respiratory outcomes (more so than for cardiovascular outcomes). This is because it is likely that a small percentage of respiratory ED visits will be admitted to the hospital and, therefore, may represent potentially less serious but more common outcomes. To adequately distinguish between the results presented in HAs, ED visit, and physician visit studies, each outcome is evaluated in individual sections. In addition, each section presents results separately for respiratory health

outcomes which include all respiratory diagnoses (ICD-9: 460-519) or selected diseases (e.g., asthma, COPD, pneumonia and other respiratory infections) in order to evaluate the potential effect of short-term exposure to CO on each outcome.

Table 5-20. Range of CO concentrations reported in key respiratory HA and ED visit studies that examine effects associated with short-term exposure to CO.

Study	Location	Type of Visit (ICD9)	Metric	Mean Concentration (ppm)	Middle/Upper Percentile Concentrations (ppm)
Cakmak et al. (2006, 093272)	10 Canadian cities	Hospital Admissions: Respiratory disease (i.e., Acute bronchitis and bronchiolitis; pneumonia; chronic and unspecific bronchitis; emphysema; asthma; bronchiectasis; chronic airway obstruction)	24-h avg	0.8	Maximum: 6.5
Linn et al. (2000, 002839)	Los Angeles, CA	Hospital Admissions: Pulmonary; asthma; COPD	24-h avg	Winter: 1.7; Spring: 1.0; Summer: 1.2; Fall: 2.1	Maximum: Winter: 5.3; Spring: 2.2; Summer: 2.7; Fall: 4.3;
Slaughter et al. (2005, 073854)	Spokane, WA	ED Visits and Hospital Admissions: Respiratory; asthma; COPD; pneumonia; acute respiratory infection	24-h avg	Hamilton St.: 1.73 Backdoor Tavern: 1.29 Spokane Club: 1.41 Third and Washington: 1.82 Rockwood: 0.42	95th: 3.05
Burnett et al. (2001, 093439)	Toronto, ON, Can	Hospital Admissions: Respiratory disease (i.e., asthma; acute bronchitis/bronchiolitis; croup; pneumonia)	1-h max	1.9	50th: 1.8; 75th: 2.3; 95th: 3.3; 99th: 4.0 Maximum: 6.0
Yang et al. (2003, 055621)	Vancouver, BC, Can	Hospital Admissions: Respiratory diseases	24-h avg	0.98	50th: 0.82; 75th: 1.16 Maximum: 4.90
Lin et al. (2003, 042549)	Toronto, ON, Can	Hospital Admissions: Asthma	24-h avg	1.18	50th: 1.10; 75th: 1.40 Maximum: 6.10
Lin et al. (2004, 055600)	Vancouver, BC, Can	Hospital Admissions: Asthma	24-h avg	0.96	50th: 0.80; 75th: 1.12 Maximum: 4.90
Moolgavkar (2003, 042864)	Cook County, IL; Los Angeles County, CA	Hospital Admissions: COPD	24-h avg	NR	Cook: 50th: .99; 75th: 1.25 Maximum: 3.91 Los Angeles: 50th: 1.35; 75th: 2.16 Maximum: 5.96
Yang et al. (2005, 090184)	Vancouver, BC, Can	Hospital Admissions: COPD	24-h avg	0.71	50th: 0.64 Maximum: 2.48
Karr et al. (2006, 088751)	South Coast Air Basin, CA	Hospital Admissions: Acute bronchiolitis	24-h avg	Lag 1: Index: 1.730 Referent: 1.750 Lag 4: Index: 1.760 Referent: 1.790	Lag 1: Index: 50th: 1.52; 75th: 2.26; 90th: 3.16 Maximum: 9.60 Referent: 50th: 1.51; 75th: 2.29; 90th: 3.23 Maximum: 9.60 Lag 4: Index: 50th: 1.54; 75th: 2.31; 90th: 3.23 Maximum: 8.71 Referent: 50th: 1.55; 75th: 2.35; 90th: 3.30 Maximum: 9.60

Study	Location	Type of Visit (ICD9)	Metric	Mean Concentration (ppm)	Middle/Upper Percentile Concentrations (ppm)
Karr et al. (2007, 090719)	South Coast Air Basin, CA	Hospital Admissions: Acute bronchiolitis	24-h avg; Monthly avg	24-h avg: 1.720 Monthly: 1.770	24-h avg: 50th: 1.61; 75th: 2.08; 90th: 2.75 Maximum: 5.07 Monthly avg: 50th: 1.63; 75th: 2.13; 90th: 2.88 Maximum: 8.30
Zanobetti and Schwartz (2006, 090195)	Boston, MA	Hospital Admissions: Pneumonia	24-h avg	NR	50th: 0.48; 75th: 0.60; 95th: 0.88
Lin et al. (2005, 087828)	Toronto, ON, Canada	Hospital Admissions: Respiratory infections	24-h avg	1.16	50th: 1.05; 75th: 1.37 Maximum: 2.45
Peel et al. (2005, 056305)	Atlanta, GA	ED Visits: All respiratory; asthma; COPD; URI; pneumonia	1-h max	1.8	90th: 3.4
Tolbert et al. (2007, 090316)	Atlanta, GA	ED Visits: Respiratory diseases (i.e., asthma; COPD; URI; pneumonia; bronchiolitis)	1-h max	1.6	50th: 1.3; 75th: 2.0; 90th: 3.0 Maximum: 7.7
Ito et al. (2007, 156594)	New York, NY	ED Visits: Asthma	8-h max	1.31	50th: 1.23; 75th: 1.52; 95th: 2.11
Villeneuve et al. (2006, 091179)	Toronto, ON, Canada	Physicians Visits: Allergic rhinitis	24-h avg	1.1	Maximum: 2.2
Sinclair et al. (2004, 088696)	Atlanta, GA	Urgent Care Visits: Asthma; respiratory infections	1-h max	1.3	NR

Hospital Admissions

Respiratory Disease

The majority of studies from North America that examined the association between short-term exposure to CO and HAs for all respiratory diseases were conducted in Canada, and only one of these studies presented results from a combined analysis of multiple cities (Cakmak et al., 2006, 093272). In a study of 10 of the largest Canadian cities, Cakmak et al. (2006, 093272) examined respiratory HAs (ICD-9: 466, 480-486, 490-494, 496) in relation to ambient gaseous pollutant concentrations for the time period 1993-2000. This study reported a 0.37% (95% CI: 0.12-0.50) increase in respiratory hospital admissions for all ages for a 0.5 ppm increase in 24-h avg CO (lag 2.8 days averaged over the 10 cities[1]). However, Cakmak et al. (2006, 093272) only examined the potential confounding effects of gaseous pollutants (i.e., NO_2, SO_2, and O_3) on the CO risk estimate in a multipollutant model and did not provide correlation coefficients, limiting the interpretation of the effects observed in the single-pollutant model. U.S.-based studies (Los Angeles and Spokane) that examined HAs for all respiratory diseases reported similarly weak or null associations with CO (Linn et al., 2000, 002839; Slaughter et al., 2005, 073854). But two single-city studies conducted in Canada reported stronger associations, primarily through evidence from copollutant models, between short-term exposure to CO and respiratory disease HAs (Burnett et al., 2001, 093439; Yang et al., 2003, 055621). In a study conducted in Toronto, Canada, for the time period 1980-1994, Burnett et al. (2001, 093439) reported a relatively strong association between 1-h max CO and respiratory disease HAs in children <2 yr of age for the diagnoses of asthma (493), acute bronchitis/bronchiolitis (466), croup (464.4), and pneumonia (480-486). The authors found a 9.7% (95% CI: 4.1-15.5) increase in HAs for a 2-day avg (lag 0-1) per 1 ppm increase in 1-h max CO. In the two-pollutant model analysis with O_3, the estimate for CO remained elevated (7.29% [95% CI: 1.75-13.1]), but CO

[1] To determine the lag for the combined estimate across all 10 cities, Cakmak et al. (2006, 093272) averaged the strongest associations from lags 0-5 days from each city.

was not found to be highly correlated with O_3 (r = 0.24). Yang et al. (2003, 055621) reported similar results (OR = 1.04 [95% CI: 1.01-1.06] at lag 1 per 0.5 ppm increase in 24-h avg CO) for pediatric (<3 yr of age) respiratory disease (ICD-9: 460-519) HAs in Vancouver for the time period 1986-1998. Yang et al. (2003, 055621) also reported elevated associations with 24-h avg CO and respiratory HAs (ICD-9: codes 460-519) for ages 65 yr and over in Vancouver, Canada, (OR = 1.02 [95% CI: 1.00-1.04]) at lag 1 for a 0.5 ppm increase in 24-h avg CO. The authors found that the CO risk estimates remained the same when O_3 was included in the model, which could be attributed to the lack of collinearity between CO and O_3 due to their negative correlation (r = -0.52).

Asthma

Some studies that examined the effect of short-term exposure to CO on asthma HAs conducted all age and age-stratified analyses, specifically to examine effects in children. In a few studies conducted in Canada, evidence was observed for increased pediatric (ages 6-12 yr) asthma HAs (ICD-9: 493) in boys but not girls (Lin et al., 2003, 042549; Lin et al., 2004, 055600); however, a biological explanation was not provided which could explain this difference. Lin et al. (2003, 042549) used a bidirectional case-crossover analysis in Toronto, Canada, for the years 1981-1993. The authors reported an OR of 1.05 (95% CI: 1.00-1.11) per 0.5 ppm increase in 24-h avg CO for a 1-day lag for boys, with similar results being reported when averaging CO concentrations up to 7 days prior to an HA. Risk estimates for girls did not provide evidence of an association using the same lag structure that was used in the boys' analysis (OR = 1.00 [95% CI: 0.93-1.06]); lag 1). In this study, CO levels were moderately correlated with NO_2 (r = 0.55) and $PM_{2.5}$ (r = 0.45), and weakly correlated with SO_2 (r = 0.37). In this study, copollutant analyses were not conducted to examine the potential confounding effect of different PM size fractions or gaseous pollutants on CO risk estimates. It should be noted that this study used a bidirectional case-crossover analysis, which may bias the results in either direction (Levy et al., 2001, 017172). Studies that examined the various referent selection strategies for the case-crossover study design have concluded that the preferred control selection strategy is the time-stratified framework (Levy et al., 2001, 017172). Lin et al. (2004, 055600) also examined the association between air pollutants and asthma HAs in children, but using a time-series study design in Vancouver during the years 1987-1998. In this study, the authors stratified results by socioeconomic status (SES) and found some evidence for an association between CO and asthma HAs for both girls and boys, of both high and low SES at lag 1 (RR=1.01-1.06 per 0.5 ppm increase in 24-h avg CO); but overall, the evidence was less consistent for a greater effect in boys versus girls compared to Lin et al. (2003, 042549). In a study that examined asthma HAs for all ages and genders combined, Slaughter et al. (2005, 073854) observed some evidence for an increase in asthma HAs (ICD-9 493) in Spokane (1995-2000) for CO at lag 2 (RR = 1.03 [95% CI: 0.98-1.08]) for a 0.5 ppm increase in 24-h avg CO but not for the other two lags examined (lag 1 and lag 3).

Chronic Obstructive Pulmonary Disease

A few of the studies examined the effect of short-term exposure to CO on COPD, or obstructive lung disease, and HAs. Moolgavkar (2003, 042864) (a reanalysis of Moolgavkar, 2000, 010274) examined HAs for COPD plus "allied diseases" (ICD-9 490-496) in two U.S. counties (Cook County, IL, and Los Angeles County, CA) for the years 1987-1995, using Poisson generalized linear models (GLMs) or generalized additive models (GAM), with the more stringent convergence criteria. Overall, the results from both models were similar. Using the GAM models, the study reported increases in HAs of 0.53-1.20% for all ages in Los Angeles County and 0.17-1.41% for ages ≥ 65 yr in Cook County, for a 0.5 ppm increase in 24-h avg CO and lags ranging from 0 to 5 days. However, CO was found to be highly correlated with NO_2 in both Cook County (r = 0.63) and Los Angeles County (r = 0.80), but Moolgavkar (2003, 042864) did not examine the influence of copollutants on CO risk estimates. Yang et al. (2005, 090184) reported similar results for COPD HAs (ICD-9 490-492, 494, 496) in Vancouver for ages ≥ 65 yr for the years 1994-1998 for a ma of 0- to 6-day lags (RR = 1.14 [95% CI: 1.03-1.23] per 0.5 ppm increase in 24-h avg CO). In this study, CO concentrations were moderately correlated with NO_2, SO_2, and PM_{10}, and moderately negatively correlated with O_3. In copollutant models, Yang et al. (2005, 090184) found that risk estimates for CO and COPD HAs remained elevated with O_3 (RR=1.19 [95% CI: 1.07-1.32]) or SO_2 (RR=1.19 [95% CI: 1.02-1.39]), but were attenuated when adjusting for NO_2 (RR=1.07 [95% CI: 0.92-1.24]) or PM_{10} (RR=1.03 [95% CI: 0.89-1.21]). Contrary to Moolgavkar (2003, 042864) and Yang et al.

(2005, 090184), Slaughter et al. (2005, 073854) found no association between short-term exposure to CO and COPD HAs (ICD-9 491, 492, 494, 496) in Spokane, WA, at lag 1-day (RR = 0.97 [95% CI: 0.93-1.01] per 0.5 ppm increase in 24-h avg CO) with similar results being reported for 2- and 3-day lags. However, this study did not examine correlations between CO and other gaseous pollutants or conduct copollutant analyses.

Acute Bronchiolitis in Infants

Karr et al. (2006, 088751; 2007, 090719) examined both short-term (lag 0 or 1) and longer term levels of CO in relation to acute bronchiolitis (ICD-9: 466) HAs during the first year of life from 1995-2000 in the South Coast Air Basin in California. Karr et al. (2006, 088751) found no evidence of a short-term association between ambient CO concentrations and HAs for acute bronchiolitis at lag 1 day (OR= 0.99 [95% CI: 0.98-1.01] per 0.5 ppm increase in 24-h avg CO). In addition, Karr et al. (2007, 090719), which examined longer term exposures (average in the month prior to a HA and lifetime average) in a matched case-control study, did not provide any evidence of an association with CO. Neither of these studies examined the correlation between CO and other pollutants nor conducted copollutant analyses.

Pneumonia and Other Respiratory Infections

In addition to examining the effect of short-term exposure to CO on health outcomes that can limit the function of the respiratory system, some studies examined the effect of CO on individuals with pneumonia (ICD-9: 480-486) separately or in combination with other respiratory infections. Zanobetti and Schwartz (2006, 090195) examined pneumonia HAs (ICD-9 480-487) in Boston, MA, for the years 1995-1999 for individuals ages 65 yr and older, using a time-stratified case-crossover analysis. The authors reported an increase in pneumonia HAs at lag 0 of 5.4% (95% CI: 1.2-10.0) per 0.5 ppm increase in 24-h avg CO. While Zanobetti and Schwartz (2006, 090195) did not report multipollutant results, they suggested that CO was most likely acting as a marker for traffic-related pollutants because CO was highly correlated with both BC (r = 0.80) and NO_2 (r = 0.67) and moderately correlated with $PM_{2.5}$ (r = 0.52). Instead of examining the effect of CO on pneumonia HAs separately, as was done by Zanobetti and Schwartz (2006, 090195), Lin et al. (2005, 087828) presented results for the overall effect of CO on respiratory infection HAs (ICD-9: 464, 466, 480-487). In this analysis, Lin et al. (2005, 087828) examined the potential increase in respiratory HAs in children <15 yr of age in Toronto, Canada, for 1998-2001, using a bidirectional case-crossover approach. The authors reported elevated estimates for boys (OR=1.17 [95% CI: 1.03-1.32] per 0.5 ppm increase in 24-h avg CO for a 6-day ma) while the estimate for girls was weaker and with wider confidence intervals (OR=1.06 [95% CI: 0.91-1.23]). In multipollutant models with both $PM_{2.5}$ and $PM_{10-2.5}$ the CO risk estimates were slightly attenuated but remained positive (boys: OR=1.10 [95% CI: 0.96-1.26]; girls: OR=1.03 [95% CI: 0.88-1.06]). Lin et al. (2005, 087828) did not provide an explanation as to why the estimates were stronger for boys than for girls. It should be noted that this study used a bidirectional case-crossover analysis, which, as discussed previously, may bias the results in either direction (Levy et al., 2001, 017172).

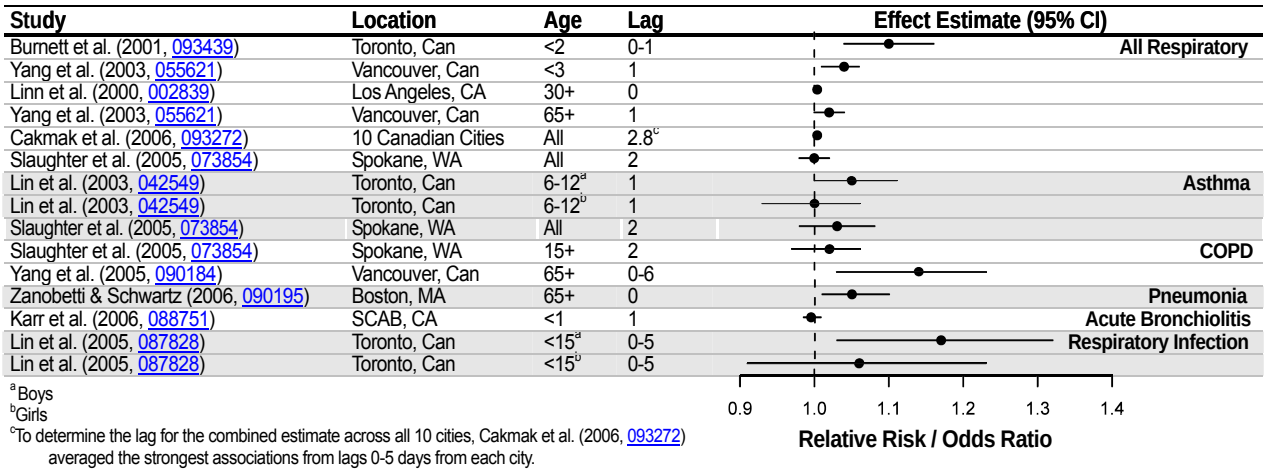


Figure 5-15. Summary of associations for short-term exposure to CO and respiratory hospital admissions.[1,2] Effect estimates were standardized depending on the averaging time used in the study: 0.5 ppm for 24-h avg, 0.75 ppm for max 8-h avg, and 1.0 ppm for 1-h max.

Emergency Department Visits

Respiratory Disease

Peel et al. (2005, 056305) conducted a large single-city respiratory disease ED visit study in Atlanta, GA, which included data from 31 hospitals for the time period 1993–2000. In this study, results were reported for various respiratory-related visits (ICD-9 460-466, 477, 480-486, 491-493, 496, 786.09). In an all-ages analysis, the authors found a RR=1.01 (95% CI: 1.00-1.02) for all respiratory disease ED visits for a 3-day avg (lag 0-2) per 1 ppm increase in 1-h max CO concentration. Tolbert et al. (2007, 090316) expanded the time period used in the Peel et al. (2005, 056305) study to include ED visits through 2004 and reported similar results for all respiratory disease ED visits (RR=1.013 [95% CI: 1.007-1.018] per 1 ppm increase in 1-h max CO). The CO risk estimates from the Atlanta, GA, ED visits studies were attenuated when O_3, NO_2, or PM were added to the model (results not presented quantitatively), which could potentially be explained by the high correlations reported in Tolbert et al. (2007, 090316) between CO and NO_2 (r = 0.70) and EC (r = 0.66) and the moderate correlation with $PM_{2.5}$ (r = 0.51). One additional ED-visits study that also examined respiratory disease (Slaughter et al., 2005, 073854) presented essentially null results at lag 1 and 2 but found similar results to Peel et al. (2005, 056305) and Tolbert et al. (2007, 090316) at lag 3 (RR=1.02 [95% CI: 1.00-1.03] per 0.5 ppm increase in 24-h avg CO). Slaughter et al. (2005, 073854) reported a weak to moderate correlation between CO and various PM size fractions but did not report the correlation between CO and gaseous pollutants, limiting the comparison of this study with Peel et al. (2005, 056305) and Tolbert et al. (2007, 090316).

Asthma

The association between short-term exposure to CO and asthma ED visits (ICD-9 493, 786.09) was also examined in Atlanta, GA, by Peel et al. (2005, 056305). In this study, the authors reported

[1] Risk estimates from Moolgavkar (2003, 042864) were not included in this figure because the study presented a range of effect estimates using different statistical models. The results from this study were more adequately highlighted in the evaluation of the study in the COPD section.

[2] Risk estimates from Lin et al. (2004, 055600) were not included in the figure because the results were stratified by SES and therefore could not be readily compared to effect estimates from Lin et al. (2003, 042549).

results from distributed lag models including lags 0-13 in addition to a ma of lags 0, 1, and 2 (lag 0-2) for specific respiratory outcomes (e.g., asthma). Effect estimates from the distributed lag models were stronger than those produced from models that used 3-day ma CO concentrations (RR = 1.01 [95% CI: 0.99-1.02] for lags 0-2 compared to RR=1.08 [95% CI: 1.05-1.11] for an unconstrained distributed lag of 0-13 for a 1 ppm increase in 1-h max CO). These results demonstrated the potential effect of CO exposures up to 13 days prior to an asthma ED visit. Estimates were stronger for pediatric ED visits (ages 2-18 yr) (RR=1.02 [95% CI: 1.00-1.04] per 1 ppm increase in 1-h max CO) for a 3-day avg (lag 0-2) compared to all ages (Peel et al., 2005, 056305). Slaughter et al. (2005, 073854), which also examined ED visits for Spokane (1995-2001), reported an increase in asthma ED visits for all ages for CO at lag 3 (RR=1.03 [95% CI: 1.00-1.05] per 0.5 ppm increase in 24-h avg CO) but not for the other two lags examined (lags 1 and 2). The results from Ito et al. (2007, 156594) also provide evidence of increased ED visits for asthma (ICD-9 493) for all ages in New York City for 1999-2002. Using three different models that adjusted for weather variables via different degrees of smoothing and/or a different number of weather variables, the authors found that CO effect estimates remained elevated in both an all-year analysis and in analyses stratified by warm (i.e., April to August) and cold (i.e., November to March) months. Using Model C, which adjusted for temporal trends using 8 degrees of freedom (df) and included variables to adjust for weather and day of the week, an all-year RR of 1.03 (95% CI: 1.01-1.06) per 0.75 ppm increase in maximum 8-h avg CO concentrations was reported. Ito et al. (2007, 156594) also examined copollutant models using Model C but only during the warm season. In this model CO effect estimates were robust to the inclusion of $PM_{2.5}$ (RR = 1.06 [95% CI: 1.00-1.11]), O_3 (RR=1.10 [95% CI: 1.05-1.15]), and SO_2 (RR=1.04 [95% CI: 0.99, 1.09]) in the model, but the CO risk estimate was attenuated, resulting in a negative effect estimate when including NO_2 (RR=0.97 [95% CI: 0.92-1.03]) in the model.

Chronic Obstructive Pulmonary Disease

In the examination of the effect of short-term exposure to CO on COPD ED visits (ICD-9 491, 492, 496), Peel et al. (2005, 056305) reported elevated estimates for Atlanta, GA, for 1993-2000 (RR=1.03 [95% CI: 1.00-1.05] per 1 ppm increase in 1-h max CO for lag 0-2 ma) with similar results for the distributed lag model (RR=1.03 [95% CI: 0.98-1.09). However, results from Slaughter et al. (2005, 073854) from Spokane, WA, were consistent with a null or slightly protective association at lag 1 (RR=0.96 [95% CI: 0.92-1.00] per 0.5 ppm increase in 24-h avg CO at lag 1) with similar results for lags 2 and 3.

Pneumonia and Other Respiratory Infections

Similar to the HA analysis conducted by Zanobetti and Schwartz (2006, 090195) discussed above, Peel et al. (2005, 056305) examined the effect of CO on pneumonia separately (ICD-9: 480-486) but also included an analysis of upper respiratory infection (ICD-9: 460-466, 477) ED visits for all ages in Atlanta, GA, during the years 1993-2000. The authors reported a weak estimate for pneumonia for the 3-day ma (lag 0-2) (RR=1.01 [95% CI: 0.996-1.021] per 1 ppm increase in 1-h max CO). However, when using an unconstrained distributed lag model (days 0-13), Peel et al. (2005, 056305) observed evidence of an association (RR=1.045 [95% CI: 1.01-1.08]). An examination of upper respiratory infection (URI) ED visits, the largest of the respiratory ED groups, found slightly increased risk estimates for both the 3-day ma (lag 0-2) (RR=1.01 [95% CI: 1.00-1.02]) and the unconstrained distributed lag for days 0-13 (RR=1.07 [95% CI: 1.05-1.09]) per 1 ppm increase in 1-h max CO. In copollutant models, CO risk estimates were largely attenuated when PM_{10}, O_3, or NO_2 were included in the model (not reported quantitatively). Upon conducting an age-stratified analysis, Peel et al. (2005, 056305) also found that infant (<1 yr of age) and pediatric (ages 2-18 yr) URI ED visit CO risk estimates were substantially stronger than the all-age risk estimates.

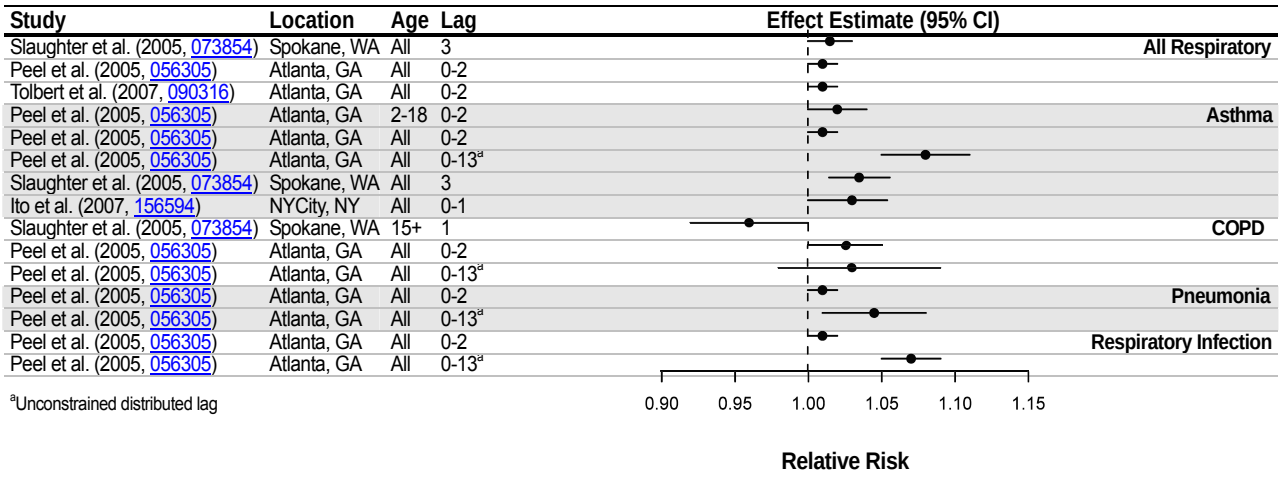


Figure 5-16. Summary of associations for short-term exposure to CO and respiratory ED visits. Effect estimates were standardized depending on the averaging time used in the study: 0.5 ppm for 24-h avg, 0.75 ppm for max 8-h avg, and 1.0 ppm for 1-h max.

Physician Visits

Although HAs and ED visits are the two most well-studied measures of morbidity, a few studies also examined the effect of CO on unscheduled physician visits. In a time-series study, Villeneuve et al. (2006, 091179) examined the effect of CO on physician visits for allergic rhinitis in individuals 65 yr and older in Toronto, Canada. Although quantitative results were only presented in figures, upon observation it was evident that estimates were consistent with a null association for lags 0-6 (Villeneuve et al., 2006, 091179). In an additional study, Sinclair et al. (2004, 088696) reported results for urgent care visits for asthma and respiratory infections in a health maintenance organization in Atlanta, GA; however, the study only reported statistically significant results, of which none were for CO.

Summary of Associations between Short-Term Exposure to CO and Respiratory Hospital Admissions, ED Visits, and Physicians Visits

Compared to other criteria air pollutants (e.g., O_3 and PM), relatively few studies evaluated the association between short-term exposure to ambient CO and HAs and ED visits for various respiratory outcomes. Although evidence for consistent positive associations (Figure 5-15 and Figure 5-16) has been found across the studies evaluated, there remains uncertainty as to a biologically plausible mechanism which could explain the association between CO exposure and respiratory-related health effects. As observed in the preceding section, several authors suggest that the observed associations are due to CO acting as an indicator of combustion-related pollution (e.g., traffic). The interpretation of the associations observed in the studies evaluated is further complicated by the moderate to high correlations reported between CO and other traffic-related pollutants such as NO_2, $PM_{2.5}$, EC, or BC. Only a few studies examined potential confounding of CO risk estimates by copollutants, and these studies found that CO risk estimates were generally robust to the inclusion of O_3, SO_2, and PM in two-pollutant models. However, those studies that examined two-pollutant models with NO_2 found that CO risk estimates, although positive, were slightly attenuated.

5.5.2. Epidemiologic Studies with Long-Term Exposure

The 2000 CO AQCD (U.S. EPA, 2000, 000907) did not evaluate any studies that examined the effect of long-term exposure to CO on respiratory health. The following section discusses those studies that analyze the effect of long-term exposure to CO on pulmonary function, asthma/asthma symptoms, and allergic rhinitis. Table 5-21 lists the studies evaluated in this section along with the respiratory health outcomes examined and CO concentrations reported.

Table 5-21. Range of CO concentrations reported in key respiratory morbidity studies that examined effects associated with long-term exposure to CO.

Study[a]	Location (Sample Size)	Year(s)	Health Outcome	Metric	Mean Concentration (ppm)	Middle/Upper Percentile Concentrations (ppm)
Mortimer et al. (2008, 122163)	San Joaquin Valley, CA (n=232)	1989-2000	Pulmonary function	Monthly mean of max 8-h avg	NR	NR
Meng et al. (2007, 093275)	Los Angeles and San Diego counties, CA	11/2000-9/2001	Asthma symptoms	Annual mean of 1-h avg	NR	NR
Wilhelm et al. (2008, 191912)	Los Angeles and San Diego Counties, CA (n=612)	1999-2001	Asthma symptoms	Annual mean of 1-h avg	1.0	Maximum: 1.8
Goss et al. (2004, 055624)	U.S.	2000	Pulmonary function; Asthma symptoms	Annual mean of 1-h avg	0.69	25th: 0.48 50th: 0.59 75th: 0.83
Hirsch et al. (1999, 003537)	Dresden, Germany	9/1995-6/1996	Respiratory symptoms	Annual mean of 0.5-h avg	0.60	75th: 0.76 Maximum: 1.34
Guo et al. (1999, 010937)	Taiwan	1994	Asthma; Asthma symptoms	Annual mean of monthly avg	0.85	50th: 0.84 75th: 1.00 Maximum: 1.61
Wang et al. (1999, 008105)	Kaohsiung and Pintong, Taiwan	1996	Asthma	Annual avg	NR	50th: 0.80
Hwang et al. (2005, 089454)	Taiwan	2000	Asthma	Annual mean of monthly avg	0.66	50th: 0.65 75th: 0.75 Maximum: 0.96
Hwang et al. (2006, 088971)	Taiwan	2000	Allergic rhinitis	Annual mean of monthly avg	0.66	50th: 0.65 75th: 0.75 Maximum: 0.96
Lee et al. (2003, 049201)	Taiwan	1994	Allergic rhinitis	Annual avg	0.85	50th: 0.84 75th: 1.00 Maximum: 1.61
Arnedo-Pena et al. (2009, 190238)	7 Spanish cities	2000	Asthma, allergic rhinitis, atopic eczema	Annual avg		50th: 0.61 75th: 0.78 Maximum: 1.04
Mortimer et al. (2008, 187280)	Fresno, CA (n=170)	11/2000-4/2005	Allergic sensitization	Monthly mean of 24-h avg	NR[b]	NR[b]

[a]The number of individuals included in the study population was only provided for those studies that included less than 1,000 participants.
[b]This study only presented air quality data graphically.

5.5.2.1. Pulmonary Function

Mortimer et al. (2008, 122163) examined the effect of prenatal and lifetime exposures to air pollutants on pulmonary function in 232 asthmatic children who resided in the San Joaquin Valley of California. The strong temporal correlation between pollutants and pollutant metrics for different time periods in the study area contributed to the inability to draw conclusions about the effect of

individual pollutant metrics on pulmonary function (Mortimer et al., 2008, 122163). The authors used a newly developed Deletion/Substitution/Addition (DSA) algorithm "to identify which pollutant metrics were most predictive of pulmonary function" (Mortimer et al., 2008, 122163). This methodology uses an exploratory process to identify the best predictive model for each outcome of interest. Focusing specifically on the exposure durations after birth, using this approach, Mortimer et al. (2008, 122163) found that exposure to CO early in life, ages 0-3 yr, was negatively associated with FEV_1/FVC, resulting in an effect size of -2.5% per IQR increase in CO.[1] Additional negative associations were observed between exposure to CO during the first 6 yr of life and FEF_{25} (-6.7%) and FEF_{25-75}/FVC (-4.8%) in children diagnosed with asthma prior to 2 yr of age. Overall, Mortimer et al. (2008, 122163) found that these effects were limited to subgroups, including African-Americans and individuals diagnosed with asthma before the age of 2 yr. It must be noted that research still needs to be conducted to validate the aforementioned results obtained using the DSA algorithm and the subsequent calculation of effect estimates using GEE because the current model could underestimate the uncertainty surrounding the associations reported (Mortimer et al., 2008, 122163). Although the authors did find associations between long-term exposure to CO and decrements in pulmonary function, they also observed high correlations between CO and NO_2, which together are markers for pollutants generated by urban combustion sources (e.g., mobile sources) (Mortimer et al., 2008, 122163).

Goss et al. (2004, 055624) also examined the effect of long-term exposure to CO on pulmonary function in a cohort of cystic fibrosis patients >6 yr of age enrolled in the Cystic Fibrosis National Patient Registry in 1999 and 2000. When examined cross-sectionally in 2000 using a multiple linear regression model, the authors found no association between CO and a reduction in FEV_1. However, Goss et al. (2004, 055624) recognize that the CO results could be influenced by measurement error and subsequently exposure misclassification.

5.5.2.2. Asthma and Asthma Symptoms

U.S.-based studies consistently reported no association between long-term exposure to CO and asthma and asthma symptoms. Wilhelm et al. (2008, 191912) and Meng et al. (2007, 093275) both examined the association between long-term exposure to air pollutants and asthma symptoms in respondents to the 2001 California Health Interview Survey (CHIS) in populations consisting of children (0-17 yr) and adults (≥ 18 yr), respectively, who resided in Los Angeles and San Diego counties. Using a cross-sectional study design, Meng et al. (2007, 093275) found no association between long-term exposure to CO and poorly controlled asthma in adults, while Wilhelm et al. (2008, 191912) reported no associations between long-term exposure CO and asthma symptoms or asthma HA and ED visits in children during the study period (i.e., 2000-2001). In an additional U.S.-based study, Goss et al. (2004, 055624) found no association (OR=1.01 [95% CI: 0.92-1.10] per 0.5 ppm increase in annual average CO concentrations) between long-term exposure to CO and pulmonary exacerbations in a national cohort of individuals with cystic fibrosis >6 yr of age.

Among studies conducted in other countries, a study conducted in Germany (Hirsch et al., 1999, 003537) and studies conducted in Taiwan (Guo et al., 1999, 010937; Hwang et al., 2005, 089454; Wang et al., 1999, 008105), all found positive associations between long-term exposure to CO and asthma or asthma symptoms in populations ranging from 6 to 16 yr old. In these studies, the authors addressed the observed associations differently. Guo et al. (1999, 010937) and Hwang et al. (2005, 089454) both concluded that it is unlikely CO directly affects the respiratory system; Hirsch et al. (1999, 003537) attributed the increase in the prevalence of cough and bronchitis to exposure to traffic-related air pollutants (i.e., NO_2, CO, and benzene); and Wang et al. (1999, 008105) did not interpret the association observed between long-term exposure to CO and adolescent asthma. Only Hwang et al. (2005, 089454) conducted a copollutant analysis and found that the asthma effects observed were robust to the inclusion of PM_{10}, SO_2 and O_3 in the model. However, this study did not include NO_X in a copollutant model, which is notable because NO_X was found to be highly correlated with CO (r = 0.88).

[1] The study did not present the IQR for CO; therefore, the effect estimates presented were not standardized using the approach mentioned previously in this ISA.

5.5.2.3. Respiratory Allergy and Other Allergic Responses

Allergy is a major contributor to asthma and upper respiratory symptoms; as a result, studies have examined the effect of air pollutants on allergic outcomes. The studies evaluated that examined the association between long-term exposure to CO and allergic outcomes were primarily conducted outside of the U.S. and Canada. A multicity study conducted in 7 Spanish cities found that the annual average concentration of CO was associated with a higher prevalence of allergic rhinitis, rhinoconjunctivitis, and atopic eczema in 6- to 7-yr-old children (Arnedo-Pena et al., 2009, 190238). NO_2 was also examined and found to be positively associated with allergic rhinitis, but, unlike CO, was negatively associated with eczema and rhinoconjunctivitis. It should be noted that in this data set CO and NO_2 concentrations were negatively correlated ($r = -0.55$). Additionally, SO_2 was positively associated with all allergic outcomes, while TSP matter was inversely associated with rhinitis and rhinoconjunctivitis. Hwang et al. (2006, 088971) and Lee et al. (2003, 049201) both examined the effect of long-term exposure to air pollutants on the prevalence of allergic rhinitis in a population of schoolchildren in Taiwan. Both studies found an association between allergic rhinitis prevalence and CO, but they also observed an association with NO_X. As a result, although Hwang et al. (2006, 088971) and Lee et al. (2003, 049201) observed an increase in the prevalence of allergic rhinitis in response to an increase in long-term CO levels, they concluded that the combination of an association being observed for both CO and NO_X can be attributed to the complex mixture of traffic-related pollutants and not necessarily CO alone. Although questions surround the associations observed between long-term exposure to CO and allergic outcomes, the results are consistent with those presented in a multicity study that examined the association between short-term exposure to CO and allergic symptoms. Moon et al. (2009, 190297) observed associations between short-term CO exposure and allergic symptoms in children in South Korea. However, allergic symptoms were also associated with other pollutants, including PM_{10}, SO_2, and NO_2, and the study did not present correlation coefficients to allow for further analysis of the results. It should be noted that toxicological experiments suggest that endogenously produced CO may play an integral part in the pathogenesis of allergic rhinitis, resulting in an additional potential pathway for CO-induced allergic outcomes (Shaoqing et al., 2008, 192384).

Allergic symptoms such as rhinitis are a direct result of allergic sensitization, which is commonly measured by skin prick testing or IgE antibody measurement. Hirsch et al. (1999, 003537), in a single-city study conducted in Dresden, Germany, observed no associations between annual average concentrations of CO, NO_2, SO_2, or O_3 and allergy assessed by skin prick testing or serum IgE measurement in schoolchildren. However, prenatal exposure to CO was associated with allergic sensitization in a cohort of 6- to 11-year-old asthmatic children in California (Mortimer et al., 2008, 187280). Skin prick tests indicated higher levels of sensitization to indoor and outdoor allergens with an increase in CO exposure during the prenatal period; the association with sensitization to outdoor allergens remained after adjustment for effect modifiers, copollutants, and other potential confounders. Mortimer et al. (2008, 187280) also found that PM_{10} exposure was associated with sensitization to indoor allergens but was not significant after adjustment. Additionally, despite strong correlations between CO and NO_2, no associations were reported with NO_2. It should be noted that these results were produced using the DSA algorithm and, as discussed previously, additional research is still needed to evaluate the use of this method in air pollution epidemiology (Mortimer et al., 2008, 122163).

5.5.2.4. Summary of Associations between Long-Term Exposure to CO and Respiratory Morbidity

To date, a limited number of studies have examined the potential association between long-term exposure to CO and respiratory morbidity. Although studies have reported positive associations for various respiratory outcomes, the limited evidence available, the new analytical methods employed, and the lack of studies that examined potential confounders of the CO-respiratory morbidity relationship, especially due to the high correlation between CO and other traffic-related pollutants, makes it difficult to attribute the associations observed to CO independent of other air pollutants.

5.5.3. Controlled Human Exposure Studies

Human clinical studies provide very little and inconsistent evidence of changes in pulmonary function following exposure to CO. In one older study, Chevalier et al. (1966, 010641) observed a significant decrease in total lung capacity following a short-term exposure to 5,000 ppm resulting in a COHb level of 4%. However, a similar study conducted at a higher CO concentration resulting in COHb levels of 17-19% found no CO-induced changes in lung volume or mechanics (Fisher et al., 1969, 012381). The 2000 CO AQCD (U.S. EPA, 2000, 000907) reported no evidence of CO-induced changes in exercise ventilation at COHb levels <15% during submaximal exercise (Koike et al., 1991, 013500). In two recent human clinical studies, exposure to CO (COHb ≈ 10%) was not found to significantly affect resting pulmonary ventilation compared with exposure to clean air under either hypoxic or hyperoxic exposure conditions (Ren et al., 2001, 193850; Vesely et al., 2004, 194000). The results of these studies demonstrate that the hypoxia- and CO_2-induced increases in pulmonary ventilation are not affected by CO. One recent study evaluated the potential anti-inflammatory effects of controlled exposures to CO in the airways of 19 individuals with COPD (Bathoorn et al., 2007, 193963). Subjects were exposed to both CO at concentrations of 100-125 ppm as well as room air for 2 h on each of 4 consecutive days. The authors reported a small decrease in sputum eosinophils, as well as a slight increase in the provocative concentration of methacholine required to cause a 20% reduction in FEV_1 following exposure to CO. Although this study appears to demonstrate some evidence of an anti-inflammatory effect of CO among subjects with COPD, it must be noted that two of these patients experienced exacerbations of COPD during or following CO exposure. A similar study found no evidence of systemic anti-inflammatory effects following exposure to higher CO concentrations (500 ppm for 1 h) in a group of healthy adults (Mayr et al., 2005, 193984).

5.5.4. Toxicological Studies

As discussed in Section 5.2.5, the work of Thom, Ischiropoulos and colleagues (Ischiropoulos et al., 1996, 079491; Thom and Ischiropoulos, 1997, 085644; Thom et al., 1997, 084337; Thom et al., 1999, 016753; Thom et al., 1999, 016757) focused on CO-mediated displacement of NO from heme-binding sites. Although the concentrations of CO used in many of their studies were far higher than ambient levels, some of this research involved more environmentally-relevant CO levels. In one study (Thom et al., 1999, 016757), 1-h exposure of rats to 50 ppm CO resulted in increased lung capillary leakage 18 h later. Increased NO was observed in the lungs by electron paramagnetic resonance during 1-h exposure to 100 ppm CO and was accompanied by increases in H_2O_2 and nitrotyrosine. All of these effects were blocked by inhibition of NOS. These results, which were partially discussed in the 2000 CO AQCD (U.S. EPA, 2000, 000907), demonstrate the potential for exogenous CO to interact with NO-mediated pathways and to lead to pathophysiological effects in the lung.

Recent work by Ghio et al. (2008, 096321) showed a disruption of cellular iron homeostasis following exposure to a low level of CO (50 ppm for 24 h) in rats. In lungs of inhalation-exposed rats, non-heme iron was significantly reduced, while lavagable iron was increased dramatically, suggesting an active removal of cellular iron. Lavagable ferritin was also increased following the CO exposure. Concurrently, liver iron levels increased, implying that the anatomical distribution of iron stores may significantly shift during/after CO exposures. These investigators were able to replicate the effect of loss of cellular iron in an in vitro model of cultured BEAS-2B cells and reported statistically significant effects at 10 ppm CO and an apparent maximal effect at 50 ppm CO (concentrations up to 500 ppm did not significantly enhance the iron loss beyond 50 ppm). Similar responses were observed for cellular ferritin. Both enhancement of iron removal and diminished iron uptake were noted in CO-exposed cells. Furthermore, decreased oxidative stress, mediator release and proliferation were noted in respiratory cells. These effects were reversible with a recovery period in fresh air. Interestingly, the in vivo exposure to CO induced mild but significant neutrophilia in the lungs compared to air-exposed rats. This finding is contrary to the concept that CO acts as an anti-inflammatory agent; however, with alterations in iron handling several potential pathways could be initiated to recruit inflammatory cells into airways. The authors pointed out that while CO derived from HO activity may have an important role in iron regulation, the nonspecific application of exogenous CO would have little capacity to discriminate between excessive and/or inappropriate iron which catalyzes oxidative stress and iron which may be required for normal homeostasis.

A chronic inhalation study by Sorhaug et al. (2006, 180414) demonstrated no alterations in lung morphology in Wistar rats exposed to 200 ppm CO for 72 wk. COHb levels were reported to be 14.7%, and morphological changes were noted in the heart as described in Section 5.2.5.2.

A recent study by Carraway et al. (2002, 026018) involved continuous exposure of rats to HH (380 torr) with or without co-exposure to CO (50 ppm) for up to 21 days. The focus of this study was on remodeling of the pulmonary vasculature. While the addition of CO to HH did not alter the thickness or diameter of vessels in the lung, there was a significant increase in the number of small (<50 μm) diameter vessels compared to control, HH-only, and CO-only exposures. Despite the greater number of vessels, the overall pulmonary vascular resistance was increased in the combined CO + HH exposure, which the authors attribute to enhancement of muscular arterioles and β-actin.

One new study found an association between increased endogenous CO and the development of allergic rhinitis (Shaoqing et al., 2008, 192384). In this model, guinea pigs which were sensitized and challenged with ovalbumin exhibited high immunoreactivity of HO-1 in the nasal mucosa and a more than doubling of blood COHb levels (measured by gas chromatography). It is not known whether the observed increase in endogenous CO resulting from ovalbumin-mediated inflammation/oxidative stress plays a role in the development of allergic rhinitis but suggests a potential mechanism by which exogenous CO could impact an allergic phenotype.

In summary, one older study (Thom et al., 1999, 016757) and two new studies (Carraway et al., 2002, 026018; Ghio et al., 2008, 096321) demonstrated effects of 50-100 ppm CO on the lung. Responses included an increase in alveolar capillary permeability, disrupted iron homeostasis, mild pulmonary inflammation, and an exacerbation of pulmonary vascular remodeling elicited by HH. These results should be considered in view of the potential for inhaled CO to interact directly with lung epithelial cells and resident macrophages. However, a chronic study involving 200 ppm CO demonstrated no changes in pulmonary morphology (Sorhaug et al., 2006, 180414).

5.5.5. Summary of Respiratory Health Effects

5.5.5.1. Short-Term Exposure to CO

New epidemiologic studies, supported by the body of literature summarized in the 2000 CO AQCD (U.S. EPA, 2000, 000907), provide evidence of positive associations between short-term exposure to CO and respiratory-related outcomes including pulmonary function, respiratory symptoms, medication use, HAs, and ED visits. The majority of the studies evaluated did not conduct extensive analyses to examine the potential influence of model selection or effect modifiers on the association between CO and respiratory morbidity. A limited number of studies examined the potential confounding effects of copollutants on CO risk estimates and found that CO risk estimates were generally robust to the inclusion of O_3, SO_2, and PM in two-pollutant models but were slightly attenuated in models with NO_2. However, the limited amount of evidence from studies that examined the effect of gaseous pollutants on CO-respiratory morbidity risk estimates in two-pollutant models, specifically NO_2, has contributed to the inability to disentangle the effects attributed to CO from the larger complex air pollution mix (particularly motor vehicle emissions), and this limits interpretation of the results observed in the epidemiologic studies evaluated. A key uncertainty in interpreting the epidemiologic studies evaluated is the biological mechanism(s) that could explain the effect of CO on respiratory health. Animal toxicological studies, however, provide some evidence that short-term exposure to CO (50-100 ppm) can cause oxidative injury and inflammation and alter pulmonary vascular remodeling. Controlled human exposure studies have not extensively examined the effect of short-term exposure to CO on respiratory morbidity, with a very limited number of studies reporting inconsistent effects of CO on pulmonary function. Although these controlled human exposure studies do not provide evidence to support CO-related respiratory health effects, epidemiologic studies show positive associations for CO-induced lung-related outcomes and animal toxicological studies demonstrate the potential for an underlying biological mechanism, which together provide evidence that is **suggestive of a causal relationship between relevant short-term exposures to CO and respiratory morbidity.**

5.5.5.2. Long-Term Exposure to CO

Currently, only a few studies have been conducted that examine the association between long-term exposure to CO and respiratory morbidity including allergy. Although some studies did observe associations between long-term exposure to CO and respiratory health outcomes, key uncertainties still exist. These uncertainties include: the lack of replication and validation studies to evaluate new methodologies (i.e., Deletion/Substitution/Addition (DSA) algorithm) that have been used to examine the association between long-term exposure to CO and respiratory health effects; whether the respiratory health effects observed in response to long-term exposure to CO can be explained by the proposed biological mechanisms; and the lack of copollutant analyses to disentangle the respiratory effects associated with CO due to its high correlation with NO_2 and other combustion-related pollutants. Overall, the evidence available is **inadequate to conclude that a causal relationship exists between relevant long-term exposures to CO and respiratory morbidity.**

5.6. Mortality

5.6.1. Epidemiologic Studies with Short-Term Exposure to CO

Epidemiologic studies have traditionally focused on mortality effects associated with exposure to PM and O_3, resulting in a limited number of studies that have conducted extended analysis to examine the potential influence of model selection, effect modifiers, or confounders on the association between CO and mortality. This has contributed to the inability to formulate a clear understanding of the association between short-term exposure to CO and mortality. This section summarizes the main findings of the 2000 CO AQCD (U.S. EPA, 2000, 000907) and evaluates the newly available information on the relationship between short-term exposure to CO and daily mortality in an effort to disentangle the CO-mortality effect from those effects attributed to other criteria air pollutants.

5.6.1.1. Summary of Findings from 2000 CO AQCD

The 2000 CO AQCD (U.S. EPA, 2000, 000907) examined the association between short-term exposure to CO and mortality through the analysis of primarily single-city time-series studies, with additional evidence from one multicity study which included 11 Canadian cities. While the results presented by these studies did provide suggestive evidence that an association exists between CO and mortality, the AQCD concluded that inadequate evidence existed to infer a causal association between mortality and short-term exposure to ambient concentrations of CO. Multiple uncertainties were identified in the epidemiologic literature that contributed to this conclusion, which were discussed in Section 5.2.1.

The majority of the recent time-series mortality studies, as mentioned previously, have not extensively examined the CO-mortality relationship. As such, CO has usually been considered as one of the potential confounding copollutants in air pollution epidemiologic studies. Given the limitation that most of these studies were not conducted to examine CO, the goal of this review is to evaluate the CO-mortality association and specifically the consistency of associations across studies, along with evidence of confounding and effect modification.

5.6.1.2. Multicity Studies

The following sections evaluate the recent literature that examined the association between short-term exposure to CO and mortality, and, in addition, discuss newly available information with regard to the issues specific to CO mentioned above. This evaluation focuses primarily on multicity studies because they provide a more representative sample of potential CO-related mortality effects and especially useful information by analyzing data from multiple cities using a consistent method,

and thus avoiding potential publication bias.[1] Table 5-22 details the multicity studies evaluated along with the mean CO concentrations reported in each study.

Table 5-22. Range of CO concentrations reported in multicity studies that examine mortality effects associated with short-term exposure to CO.

Study	Location	Years	Averaging Time	Mean Concentration (ppm)	Range of Mean Concentrations Across Cities (ppm)
Dominici et al. (2003, 056116; 2005, 087912); Reanalysis of Samet et al. (2000, 156939)	82 US cities[a] (NMMAPS)	1987-1994	24-h avg	1.02	Baton Rouge = 0.43 Spokane = 2.19
Burnett et al. (2004, 086247)	12 Canadian cities	1981-1999	24-h avg	1.02	Winnipeg = 0.58 Toronto = 1.31
Samoli et al. (2007, 098420)[b]	19 European cities (APHEA2)	1990-1997[c]	8-h max	2.12	Basel = 0.52 Athens = 5.3

[a]The study actually consisted of 90 U.S. cities, but only 82 had CO data.
[b]This study presented CO concentrations in the units mg/m^3. The concentrations were converted to ppm using the conversion factor 1 ppm = 1.15 mg/m^3, which assumes standard atmosphere and temperature.
[c]The study period varied from city to city. These years represent the total years in which data was collected across all cities.

National Morbidity, Mortality, and Air Pollution Study of 90 U.S. Cities

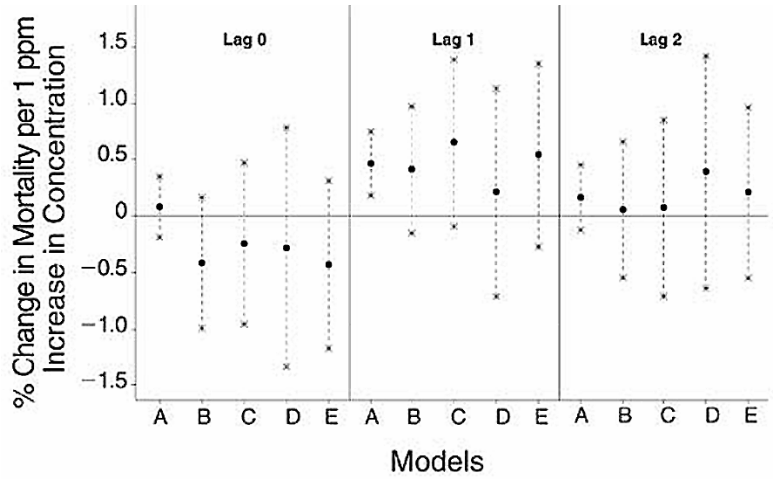
The time-series analysis of the 90 largest U.S. cities (82 cities for CO) in the National Morbidity, Mortality, and Air Pollution Study (NMMAPS) (Dominici et al., 2003, 056116; Dominici et al., 2005, 087912; a reanalysis of Samet et al., 2000, 156939) is by far the largest multicity study conducted to date to investigate the mortality effects of air pollution; however, the study primarily focused on PM_{10}. The range in 24-h avg CO concentrations in a subset of the largest 20 cities (by population size) was 0.66 ppm (Detroit, MI) to 2.04 ppm (New York City). The analysis in the original report used GAM with default convergence criteria. In response to the bias observed in the estimates generated using GAM models with default convergence criteria (Dominici et al., 2002, 030458), Dominici et al. (2003, 056116; 2005, 087912)(reanalysis of Samet et al. (2000, 156939) conducted a reanalysis of the original data using GAM with stringent convergence criteria as well as GLM.

Focusing on the results obtained using GLM, PM_{10} and O_3 (in summer) appeared to be more strongly associated with mortality than the other gaseous pollutants. The authors stated that the results did not indicate associations between CO, SO_2, or NO_2, and total (nonaccidental) mortality. However, as with PM_{10}, the gaseous pollutants CO, SO_2, and NO_2 each showed the strongest association at a 1-day lag (for O_3, a 0-day lag). Figure 5-17 presents the total mortality risk estimates for CO from Dominici et al. (2003, 056116). The authors found a mortality risk estimate of 0.23% (95% PI: 0.09-0.36) per 0.5 ppm increase in 24-h avg CO for a 1-day lag in a single-pollutant model. The inclusion of PM_{10} or PM_{10} and O_3 in the model did not reduce CO risk estimates. However, the confidence intervals were wider in the multipollutant models; however, this could be attributed to: (1) PM_{10} data in many of the cities being collected every 6th day as opposed to daily data for gaseous pollutants; and (2) O_3 being collected in some cities only during warm months. The addition of NO_2 (along with PM_{10}) to the model resulted in a reduced CO risk estimate. Some caution is required when interpreting this apparent reduction because a smaller number of cities (57 cities[2]) were available for the CO multipollutant analysis with PM_{10} and NO_2 compared to the single-pollutant CO analysis (82 cities). However, most of the 32 cities that were excluded due to the lack of NO_2 data were some of the least populated cities. Thus, the difference in the number of cities in the multi- and single-pollutant analyses is unlikely to be the underlying cause for the reduction in the

[1] To compare studies in this section that used different averaging times, effects estimates were standardized to the following: 0.5 ppm for studies that used 24-h avg concentrations and 0.75 ppm for studies that used max 8-h avg concentrations. These standardized values represent the range of current mean ambient concentrations across the U.S.

[2] One city was excluded from the multipollutant analysis because it contained NO_2 data but did not contain CO data.

CO risk estimate in the CO multipollutant analysis with PM_{10} and NO_2. In comparison to the PM_{10} risk estimates which were not reduced in multipollutant models, the CO risk estimates from multipollutant models indicate less consistent associations with mortality.



Source: Reprinted with Permission of HEI from Dominici et al.(2003, 056116)

Figure 5-17. Posterior means and 95% posterior intervals of national average estimates for CO effects on total (nonaccidental) mortality at lags 0, 1, and 2 within sets of the 90 U.S. cities with available pollutant data. Models A = CO alone; B = CO + PM_{10}; C = CO + PM_{10} + O_3; D = CO + PM_{10} + NO_2; E = CO + PM_{10} + SO_2.

Canadian Multicity Studies

Since the 2000 CO AQCD (U.S. EPA, 2000, 000907), two Canadian multicity studies have been published that examined the association between mortality and short-term exposure to air pollutants: (1) an analysis of PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, and gaseous pollutants in 8 cities from 1986 to 1996 (Burnett et al., 2000, 010273); and (2) an analysis of PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, and gaseous pollutants in 12 cities from 1981 to 1999 (Burnett et al., 2004, 086247). The 2000 study (Burnett and Goldberg, 2003, 042798) utilized GAM with default convergence criteria and, upon reanalysis, only examined PM indices.

Burnett et al. (2004, 086247) is the most extensive Canadian multicity study conducted to date, both in terms of the length of the study and the number of cities covered. This study focused primarily on NO_2-mortality associations because it was found to be the best predictor of fluctuations in mortality among the air pollutants examined (NO_2, O_3, SO_2, CO, $PM_{2.5}$, and $PM_{10-2.5}$); however, the study did present single- and copollutant results for all pollutants included in the analysis. The mean CO concentrations reported by Burnett et al. (2004, 086247) are similar to those reported in NMMAPS (Table 5-22).

Burnett et al. (2004, 086247) examined the effect of short-term exposure to CO on total (nonaccidental) mortality. The authors found the strongest mortality association at lag 1-day for CO, SO_2, $PM_{2.5}$, $PM_{10-2.5}$, PM_{10} (arithmetic addition of $PM_{2.5}$ and $PM_{10-2.5}$), and CoH, whereas for NO_2, the strongest association was for the 3-day ma (i.e., average of 0-, 1-, and 2-day lags), and for O_3, it was the 2-day ma. In this study, Burnett et al. (2004, 086247) used 24-h avg pollutant concentrations because these values showed stronger associations with mortality than the daily 1-h max values for all of the gaseous pollutants and CoH but not for O_3. In a single-pollutant model, the CO risk estimate for total (nonaccidental) mortality was 0.33% (95% CI: 0.12-0.54) per 0.5 ppm increase in 24-h avg CO at lag 1. After adjusting for NO_2, the CO risk estimate was reduced to 0.04% (95% CI: -0.19 to 0.26), while the NO_2 risk estimate was only slightly affected (increased from 2.25 to 2.35%) when including CO in the model. In this analysis, a copollutant model including both CO

and PM was not presented. The results presented in this Canadian multicity study and NMMAPS are similar in that the CO risk estimates appeared to be sensitive to the addition of NO_2 in the regression model. However, interpretation of these results requires some caution because: (1) NO_2 tends to have a more spatially uniform distribution within a city compared to CO; (2) CO and NO_2 share common sources (e.g., traffic); and (3) CO and NO_2 are often moderately to highly correlated.

Air Pollution and Health: A European Approach

Most of the Air Pollution and Health: A European Approach (APHEA) analyses have focused on the mortality effects of PM (PM_{10} and BS), SO_2, NO_2, and O_3, but not CO. In addition, some of the analyses have not even considered CO as a potential confounder, such as the extended analysis (APHEA2) of PM (Katsouyanni et al., 2001, 019008) and NO_2. Gryparis et al. (2004, 057276) did consider CO as a potential confounder in an analysis of O_3 and found that the addition of CO increased O_3 mortality risk estimates both in the summer and winter, although the number of cities included in the copollutant model were reduced from 21 to 19. However, the study did not present CO risk estimates. Unlike other APHEA studies (or the NMMAPS and Canadian multicity studies), the Samoli et al. (2007, 098420) analysis focused specifically on CO.

Samoli et al. (2007, 098420) investigated the effect of short-term exposure to CO on total (nonaccidental) and cardiovascular mortality in 19 European cities participating in the APHEA2 project by using a two-stage analysis to examine city-specific effects and potential sources of heterogeneity in CO-mortality risk estimates. The mean levels of the max 8-h avg CO concentration in this study ranged from 0.52 ppm (Basel, Switzerland, and The Netherlands) to 5.3 ppm (Athens, Greece). The max 8-h avg CO concentration across all cities in the APHEA2 study of 2.12 ppm is higher than the estimated max 8-h avg CO concentrations reported for the U.S. cities examined in Dominici et al. (2003, 056116; 2005, 087912) and the Canadian cities examined in Burnett et al. (2004, 086247) of 1.53 ppm.[1] In APHEA cities, the correlation between CO and BS (r = 0.67-0.82) was higher than the correlation between CO and PM_{10} (r = 0.16-0.70) or CO and 1-h max NO_2 (r = 0.03-0.68).

To examine the CO-mortality relationship, Samoli et al. (2007, 098420) conducted a time-series analysis of individual cities following the revised APHEA2 protocol.[2] The primary results presented by the authors are from a sensitivity analysis that used two alternative methods to select the extent of adjustment for temporal confounding. These methods consisted of: (1) confining the extent of smoothing to 8 df/yr; and (2) selecting the appropriate extent of smoothing through minimization of the absolute value of the sum of partial autocorrelation functions (PACF) of the residuals, which resulted in the analysis using on average 5 df/yr for total (nonaccidental) mortality and 4 df/yr for cardiovascular mortality. The authors also conducted copollutant analyses using PM_{10}, BS, SO_2, NO_2, or O_3 (1 h). In the second stage model, Samoli et al. (2007, 098420) examined heterogeneity in CO risk estimates between cities by regressing risk estimates from individual cities on potential effect modifiers including: (1) the air pollution level and mix in each city (i.e., mean levels of pollutants, ratio PM_{10}/NO_2); (2) the exposure (number of CO monitors, correlation between monitors' measurements); (3) variables describing the health status of the population (e.g., crude mortality rate);(4) the geographic area (northern, western, and central-eastern European cities); and (5) climatic conditions (mean temperature and relative humidity levels).

Samoli et al. (2007, 098420) found that CO was associated with total (nonaccidental) and cardiovascular mortality. The primary results represent the combined random effects estimate for a 0.75 ppm increase in max 8-h avg CO concentrations for the average of 0- and 1-day lag for total (nonaccidental) mortality (1.03% [95% CI: 0.55-1.53]) and for cardiovascular mortality (1.08% [95% CI: 0.25-1.90]). These results were obtained using PACF to choose the extent of adjustment for temporal trends. Although the results obtained using PACF are insightful, the use of 8 df/yr would have been more consistent with the NMMAPS model (7 df/yr) and would have allowed for a more accurate comparison of the results between APHEA2 and NMMAPS. The corresponding risk estimates obtained using the 8 df/yr model are 0.57% (95% CI: 0.23-0.91) for total (nonaccidental) mortality and 0.70% (95% CI: 0.31-1.09) for cardiovascular mortality. In the sensitivity analysis,

[1] The max 8-h avg concentration for the Dominici et al. (2003, 056116) and Burnett et al. (2004, 086247) studies was calculated using the conversion factor of 2:3 to convert 24-h avg concentrations to max 8-h avg concentrations.

[2] The APHEA2 protocol used a Poisson GAM model with penalized splines as implemented in the statistical package R.

Samoli et al. (2007, 098420) used 8 or 12 df/yr to adjust for temporal confounding. Both approaches resulted in similar risk estimates, but using PACF to choose the extent of smoothing separately in each city generally resulted in larger CO risk estimates (by ~50-80%). This can be attributed to the smaller number of df/yr used in the model (on average 5 df/yr for total [nonaccidental] mortality and 4 df/yr for cardiovascular mortality), which increases the magnitude of the effect and the amount of observed heterogeneity (Samoli et al., 2007, 098420).

During the examination of the results obtained from the copollutant models, the authors noted that there was indication of confounding of CO risk estimates by BS and NO_2 but not PM_{10}. These results are consistent with CO, BS, and NO_2 being part of the traffic-pollution mixture, and PM_{10} likely including secondary aerosols that do not correlate well with traffic-derived pollution. The risk estimates from the model using 8 df/yr that included NO_2 were 0.26% (-0.09 to 0.61) for total (nonaccidental) mortality and 0.37% (-0.05 to 0.80) for cardiovascular mortality. Thus, the inclusion of NO_2 in the model nearly halved the CO risk estimates (whereas the NO_2 risk estimate was not sensitive to the inclusion of CO in the model). CO risk estimates were reduced by a similar magnitude when including BS in the model. Overall, the sensitivity of CO risk estimates to the inclusion of NO_2 in the model is consistent with the results presented in NMMAPS (Dominici et al., 2003, 056116) and the Canadian multicity study (Burnett et al., 2004, 086247).

In the second-stage model, Samoli et al. (2007, 098420) found that geographic region was the most significant effect modifier, while the other effect modifiers (mentioned above) did not result in strong associations. Effects were primarily found in western and southern European cities and were larger in cities where the standardized mortality rate was lower. Earlier APHEA studies also reported a regional pattern of air pollution associations for BS and SO_2 and found that western cities showed stronger associations than eastern cities. However, the heterogeneity in CO risk estimates by geographic region does not provide specific information to evaluate the CO-mortality association.

An ancillary analysis conducted by Samoli et al. (2007, 098420) examined the possible presence of a CO threshold. The authors compared city-specific models to the threshold model, which consisted of thresholds at 0.5 mg/m^3 (0.43 ppm) increments. Samoli et al. (2007, 098420) then computed the deviance between the two models and summed the deviances for a given threshold over all cities. While the minimum deviance suggested a potential threshold of 0.43 ppm (the lowest threshold examined), the comparison with the linear no-threshold model indicated very weak evidence (p-value >0.9) for a threshold. However, determining the presence of a threshold at the very low range of CO concentrations (i.e., 0.43 ppm) in this data set is challenging because in 7 of the 19 European cities examined, the lowest 10% of the CO distribution was at or above 2 mg/m^3 (1.74 ppm).

In summary, the APHEA2 analysis of CO in 19 cities found an association between CO and total (nonaccidental) and cardiovascular mortality in single-pollutant models, but the associations were substantially reduced when NO_2 or BS was included in copollutant models. The evidence for potential confounding of CO risk estimates by NO_2 is consistent with the findings from NMMAPS and the Canadian 12-city study. In addition, Samoli et al. (2007, 098420) found that geographic region was a potential effect modifier, but such geographic heterogeneity is not specific to CO, based on previously conducted APHEA studies. Finally, examination of the CO concentration-response relationship found very weak evidence of a CO threshold, which requires further investigation.

Other European Multicity Studies

An additional European multicity study was conducted by Biggeri et al. (2005, 087395) in eight Italian cities. The authors examined the effect of short-term exposure to CO on mortality in single-pollutant models using a time-series approach. In this analysis, all of the pollutants showed positive associations with the mortality endpoints examined. However, copollutant models were not examined, and the correlations among the pollutants were not presented; therefore, it is unclear if the observed associations are shared or confounded.

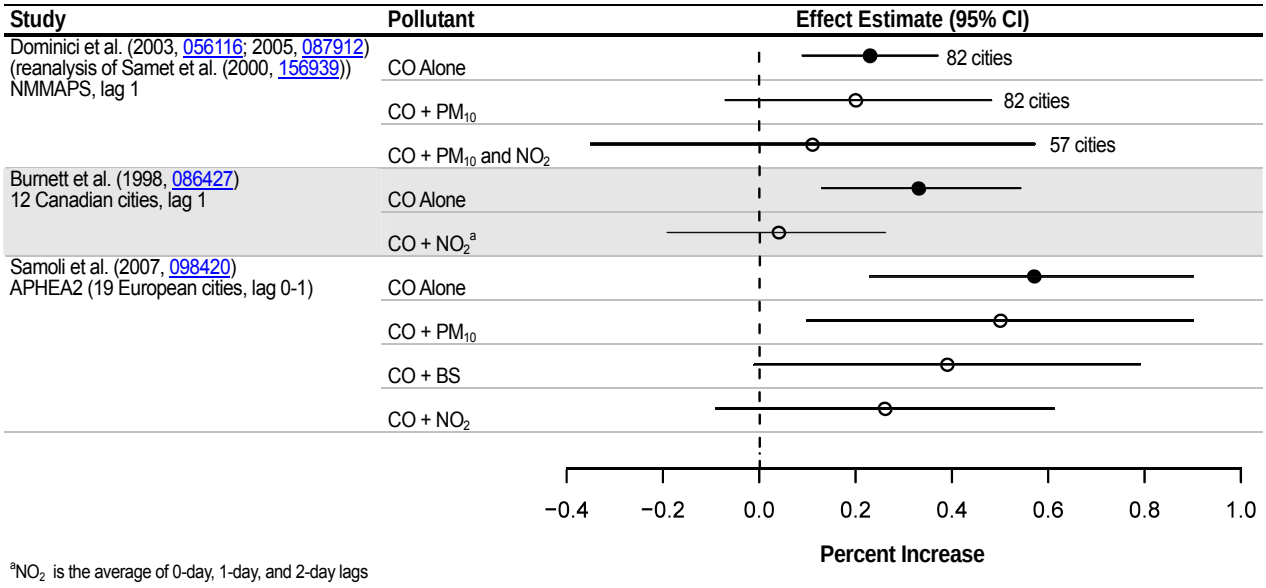
Summary of Multicity Studies

In summary, the mortality risk estimates from single-pollutant models are comparable for the NMMAPS and Canadian 12-city studies, 0.23% and 0.33%, respectively, with the estimate from the

APHEA2 study being slightly larger (0.57%) (Figure 5-18). In both the NMMAPS and Canadian studies, a 1-day lag showed the strongest association; however, the APHEA2 study used an a priori exposure window (i.e., average of 0- and 1-day lags), which has been found to be the exposure window most strongly associated with mortality in PM analyses.

The APHEA2 risk estimates presented in Figure 5-18 are from a model that used a fixed amount of smoothing to adjust for temporal confounding (8 df/yr), which is similar to that used in the NMMAPS study (7 df/yr). However, the APHEA2 sensitivity analysis suggested an approximate 50-80% difference in CO risk estimates between the models that used 8 or 12 df/yr and the models that used minimization of the absolute value of the sum of PACF of the residuals as a criterion to choose the smoothing parameters. Thus, some model uncertainty likely influences the range of CO risk estimates obtained from the studies evaluated.

The CO risk estimates from the aforementioned studies are also consistently sensitive to the inclusion of NO_2 in a copollutant model (0.11, 0.03, and 0.26%, for the NMMAPS, Canadian 12-city study, and APHEA2, respectively). Thus, these results suggest confounding by NO_2. However, this interpretation is further complicated because as with CO, NO_2 itself may be an indicator of combustion sources, such as traffic.



[a]NO_2 is the average of 0-day, 1-day, and 2-day lags

Figure 5-18. Summary of percent increase in total (nonaccidental) mortality for short-term exposure to CO from multicity studies. Estimates were standardized to 0.5 ppm and 0.75 ppm for studies that used 24-h avg CO and max 8-h avg CO exposure metrics, respectively.

5.6.1.3. Meta-Analysis of All Criteria Pollutants

Stieb et al. (2002, 025205) reviewed the 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. Because many of the studies reviewed in the 2000 analysis used GAM with default convergence criteria, Stieb et al. (2003, 056908) updated the estimates from the meta-analysis by separating the GAM versus non-GAM studies. In this meta-analysis, the authors also presented separate combined estimates for single- and multipollutant models. Overall, there were more GAM estimates than non-GAM estimates for all of the pollutants except SO_2. For CO, 4 single-pollutant model risk estimates were identified, resulting in a combined estimate of 3.18% (95% CI: 0.76-5.66) per 0.5 ppm increase in 24-h avg CO, and only 1 multipollutant model risk estimate (0.00% [95% CI: -1.71 to 1.74]) from the non-GAM studies. Thus, for CO, this study did not provide useful meta-estimates because the number of studies that contributed to the combined estimates for CO was small.

5.6.1.4. Single-City Studies

In addition to the multicity studies discussed above, there have also been several single-city U.S.- and Canadian-based time-series mortality studies that examined CO. The single-city studies, similar to the multicity studies, often focused on the PM-mortality association but also provided additional information that is not available in the multicity studies. Because the sample size used in each single-city study is small and subsequently results in wide confidence intervals, a quantitative comparison of the results from single- and multicity studies is difficult. In addition, some studies do not present CO results quantitatively, adding to the inability to adequately compare studies. Table 5-23 lists the single-city studies evaluated along with the mean CO concentrations reported in each study.

Table 5-23. Range of CO concentrations reported in single-city studies that examine mortality effects associated with short-term exposure to CO.

Study	Location	Years	Averaging Time	Mean Concentration (ppm)	Upper Percentile Concentrations (ppm)
De Leon et al. (2003, 055688)	New York, NY	1985-1994	24-h avg	2.45	95th: 4.04
Klemm et al. (2004, 056585)	Atlanta, GA	1998-2000	1-h max	1.31	Max: 7.40 75th: 1.66
Vedal et al. (2003, 039044)[a]	Vancouver, BC, Can	1994-1996	24-h avg	0.5	Max: 1.9 90th: 0.9
Villeneuve et al. (2003, 055051)	Vancouver, BC, Can	1986-1999	24-h avg	1.0	Max: 4.9 90th: 1.6
Goldberg et al. (2003, 035202)	Montreal, Quebec, Can	1984-1993	24-h avg	0.8	Max: 5.1 75th: 1.0
Hoek et al. (2000, 010350; 2001, 016550); Reanalyzed by Hoek (2003, 042818)	The Netherlands	1986-1994	24-h avg	Entire Country: 0.46 Four Major Cities: 0.59	Max. Entire Country: 2.6 Four Major Cities: 4.6

[a]Study reported median CO concentrations.

Single-City Studies Conducted in the United States

De Leon et al. (2003, 055688) focused on the role of contributing respiratory diseases on the association between air pollution (i.e., PM_{10}, O_3, NO_2, SO_2, and CO) and primary nonrespiratory mortality (circulatory and cancer) in New York City, NY, during the period 1985-1994. This study only presented risk estimates graphically for each of the pollutants analyzed, except PM_{10}. In single-pollutant models, PM_{10}, CO, SO_2, and NO_2 all showed the same pattern of association with circulatory mortality for individuals ≥ 75 yr, indicating a larger risk of death in individuals with contributing respiratory diseases compared to those without. In two-pollutant models, PM_{10} and CO risk estimates were reduced but each remained significantly positive.

Klemm et al. (2004, 056585) analyzed 15 air pollutants for their associations with mortality in Atlanta, GA, for a 2-yr period starting in August 1998. These pollutants included $PM_{2.5}$, $PM_{10-2.5}$, UFP surface area and counts, aerosol acidity, EC, OC, SO_4^{2-}, O_3, CO, SO_2, and NO_2. This study presented risk estimates using three levels of smoothing (quarterly, monthly, and biweekly knots) for temporal trend adjustment and suggested that the risk estimates were rather sensitive to the extent of smoothing. It should be noted that temporal smoothing using biweekly knots is a more aggressive modeling approach than the degrees-of-freedom approach used by most studies. In the single-pollutant models for nonaccidental mortality, the strongest association, which was also statistically significant, was found for $PM_{2.5}$. CO, SO_4^{2-}, and $PM_{10-2.5}$ also showed positive associations with nonaccidental mortality (CO: Quarterly knots and Monthly Knots $\beta = 0.00002$ [SE = 0.00001]; Biweekly knots $\beta = 0.00001$ [SE = 0.00002]). However, CO was significantly associated with circulatory mortality in older adults (≥ 65 yr), and these associations remained when $PM_{2.5}$ was included in the model (results were presented graphically).

Single-City Studies Conducted in Canada

Vedal et al. (2003, 039044) examined the association between short-term exposure to "low levels" of air pollution (i.e., PM_{10}, O_3, NO_2, SO_2, and CO) and daily mortality in Vancouver, British Columbia, Canada, for the years 1994-1996. In this analysis, all of the risk estimates were presented graphically; however, the results suggested that O_3 in the summer and NO_2 in the winter showed the strongest associations with mortality. Vedal et al. (2003, 039044) found that CO was positively but not significantly associated with mortality. Additionally, the association between short-term exposure to NO_2 and mortality was found to be consistent with the results from the Canadian multicity study conducted by Burnett et al. (2004, 086247).

Villeneuve et al. (2003, 055051) also conducted an analysis using data from Vancouver, Canada, using a cohort of 550,000 individuals whose vital status was ascertained between 1986 and 1999. In this study, $PM_{2.5}$, $PM_{10-2.5}$, TSP, CoH, PM_{10}, SO_4^{2-}, O_3, CO, SO_2, and NO_2 were examined for their associations with all-cause (nonaccidental), cardiovascular, and respiratory mortality. When examining the association between gaseous pollutants and all-cause (nonaccidental) mortality in this data set, NO_2 and SO_2 showed the strongest associations, while the association between CO and all-cause mortality were generally weaker than those for NO_2 and SO_2. For cardiovascular mortality, SO_2 risk estimates were smaller than those for NO_2 or CO, while for respiratory mortality, SO_2 showed the strongest associations. However, the wider confidence intervals for these categories and the smaller daily counts make it difficult to assess CO associations with cause-specific mortality outcomes.

Goldberg et al. (2003, 035202) contrasted associations between air pollution and mortality in individuals with underlying CHF versus mortality in individuals who were identified as having CHF 1 yr prior to death based on information from the universal health insurance plan in Montreal, Quebec, Canada, during the period 1984-1993. In this study, Goldberg et al. (2003, 035202) examined associations between $PM_{2.5}$, CoH, SO_4^{2-}, O_3, CO, SO_2, and NO_2, and mortality. The authors found no association between any of the air pollutants and mortality with underlying CHF. However, Goldberg et al. (2003, 035202) found positive associations between air pollution and mortality in individuals diagnosed with CHF 1 yr prior to death. Of the air pollutants examined, CoH, NO_2, and SO_2 were most consistently associated with mortality for ages 65 yr and older, while CO showed positive but weaker associations compared to these three pollutants.

Single-City Studies Conducted in Other Countries

Of the epidemiologic studies conducted in other countries that examine the association between short-term exposure to CO and mortality, only those studies conducted in European countries that have CO levels comparable to the U.S. were evaluated. However, because Samoli et al. (2007, 098420) conducted a multicity study of European cities that focused on short-term exposure to CO, there are only a few single-city studies that provide additional information, specifically those studies conducted in The Netherlands. The Netherland studies were evaluated because they provide risk estimates for multiple pollutants and cause-specific mortality and consisted of relatively large sample sizes (i.e., the mortality time-series of the entire country was analyzed).

Hoek et al. (2000, 010350) (reanalyzed by Hoek) (2003, 042818) examined associations between air pollution and all-cause (nonaccidental), cardiovascular, COPD, and pneumonia deaths in the entire Netherlands, the four major cities combined, and the entire country minus the four major cities for the period 1986-1994. The air pollutants analyzed included BS, PM_{10}, O_3, NO_2, SO_2, CO, SO_4^{2-} and NO_3^-. In the single-pollutant models, all of the pollutants were significantly associated with nonaccidental mortality at lag 1-day and 0-6 days when using the entire Netherlands data set. In the two-pollutant model, CO risk estimates were reduced to null when PM_{10}, BS, SO_4^{2-} and NO_3^- were included in the model, while the risk estimates for these copollutants remained significantly positive. BS, CO, and NO_2 were highly correlated ($r > 0.85$) in this data set, and the authors noted "all these pollutants should be interpreted as indicators for motorized traffic emissions" (Hoek et al., 2000, 010350). The authors found that O_3 showed the most consistent and independent associations with mortality and that the risk estimates for all of the pollutants were substantially higher in the summer months than in the winter months. Pneumonia deaths showed the largest risk estimates for most pollutants including CO. The result from the Hoek et al. (2000, 010350) study is somewhat in

contrast to the result from the Samoli et al. (2007, 098420) multicity study in that in the Hoek et al. (2000, 010350) analysis, CO was more sensitive to the addition of PM indices in copollutant models. This may be due to the high correlation between CO and PM indices in The Netherlands.

Hoek et al. (2001, 016550) (reanalysis by Hoek) (2003, 042818) analyzed The Netherlands data using more specific cardiovascular causes of death: MI and other IHD, arrhythmia, heart failure, cerebrovascular mortality, and embolism/thrombosis. In this analysis, the authors analyzed O_3, BS, PM_{10}, CO, SO_2, and NO_2 in only single-pollutant models. For all of the pollutants, risk estimates were larger for arrhythmia, heart failure, and cerebrovascular mortality than for the combined cardiovascular mortality outcome. Thus, the results suggested larger impacts of air pollution on more specific cardiovascular causes; however, it is difficult to distinguish the effects of each pollutant from the larger air-pollution mixture.

5.6.1.5. Summary of Mortality and Short-Term Exposure to CO

The recently available multicity studies, which consist of larger sample sizes, along with the single-city studies evaluated reported associations that are generally consistent with the results of the studies evaluated in the 2000 CO AQCD (U.S. EPA, 2000, 000907). However, to date the majority of the literature has not conducted extensive analyses to examine the potential influence of model selection, effect modifiers, or confounders on the association between CO and mortality.

The multicity studies reported comparable CO mortality risk estimates for total (nonaccidental) mortality, with the APHEA2 European multicity study (Samoli et al., 2007, 098420) showing slightly higher estimates for cardiovascular mortality in single-pollutant models. However, when examining potential confounding by copollutants these studies consistently showed that, although CO mortality risk estimates remained positive, they were reduced when NO_2 was included in the model. But this observation may not be confounding in the usual sense in that NO_2 may also be an indicator of other pollutants or pollution sources (e.g., traffic).

Of the studies evaluated, only the APHEA2 study focused specifically on the CO-mortality association (Samoli et al., 2007, 098420), and, in the process, examined: (1) model sensitivity; (2) the CO-mortality concentration-response (C-R) relationship; and (3) potential effect modifiers of CO mortality risk estimates. The sensitivity analysis indicated an approximate 50-80% difference in CO risk estimates from a reasonable range of alternative models, which suggests that some model uncertainty likely influences the range of CO mortality risk estimates obtained in the studies evaluated. The examination of the CO-mortality concentration-response relationship found very weak evidence for a CO threshold at 0.5 mg/m^3 (0.43 ppm). Finally, when examining a variety of city-specific variables to identify potential effect modifiers of the CO-mortality relationship, the APHEA2 study found that geographic region explained most of the heterogeneity in CO mortality risk estimates.

The results from the single-city studies are generally consistent with the multicity studies in that some evidence of a positive association was found for mortality upon short-term exposure to CO. However, the CO-mortality associations were often but not always attenuated when copollutants were included in the regression models. In addition, limited evidence was available to identify cause-specific mortality outcomes (e.g., cardiovascular causes of death) associated with short-term exposure to CO.

The evidence from the recent multi- and single-city studies suggests that an association between short-term exposure to CO and mortality exists. But limited evidence is available to evaluate cause-specific mortality outcomes associated with CO exposure. In addition, the attenuation of CO risk estimates which was often observed in copollutant models contributes to the uncertainty as to whether CO is acting alone or as an indicator for other combustion-related pollutants. Overall, the epidemiologic evidence is **suggestive of a causal relationship between relevant short-term exposures to CO and mortality.**

5.6.2. Epidemiologic Studies with Long-Term Exposure to CO

The 2000 CO AQCD (U.S. EPA, 2000, 000907) did not evaluate the association between long-term exposure to CO and mortality because there were no studies at the time that examined this relationship. Since then there have been several new studies that examined the association between long-term exposure to CO and mortality. It should be noted, however, that these studies focused

primarily on PM, and that CO was only considered in these studies as a potential confounder. Therefore, the information available from these new long-term exposure studies is somewhat limited, especially in comparison to that for PM. Table 5-24 lists the U.S.-based studies evaluated that examined the association between long-term exposure to CO and mortality, along with the mean CO concentrations reported in each study.

Table 5-24. Range of CO concentrations reported in U.S.-based studies that examine mortality effects associated with long-term exposure to CO.

Study	Location	Years	Averaging Time	Mean Concentration (ppm)	Upper Percentile Concentrations (ppm)
Jerrett et al. (2003, 087380)	107 US cities	1980	Annual avg	1.56	Maximum: 3.95
Pope et al. (2002, 024689)	1980: 113 US cities 1982-1998: 122 US cities	1980 1982-1998	Annual avg	1980: 1.7 1982-1998: 1.1	NR
Krewski et al. (2009, 191193)	108 US cities	1980	Annual avg	1.68	75th: 2.13 90th: 2.58 95th: 3.05 Maximum: 3.95
Miller et al. (2007, 090130)	36 US cities	2000	Annual avg	NR	NR
Lipfert et al. (2000, 004087)	US	1960-1974 1975-1981 1982-1988 1989-1996	Mean annual 95th percentile of hourly CO values	1960-1974: 10.82 1975-1981: 7.64 1982-1988: 3.42 1989-1996: 2.36	1960-1974 50th: 9.31 Maximum: 35.3 1975-1981 50th: 7.04 Maximum: 22.4 1982-1988 50th: 3.33 Maximum: 15.20 1989-1996 50th: 2.30 Maximum: 7.10
Lipfert et al. (2006, 088756)	US	1999-2001	Mean annual 95th percentile of hourly CO values	1.63	Maximum: 6.7
Lipfert et al. (2006, 088218)	US	1976-1981 1982-1988 1989-1996 1997-2001	Mean annual 95th percentile of hourly CO values	1976-1981: 7.6 1982-1988: 3.4 1989-1996: 2.4 1997-2001: 1.6	NR
Lipfert and Morris (2002, 019217)	1960-1969: 44 US counties 1970-1974: 206 US counties 1979-1981: 272 US counties 1989-1991: 246 US counties 1995-1997: 261 US counties	1960-1969 1970-1974 1979-1981 1989-1991 1995-1997	Mean annual 95th percentile of hourly CO values	1960-1969: 13.8 1970-1974: 9.64 1979-1981: 5.90 1989-1991: 2.69 1995-1997: 1.72	NR

5.6.2.1. U.S. Cohort Studies

American Cancer Society Cohort Studies

Pope et al. (1995, 045159) investigated associations between long-term exposure to PM and mortality outcomes in the ACS cohort. In this study, 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 SO_4^{2-} were associated with total (nonaccidental), cardiopulmonary, and lung cancer mortality, but not with mortality for all other causes (i.e., nonaccidental minus cardiopulmonary and lung cancer). Gaseous pollutants were not analyzed in Pope et al. (1995, 045159). Jerrett et al. (2003,

087380), using data from Krewski et al. (2000, 012281), conducted an extensive sensitivity analysis of the Pope et al. (1995, 045159) ACS data, augmented with additional gaseous pollutants data. Due to the smaller number of CO monitors available compared to SO_4^{2-}, the number of metropolitan statistical areas (MSAs) included in the CO analysis were reduced (from 151 with SO_4^{2-} to 107). The mean annual CO concentrations in these MSAs ranged from 0.19 to 3.95 ppm. CO was weakly negatively correlated with SO_4^{2-} (r = -0.07). Among the gaseous pollutants examined (CO, NO_2, O_3, SO_2), only SO_2 showed positive associations with mortality, and, in addition, was the only copollutant that reduced SO_4^{2-} risk estimates. For CO, the relative risk estimates for total (nonaccidental) mortality in single- and copollutant models with SO_4^{2-} was 0.99 (95% CI: 0.96-1.01) and 0.98 (95% CI: 0.96-1.01), respectively, per 0.5 ppm increase in mean annual average CO concentrations.

Pope et al. (2002, 024689) conducted an 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. (2002, 024689) study. In addition to $PM_{2.5}$, data for all of the gaseous pollutants were retrieved for the extended period and analyzed for their associations with mortality-specific outcomes. As in the 1995 analysis, the air-pollution exposure estimates were based on the MSA-level averages. The authors found that $PM_{2.5}$ and SO_4^{2-} were both associated with all-cause, cardiopulmonary, and lung cancer mortality.[1] In this study, the CO analysis used two different data sets: the first data set consisted of 1980 data and 113 MSAs; while the second data set used averages of the years 1982-1998 and 122 MSAs. The authors found, when using the 1980 data, that CO was not associated (risk estimates ~ 1) (Figure 5-19) with all-cause, cardiopulmonary, lung cancer, or mortality for all other causes. However, the analysis of the 1982-1998 data found that CO was negatively (and significantly) associated with all-cause, cardio-pulmonary, and lung cancer mortality. It is unclear why significant negative associations were observed when analyzing the 1982-1998 data, but evidence from other mortality studies that examined the association between long-term exposure to CO and mortality do not suggest that CO elicits a protective effect.

Krewski et al. (2009, 191193) further analyzed the ACS cohort by adding two additional years of mortality data (total period 1982-2000). This study extended the range of the analysis to incorporate sophisticated adjustment for bias and confounding as well as intra-urban analyses. However, the CO analysis was limited to using (1) nationwide data; (2) only 1980 CO concentrations; and (3) the standard Cox proportional hazards model. In addition to the death categories examined in Pope et al. (2002, 024689), this analysis also examined IHD mortality. As was the case with the Pope et al. (2002, 024689) analysis, Krewski et al. (2009, 191193) found that 1980 CO data was not associated with any of the mortality categories examined: all-cause mortality HR=1.00 (95%CI: 0.99-1.01); cardio-pulmonary mortality, HR=1.00 (95% CI: 0.99-1.00); and IHD mortality, HR=1.00 (95% CI: 0.99-1.01) per 0.5 ppm increase in CO.

Women's Health Initiative Cohort Study

Miller et al. (2007, 090130) studied 65,893 postmenopausal women between the ages of 50 and 79 yr without previous CVD in 36 U.S. metropolitan areas from 1994 to 1998. The authors examined the association between one or more fatal or nonfatal cardiovascular events and air-pollutant concentrations. Exposures to air pollution were estimated by assigning the year 2000 mean concentration of air pollutants measured at the nearest monitor to the location of residence of each subject on the basis of its five-digit ZIP code centroid, which allowed estimation of effects due to both within-city and between-city variation of air pollution. The investigators excluded monitors whose measurement objective focused on a single point source or those with "small measurement scale (0-100 m)." Thus, presumably, these criteria reduced some of the exposure measurement error associated with monitors that are highly impacted by local sources.

During the course of the study, a total of 1,816 women had one or more fatal or nonfatal cardiovascular event, including 261 cardiovascular-related deaths. Hazard ratios for the initial cardiovascular event were estimated. The following results are for models that included only subjects with nonmissing exposure data for all pollutants (n = 28,402 subjects, resulting in 879 CVD events). In the single-pollutant models, $PM_{2.5}$ showed the strongest associations with CVD events among all pollutants (HR = 1.24 [95% CI: 1.04-1.48] per 10 $\mu g/m^3$ increase in annual average), followed by

[1] These results were presented graphically in Pope et al. (2002, 024689) and were estimated for Figure 5-19.

SO_2 (HR = 1.07 [95% CI: 0.95-1.20] per 5 ppb increase in the annual average). For CO the single-pollutant risk estimate was slightly (but not significantly) negative (HR = 0.96 [95% CI: 0.84-1.10]). In the multipollutant model, which included all pollutants (i.e., $PM_{2.5}$, $PM_{10-2.5}$, SO_2, NO_2, and O_3), the CO risk estimate was similar to the one presented in the single-pollutant model (HR = 0.96 [95% CI: 0.82-1.14]). In addition, CO was not associated with CVD events in a single pollutant model (HR = 1.00 [95% CI: 0.90-1.10] per 0.5 ppm increase in mean annual average CO concentration) that used all available observations. Overall this study found that $PM_{2.5}$ was clearly the best predictor of cardiovascular events.

The Washington University-EPRI Veterans' Cohort Mortality Studies

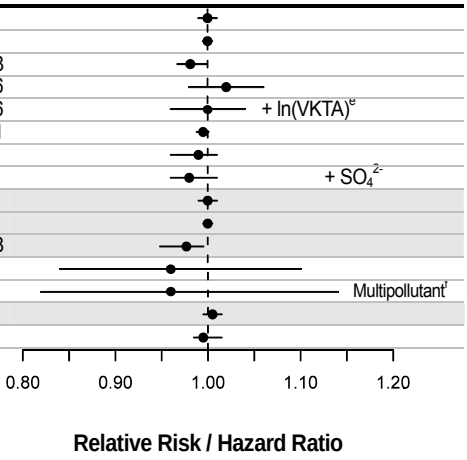
Lipfert et al. (2000, 004087) conducted an analysis of a national cohort of ~70,000 male U.S. military veterans who were diagnosed as hypertensive in the mid-1970s and were followed for approximately 21 yr (up to 1996). Demographically, 35% of the cohort consisted of African-American men and 57% of the cohort was defined as current smokers; however, 81% of the cohort had been smokers at one time in their life. The study examined mortality effects in response to long-term exposure to multiple pollutants, including, $PM_{2.5}$, PM_{10}, $PM_{10-2.5}$, TSP, SO_4^{2-}, CO, O_3, NO_2, SO_2, and Pb. Lipfert et al. (2000, 004087) estimated exposures by indentifying the county of residence at the time of entry to the study. Four exposure periods (1960-1974, 1975-1981, 1982-1988, and 1989-1996) were defined, and deaths during each of the three most recent exposure periods were considered. The mean annual 95th percentile of hourly CO values during these periods declined from 10.8 ppm to 2.4 ppm. The authors noted that the pollution risk estimates were sensitive to the regression model specification, exposure periods, and the inclusion of ecological and individual variables. Lipfert et al. (2000, 004087) reported that indications of concurrent mortality risks (i.e., associations between mortality and air quality for the same period) were found for NO_2 and peak O_3. The estimated CO mortality risks were all negative, but not significant.

Lipfert et al. (2006, 088756) examined associations between traffic density and mortality in the same Veterans' Cohort; however, in this analysis, the follow-up period was extended to 2001. As in their 2000 study, four exposure periods were considered, but more recent years were included in the 2006 analysis. The authors used the mean annual average of the 95th percentile of 24-h avg CO in each of the exposure periods as the averaging metric. The traffic-density variable was the most significant predictor of mortality in their analysis, remaining so in two- and three pollutant models with other air pollutants (i.e., CO, NO_2, O_3. $PM_{2.5}$, SO_4^{2-}, non-SO_4^{2-} $PM_{2.5}$, and $PM_{10-2.5}$). In the multipollutant models, mortality-risk estimates were not statistically significant for any of the other pollutants, except O_3. The natural log of the traffic-density variable (VKTA = vehicle-km traveled per yr) was not correlated with CO (r = -0.06) but moderately correlated with $PM_{2.5}$ (r = 0.50) in this data set. For the 1989-1996 data period, the estimated mortality relative risk was 1.02 (95% CI: 0.98-1.06) per 1 ppm increase in the mean annual 95th percentile of hourly CO concentration in a single-pollutant model. The two-pollutant model, which included the traffic-density variable, resulted in a relative risk of 1.00 (95% CI: 0.96-1.04). Lipfert et al. (2006, 088218) noted that the low risk estimates for CO in this study were consistent with those observed in other long-term exposure studies and may have been due to the localized nature of CO, which can lead to exposure errors when data from centralized monitors is used to represent an entire county. Interestingly, as Lipfert et al. (2006, 088756) pointed out, the risk estimates due to traffic density did not vary appreciably across these four periods, even though regulated tailpipe emissions declined during the study period. The authors speculated that some combination of other environmental factors such as road dust, psychological stress, and noise (all of which constitute the environmental effects of vehicular traffic), along with spatial gradients in SES, might contribute to the nonnegative effects observed.

Lipfert et al. (2006, 088218) extended the analysis of the Veterans Cohort data to include the EPA's Speciation Trends Network (STN) data, which collected chemical components of $PM_{2.5}$. The authors analyzed the STN data for the year 2002 and again used county-level averages. In addition, they analyzed $PM_{2.5}$ and gaseous pollutants data for 1999-2001. As in the other Lipfert et al. (2006, 088218) study, traffic density was the most important predictor of mortality, but associations were also observed for EC, vanadium (V), nickel (Ni), and NO_3^-. Ozone, NO_2, and PM_{10} also showed positive but weaker associations. The authors found no association between the mean annual 95th percentile of hourly CO values and mortality (RR = 0.995 [95% CI: 0.988-1.001] per 1 ppm increase

in CO concentration) in a single-pollutant model. The study did not present copollutant model results for CO.

Cause-specific Mortality	Study	Cohort	Years of Mortality Data	Year(s) of AQ Data
All-cause	Pope et al. (2002, 024689)[a]	ACS	1982-1998	1980
	Krewski et al. (2009, 191193)	ACS	1982-2000	1980
	Pope et al. (2002, 024689)[a]	ACS	1982-1998	1982-98
	Lipfert et al. (2006, 088218)	Veterans	1976-2001	1989-96
	Lipfert et al. (2006, 088218)	Veterans	1976-2001	1989-96
	Lipfert et al. (2006, 088756)	Veterans	1997-2001	1999-01
	Jerrett et al. (2003, 087380)	ACS	1982-1998	1982[c]
	Jerrett et al. (2003, 087380)	ACS	1982-1998	1982[c]
Cardiopulmonary	Pope et al. (2002, 024689)[a]	ACS	1982-1998	1980
	Krewski et al. (2009, 191193)	ACS	1982-2000	1980
	Pope et al. (2002, 024689)[a]	ACS	1982-1998	1982-98
Cardiovascular	Miller et al. (2007, 090130)[b]	WHI	1994-1998	2000
	Miller et al. (2007, 090130)[b]	WHI	1994-1998	2000
IHD	Krewski et al. (2009, 191193)	ACS	1982-2000	1980
Lung Cancer	Krewski et al. (2009, 191193)	ACS	1982-2000	1980



[a]The study does not present CO results quantitatively. This effect estimate and 95% confidence interval were estimated from Figure 5 in Pope et al. (2002, 024689).
[b]Effect estimate is only for subjects with non-missing exposure data for all pollutants.
[c]The study did not report the range of years of CO data used; however, it does specify that air quality data was obtained from pollution monitoring stations operating in 1982.
[d]Unless otherwise specified, all results represent single pollutant models
[e]Natural log of Vehicle-km Traveled variable.
[f]Multipollutant model consisted of CO + $PM_{2.5}$, $PM_{10-2.5}$, SO_2, NO_2, O_3.

Figure 5-19. Summary of mortality risk estimates for long-term exposure to CO. Estimates were standardized to 0.5 ppm and 1.0 ppm for studies that used mean annual average CO and the mean annual 95th percentile of hourly CO values exposure metrics, respectively.

5.6.2.2. U.S. Cross-Sectional Analysis

An ecological cross-sectional analysis involves regressing county- (or city-) average health outcome values on county-average explanatory variables such as air pollution and census statistics. Unlike the cohort studies described above, to the extent that individual level confounders are not adjusted for, the cross-sectional study design is considered to be subject to ecologic confounding. However, all of the cohort studies described above are also semi-ecologic in that the air-pollution exposure variables are ecologic (Kunzli and Tager, 1997, 086180). In this sense, cross-sectional studies may be useful in evaluating the correlation among exposure variables.

Lipfert and Morris (2002, 019217) conducted ecological cross-sectional regressions for U.S. counties (except Alaska) during five periods: 1960-1969, 1970-1974, 1979-1981, 1989-1991, and 1995-1997. They regressed age-specific (15-44, 45-64, 65-74, 76-84, and 85+ yr) all-cause (excluding AIDS and trauma) mortality on air pollution, demography, climate, SES, lifestyle, and diet. The authors analyzed TSP, PM_{10}, $PM_{2.5}$, SO_4^{2-}, SO_2, CO, NO_2, and O_3. However, air pollution data was only available for limited periods of time depending on the pollutant: TSP up to 1991; PM_{10} between 1995 and 1999; and $PM_{2.5}$ between 1979 and 1984 and for 1999. In response to the varying number of counties with valid air pollution data by pollutant and time, Lipfert and Morris (2002, 019217) employed a staged-regression approach. In the first stage, a national model was developed for each dependent variable, excluding air pollution variables. In the second stage, regressions were performed with the residuals on concurrent and previous periods' air pollution variables to identify the pollutants of interest. Many results were presented because of the large number of age groups, lagged-exposure time windows, and mortality study periods examined in the study; overall, the results were similar to those presented in the ACS cohort studies (i.e., $PM_{2.5}$ and SO_4^{2-} were found to be consistently and positively associated with mortality). Lipfert and Morris (2002, 019217) generally found the strongest associations in the earlier time periods and when mortality and air quality were measured in different periods (e.g., mortality data 1995-1997 and CO data 1970-1974).

Also, consistent with the Lipfert et al. (2000, 012281) and the Pope et al. (2002, 024689) cohort studies, CO was frequently negatively (and often significantly) associated with mortality in older age groups, especially when mortality was matched with CO levels in more recent time periods. The younger age group (15-44 yr) often showed a positive association with CO, but considering the small number of deaths attributed to this age group (<1% of total deaths), the association was not informative. Overall, this study highlighted that the CO-mortality associations presented in purely ecologic study designs are generally consistent with those found in semi-individual cohort studies.

5.6.2.3. Summary of Mortality and Long-Term Exposure to CO

The evaluation of new epidemiologic studies conducted since the 2000 CO AQCD (U.S. EPA, 2000, 000907) that investigated the association between long-term exposure to CO and mortality consistently found null or negative mortality risk estimates. No such studies were discussed in the 2000 CO AQCD (U.S. EPA, 2000, 000907). The reanalysis of the ACS data (Pope et al., 1995, 045159) by Jerrett et al. (2003, 087380) found no association between long-term exposure to CO and mortality. Similar results were obtained in an updated analysis of the ACS data (Pope et al., 2002, 024689) when using earlier (1980) CO data; however, negative associations were found when using more recent (1982-1998) data. These results were further confirmed in an extended analysis of the ACS data (Krewski et al., 2009, 191193). The Women's Health Initiative Study also found no association between CO and CVD events (including mortality) using the mortality data from recent years (1994-1998) (Miller et al., 2007, 090130), while the series of Veterans Cohort studies found no association or a negative association between mean annual 95th percentile of hourly CO values and mortality (Lipfert et al., 2006, 088218; Lipfert et al., 2006, 088756). An additional study (Lipfert and Morris, 2002, 019217) was identified that used a cross-sectional study design, which reported results for a study of U.S. counties that were generally consistent with the cohort studies: positive associations between long-term exposure to $PM_{2.5}$ and SO_4^{2-} and mortality, and generally negative associations with CO. Overall, the consistent null and negative associations observed across epidemiologic studies which included cohort populations encompassing potentially susceptible populations (i.e., postmenopausal women and hypertensive men) combined with the lack of evidence for respiratory and cardiovascular morbidity outcomes following long-term exposure to CO; and the absence of a proposed mechanism to explain the progression to mortality following long-term exposure to CO provide supportive evidence that there is **not likely to be a causal relationship between relevant long-term exposures to CO and mortality.**

5.7. Susceptible Populations

Interindividual variation in human responses indicates that some populations are at increased risk for the detrimental effects of ambient exposure to an air pollutant (Kleeberger and Ohtsuka, 2005, 130489). The NAAQS are intended to provide an adequate margin of safety for both general populations and sensitive subgroups, or those individuals potentially at increased risk for health effects in response to ambient air pollution (Section 1.1). To facilitate the identification of populations at the greatest risk for CO-related health effects, studies have evaluated factors that contribute to the susceptibility and/or vulnerability of an individual to CO. The definition for both of these terms varies across studies, but in most instances "susceptibility" refers to biological or intrinsic factors (e.g., lifestage, gender) while "vulnerability" refers to nonbiological or extrinsic factors (e.g., visiting a high-altitude location, medication use) (Table 5-25). Additionally, in some cases, the terms "at-risk" and sensitive populations have been used to encompass these concepts more generally. However, in many cases a factor that increases an individual's risk for morbidity or mortality effects from exposure to an air pollutant (e.g., CO) can not be easily categorized as a susceptibility or vulnerability factor. For example, a population that is characterized as having low SES, traditionally defined as a vulnerability factor, may have less access to healthcare resulting in the manifestation of disease (i.e., a susceptibility factor). But they may also reside in a location that results in exposure to higher concentrations of an air pollutant, increasing their vulnerability. Therefore, the terms "susceptibility" and "vulnerability" are intertwined and at times cannot be distinguished from one another.

As a result of the inconsistencies in the definitions of "susceptibility" and "vulnerability" presented in the literature as well as the inability to clearly delineate whether an identified factor increases an individual's susceptibility or vulnerability to an air pollutant, in this ISA, the term "susceptible population" will be used as a blanket term and defined as follows:

> *Populations that have a greater likelihood of experiencing health effects related to exposure to an air pollutant (e.g., CO) due to a variety of factors including, but not limited to: genetic or developmental factors, race, gender, lifestage, lifestyle (e.g., smoking status and nutrition) orpreexisting disease, as well as population-level factors that can increase an individual's exposure to an air pollutant (e.g., CO) such as socioeconomic status [SES], which encompasses reduced access to health care, low educational attainment, residential location, and other factors.*

Table 5-25. Range of definitions of "susceptible" and "vulnerable" in the CO literature.

Definition	Reference
Susceptible: predisposed to develop a noninfectious disease Vulnerable: capable of being hurt; susceptible to injury or disease	Merriam-Webster (2009, 192146)
Susceptible: greater likelihood of an adverse outcome given a specific exposure, in comparison with the general population. Includes both host and environmental factors (e.g., genetics, diet, physiologic state, age, gender, social, economic, and geographic attributes). Vulnerable: periods during an individual's life when they are more susceptible to environmental exposures.	American Lung Association (2001, 016626)
Susceptible: those who are more likely to experience adverse effects of CO exposure than normal healthy adults (e.g., persons with cardiovascular disease, COPD, reduced or abnormal hemoglobin, older adults, neonates).	U.S. EPA (2008, 193995)
Susceptible: greater or lesser biological response to exposure. Vulnerable: more or less exposed.	U.S. EPA (2009, 192149)
Vulnerable: to be susceptible to harm or neglect, that is, acts of commission or omission on the part of others that can wound.	Aday (2001, 192150)
Susceptible: may be those who are significantly more liable than the general population to be affected by a stressor due to life stage (e.g., children, the elderly, or pregnant women), genetic polymorphisms (e.g., the small but significant percentage of the population who have genetic susceptibilities), prior immune reactions (e.g., individuals who have been "sensitized" to a particular chemical), disease state (e.g., asthmatics), or prior damage to cells or systems (e.g., individuals with damaged ear structures due to prior exposure to toluene, making them more sensitive to damage by high noise levels). Vulnerable: differential exposure and differential preparedness (e.g., immunization).	U.S. EPA (2003, 192145)
Susceptible: intrinsic (e.g., age, gender, preexisting disease (e.g., asthma) and genetics) and extrinsic (previous exposure and nutritional status) factors.	Kleeberger and Ohtsuka (2005, 130489)

To examine whether air pollutants (e.g., CO) differentially affect certain populations, epidemiologic studies conduct stratified analyses to identify the presence or absence of effect modification. A thorough evaluation of potential effect modifiers may help identify populations that are more susceptible to an air pollutant (e.g., CO). Although the design of toxicological and controlled human exposure studies does not allow for an extensive examination of effect modifiers, the use of animal models of disease and the study of individuals with underlying disease or genetic polymorphisms do allow for comparisons between subgroups. Therefore, the results from these studies, combined with those results obtained through stratified analyses in epidemiologic studies, contribute to the overall weight of evidence for the increased susceptibility of specific populations to an air pollutant (e.g., CO).

The remainder of this section discusses the epidemiologic, controlled human exposure, and toxicological studies evaluated in previous sections of Chapter 5 that provide information on potentially susceptible populations. The studies highlighted include only those studies that presented stratified results (e.g., males versus females or <65 yr versus ≥ 65 yr). This approach allows for a direct comparison between populations exposed to similar CO concentrations and within the same study design to determine whether a factor increases the susceptibility of a population to CO-related health effects. In addition, numerous studies that focus on only one potentially susceptible population can provide supporting evidence on susceptibility and are described in Sections 5.2

through 5.6; however, these studies are not discussed in detail in this section. It is recognized that by using this approach to identify potentially susceptible populations, some individuals with underlying medical conditions (i.e., reduced O_2-carrying capacity or elevated COHb levels) or lifestyle characteristics may not be identified due to the lack of studies focusing on these populations. Discussion of conditions affecting CO uptake and elimination as well as endogenous CO production is presented in Sections 4.4 and 4.5, respectively.

5.7.1. Preexisting Disease

The 2000 CO AQCD (U.S. EPA, 2000, 000907) identified certain populations within the general population that may be more susceptible to the effects of CO exposure, including individuals (particularly older adults) with CHD and other vascular diseases, anemia, or COPD. As discussed in the 2000 CO AQCD (U.S. EPA, 2000, 000907) and reviewed in Section 4.5 of this assessment, diseases that cause inflammation and systemic stress are known to increase endogenous CO production, which could potentially increase the susceptibility of individuals with such conditions to health effects induced by ambient CO exposure. The level of COHb that results in the manifestation of health effects varies depending on health outcome and disease state of individuals. The following sections summarize the evidence presented in the 2000 CO AQCD (U.S. EPA, 2000, 000907) along with new evidence which identifies populations with various preexisting diseases that may be susceptible to CO-induced health effects.

5.7.1.1. Cardiovascular Disease

Controlled exposures to CO resulting in COHb concentrations of 2-6% have been shown to affect cardiovascular function among individuals with CAD. Several studies have reported significant decreases in the time to onset of exercise-induced angina or ST-segment changes following CO exposure in patients with stable angina. In the largest such study (Allred et al., 1989, 013018; Allred et al., 1989, 012697; Allred et al., 1991, 011871), COHb concentrations as low as 2.0-2.4% were observed to significantly decrease the time required to induce ST-segment changes indicating myocardial ischemia ($p = 0.01$) (Section 5.2.4). In addition to the effects of CO on myocardial ischemia, there is some evidence to suggest that CO may provoke cardiac arrhythmia in patients with CAD; however, this has not been observed at COHb concentrations below 6% (Sheps et al., 1990, 013286). While healthy adults have been shown to experience a decrease in exercise performance following or during exposure to CO, no changes in cardiac rhythm or ECG parameters have been demonstrated.

Evidence of CO-induced health effects in individuals with CAD is coherent with results from epidemiologic studies that examined the effect of preexisting cardiovascular conditions, through either secondary diagnoses or underlying comorbidities, on associations between CO and ED visits and HAs. Mann et al. (2002, 036723) found increased associations between CO and IHD HAs in individuals with secondary diagnoses of either CHF or dysrhythmia in southern California. Peel et al. (2007, 090442) also examined the effect of underlying cardiovascular conditions on cardiovascular-related HAs in response to short-term exposure to air pollutants, including CO in Atlanta, GA. Individuals with underlying dysrhythmia were found to have increased HAs for IHD, but unlike Mann et al. (2002, 036723), underlying CHF was not found to increase IHD HAs. Peel et al. (2007, 090442) also examined other underlying conditions and found increased HAs for additional cardiovascular effects not specifically related to IHD, including: dysrhythmia, PVCD, and CHF in individuals with underlying hypertension; dysrhythmia and PVCD in individuals with underlying CHF; and PVCD in individuals with underlying dysrhythmia. Although there is no evidence for a clear pattern of CO-induced cardiovascular effects among individuals without CAD across the epidemiologic studies evaluated, the available evidence suggests that underlying dysrhythmia increases IHD HAs in response to short-term exposure to CO.

Additional evidence for increased CO-induced cardiovascular effects not specifically related to IHD is provided by toxicological studies that used animal models of cardiovascular disease. These studies have demonstrated that short-term exposure to 50 ppm CO in rats exacerbates cardiomyopathy and vascular remodeling related to pulmonary hypertension (Carraway et al., 2002, 026018; Gautier et al., 2007, 096471; Melin et al., 2002, 037502; 2005, 193833). Although the population at risk for primary pulmonary hypertension is low, secondary pulmonary hypertension is

a frequent complication of COPD (Section 5.7.1.2) and certain forms of heart failure. These studies demonstrate the potential for short-term exposure to CO to adversely affect individuals with underlying cardiovascular conditions.

The combined evidence from controlled human exposure and epidemiologic studies provides coherence and biological plausibility for the association between CO and cardiovascular morbidity in individuals with CAD, particularly those with IHD. Approximately 13.7 million people in the U.S. have been diagnosed with CAD (also known as CHD), some fraction of whom have IHD (Table 5-26). These individuals, therefore, represent a large population that may be more susceptible to ambient CO exposure than the general population. In addition, the continuous nature of the progression of CAD and its close relationship with other forms of cardiovascular disease suggest that a larger population than just those individuals with a prior diagnosis of CAD may be susceptible to health effects from CO exposure.

Table 5-26. Adult U.S. population in 2007 with respiratory diseases and cardiovascular diseases.

Chronic Condition/ Disease	Adults (18+)	Percentage of U.S. Adult Population by Age					Percentage by Region			
COPD[a]	**(Millions)**	**All (18+)**	**18-44**	**45-64**	**65-74**	**75+**	**NE**	**MW**	**S**	**W**
Chronic bronchitis	7.6	3.4	2.3	4.2	5.5	4.8	2.8	3.2	4.0	2.9
Emphysema	3.7	1.6	0.2	2.3	4.5	5.2	1.1	1.8	1.8	1.6
Cardiovascular Diseases[b]	**(Millions)**	**All (18+)**	**18-44**	**45-64**	**65-74**	**75+**	**NE**	**MW**	**S**	**W**
All heart disease[c]	25.1	11.2	4.1	12.2	27.1	35.8	10.6	12.3	11.3	10.2
Coronary heart disease[d]	13.7	6.1	0.9	6.7	18.6	23.6	5.3	6.7	6.4	5.5
Hypertension	52.9	23.2	8.2	32.1	50.9	57.4	21.3	23.4	25.1	21.0
Stroke	5.4	2.4	0.3	2.8	6.3	10.6	2.2	2.3	2.7	2.2

[a] Respondents were asked if they had ever been told by a doctor or other health professional that they had emphysema. In a separate question, respondents were asked if they had been told by a doctor or other health professional in the last 12 mo that they had bronchitis. A person may be represented in more than one row.
[b] In separate questions, respondents were asked if they had ever been told by a doctor or other health professional that they had: hypertension (or high blood pressure), coronary heart disease, angina (or angina pectoris), heart attack (or myocardial infarction), any other heart condition or disease not already mentioned, or a stroke. A person may be represented in more than one row.
[c] Heart disease includes coronary heart disease, angina pectoris, heart attack, or any other heart condition or disease.
[d] Coronary heart disease includes coronary heart disease, angina pectoris, or heart attack.

Source: National Health Interview Survey, 2007, Tables 1-4 (Pleis and Lucas, 2009, 202833).

5.7.1.2. Obstructive Lung Disease

COPD is a progressive disease resulting in decreased air flow to the lungs and which is especially prevalent among smokers. O_2 limitation resulting from this reduction in air flow may exacerbate CO-related O_2 limitation and subsequent cardiovascular or respiratory effects in individuals with COPD. The national prevalence of chronic bronchitis and emphysema, the two main forms of COPD, was estimated to be 7.6 million and 3.7 million people in 2007, respectively (Table 5-26), although there could be overlap among these two populations. The 2000 CO AQCD (U.S. EPA, 2000, 000907) identified individuals with obstructive lung diseases, such as COPD, as a susceptible population due to a majority of COPD patients having exercise limitations as demonstrated by a decrease in O_2 saturation during mild to moderate exercise. This may heighten the sensitivity of these individuals to CO during submaximal exercise typical of normal daily activity. In addition, COPD patients who are smokers may have elevated baseline COHb levels of 4-8% (U.S. EPA, 2000, 000907). COPD is often accompanied by a number of changes in gas exchange, including increased V_D and V_A/Q inequality (Marthan et al., 1985, 086334), which could slow both CO uptake and elimination.

The few epidemiologic studies of cardiovascular effects in individuals with underlying COPD show weak positive associations between ambient CO and increased CVD HAs or ED visits. For example, Peel et al. (2007, 090442) found that associations between short-term CO exposure and HAs for PVCD or CHF were increased in individuals with a secondary diagnosis of COPD. However, underlying COPD was not associated with increased IHD or dysrhythmia HAs. As

described in Section 5.7.1.1, animal toxicological studies demonstrate CO-induced exacerbation of vascular remodeling related to pulmonary hypertension, a form of which is a frequent complication of COPD.

A controlled human exposure study of respiratory effects in individuals with COPD (Bathoorn et al., 2007, 193963), found that two of the patients experienced COPD exacerbation during or following CO exposure at 100-125 ppm for 2 h, although a slight anti-inflammatory effect was also observed. Although the majority of the evidence for CO-induced effects comes from studies that focus on individuals with COPD, epidemiologic studies also report weak positive associations for asthmatics (Section 5.5.2.2) who can also experience exercise-induced airflow limitation. In addition, preliminary evidence from a recent animal toxicological study indicates mild pulmonary inflammation in response to 50 ppm CO (Ghio et al., 2008, 096321). Since pulmonary inflammation plays an important role in the exacerbation of COPD and asthma, it may serve as a mechanism underlying CO-induced respiratory effects; however, additional research is needed to confirm these results. Taken together, the limited evidence from epidemiologic and controlled human exposure studies and some preliminary evidence from toxicological studies suggests that individuals with obstructive lung disease (e.g., COPD patients with underlying hypoxia, asthmatics) may be susceptible to cardiovascular or respiratory effects due to CO exposure.

5.7.1.3. Diabetes

Exhaled CO concentrations are elevated in individuals with diabetes and are correlated with blood glucose levels and duration of disease, indicating increased endogenous CO production (Section 4.5). As a result, it has been speculated that elevated baseline COHb levels in diabetic individuals could increase the susceptibility of diabetics to CO-induced health effects in response to ambient CO exposures. Epidemiologic studies provide evidence which suggests that diabetics are at increased risk for cardiovascular ED visits and HAs compared to nondiabetics in response to short-term exposure to CO (Pereira Filho et al., 2008, 190260; Zanobetti and Schwartz, 2001, 016710). This is consistent with results reported by Peel et al. (2007, 090442), who observed an increase in cardiovascular-related ED visits for dysrhythmias and PVCD in individuals with diabetes but not for IHD or CHF ED visits. The results from Peel et al. (2007, 090442) that indicate an increase in dysrhythmia ED visits for individuals with diabetes are consistent with results from a panel study conducted by Min et al. (2009, 199514) to investigate the relationship between CO and HRV in individuals with metabolic syndrome. Metabolic syndrome is characterized by risk factors for both diabetes and CVD, including elevations in blood pressure, fasting blood glucose, triglycerides, and waist circumference, as well as low levels of HDL cholesterol. Min et al. (2009, 199514) observed associations between short-term exposure to CO and changes in HRV parameters among subjects with metabolic syndrome but not among healthy subjects. In addition, the observed associations were robust in copollutant models with either PM_{10} or NO_2. In an analysis of individual risk factors, the CO effects were stronger among subjects with higher levels of fasting blood glucose or triglycerides. Although no evidence was identified from controlled human exposure or toxicological studies regarding CO exposure and diabetes, vascular dysfunction was demonstrated in an animal model of metabolic syndrome and was attributed to increased endogenous CO production (Johnson et al., 2006, 193874). Thus, increased endogenous CO production and the potential for higher baseline COHb concentrations, combined with the limited epidemiologic evidence showing cardiovascular effects, suggests that diabetics are potentially susceptible to short-term exposure to CO.

5.7.1.4. Anemia

Although no controlled human exposure or epidemiologic studies were identified that specifically examined CO-related health effects in individuals with anemia, the 2000 CO AQCD (U.S. EPA, 2000, 000907) suggested that conditions such as anemia that produce tissue hypoxia by lowering the blood O_2 carrying capacity or content will result in a greater risk of effects from COHb-induced hypoxia due to the combined effects of both sources of hypoxia. As discussed in Section 4.4.4 of this ISA, anemias are a group of diseases that lower hematocrit and result in reduced arterial O_2 content due to Hb deficiency through hemolysis, hemorrhage, or reduced hematopoiesis. Hereditary hemoglobinopathies such as sickle cell anemia and thalassemia also reduce the O_2-carrying capacity of the blood. Anemia may also result from pathologic conditions characterized by

chronic inflammation such as malignant tumors or chronic infections (Cavallin-Ståhl et al., 1976, 086306; Cavallin-Ståhl et al., 1976, 193239). The cardiovascular system of people with anemia compensates for the reduction in O_2 carrying capacity by increasing cardiac output as both heart rate and stroke volume increase. One of the most prevalent forms of anemia arises from a single-point mutation in the Hb gene, resulting in sickle cell diseases. The affinity of Hb for O_2 and its O_2 carrying capacity is reduced, causing a shift to the right in the O_2 dissociation curve. It is well documented that African-American populations have a higher incidence of sickle cell anemia, which may be a risk factor for effects due to CO-mediated hypoxia. Other hereditary hemoglobinopathies, such as thalassemia, also reduce the O_2-carrying capacity of the blood due to the production of an abnormal form of hemoglobin. Overall, lowered hematocrit due to anemia may result in increased susceptibility and a greater response to inhalation of ambient CO.

Anemia may also increase the susceptibility of an individual to CO exposure in a different manner through the increased production of endogenous CO as a result of the disturbance of RBC hemostasis by accelerated destruction of hemoproteins (Section 4.5). Pathologic conditions such as hemolytic anemias, hematomas, thalassemia, Gilbert's syndrome with hemolysis, and other hematological diseases and illness will accelerate endogenous CO production (Berk et al., 1974, 012386; Hampson and Weaver, 2007, 190272; Meyer et al., 1998, 047530; Solanki et al., 1988, 012426; Sylvester et al., 2005, 191954). Patients with hemolytic anemia exhibit COHb levels at least two- to threefold higher than healthy individuals and CO production rates two- to eightfold higher (Coburn et al., 1966, 010984). Recent studies report elevated COHb levels of 4.6-9.7% due to drug-induced hemolytic anemia (Hampson and Weaver, 2007, 190272) and between 3.9% and 6.7% due to an unstable hemoglobin disorder (Hb Zürich) (Zinkham et al., 1980, 011435). Taken together, this evidence suggests that individuals with anemia who have diminished O_2-carrying capacity and/or high baseline COHb levels may be more susceptible to health effects due to ambient CO exposure, although no studies were identified that evaluated specific CO-related health effects in anemic individuals.

5.7.2. Lifestage

Age alters the variables that influence the uptake, distribution, and elimination of CO (Section 4.4.3). COHb levels decline more rapidly in young children compared to adults after CO exposure (Joumard et al., 1981, 011330; Klasner et al., 1998, 087196). After infancy, the COHb half-life increases with age, practically doubling between the ages of 2 and 70 yr (Joumard et al., 1981, 011330). However, it should be noted that the rate of this reduction in CO elimination is very rapid in the growing years (2-16 yr of age) but slows beyond adolescence. An increase in alveolar volume and D_LCO were observed with increasing body length of infants and toddlers (Castillo et al., 2006, 193234); these changes suggest faster CO uptake due to more advanced lung development. After infancy, increasing age decreases D_LCO and increases V_A/Q mismatch, resulting in a longer duration for both loading and elimination of CO from the blood (Neas and Schwartz, 1996, 079363).

5.7.2.1. Older Adults

The 2000 CO AQCD (U.S. EPA, 2000, 000907) noted that changes in metabolism that occur with age, particularly declining maximal oxygen uptake, may make the aging population susceptible to the effects of CO via impaired oxygen delivery to the tissues. Several epidemiologic studies compared cardiovascular outcomes in older and younger adults, although no such studies were conducted in the U.S. In a study in Australia and New Zealand, Barnett et al. (2006, 089770) found an increase in IHD and MI HAs among individuals ≥ 65 yr of age compared with individuals aged 15-64 yr in response to short-term exposure to CO. Lee et al. (2003, 095552) also found an association with IHD HAs in Seoul, Korea, for individuals ≥ 65 yr of age but not when all individuals were included in the analysis. Lanki et al. (2006, 089788) found an association with HAs for nonfatal MI in a multicity European study among those aged ≥ 75 yr but not for those <75 yr old. In contrast, D'Ippoliti et al. (2003, 074311) observed higher associations for MI hospital admissions in Rome among 18- to 64-yr olds than among either 65- to 74-yr olds or those 75 yr and over. Szyszkowicz (2007, 193793) found slightly lower associations for IHD hospital admissions in Montreal, Canada among those >64 yr of age than for the all-age group. Another Canadian study (Fung et al., 2005, 074322) conducted in Windsor, Ontario, found some evidence of increased

associations for between CO and CVDs (defined as HF, IHD, or dysrhythmia) among individuals ≥ 65 yr of age compared with the <65-yr age group. No controlled human exposure studies or toxicological studies were identified that compared CO effects among older and younger adults or animal models of senescence, respectively. Overall, the epidemiologic studies evaluated provide limited evidence that older adults may be susceptible to CO exposure.

A combination of factors may be responsible for increased susceptibility to CO-related health effects among older adults. One important factor which may contribute to the observed increases in CO-induced cardiovascular effects is the much higher prevalence of CAD and other cardiovascular conditions in older adults compared with the general population. As shown in Table 5-26,18.6% of adults aged 65-74 yr and 23.6% of adults aged 75 yr and over reported having CHD, as compared with 6.1% of the population as a whole. Both the higher prevalence of CAD and the gradual decline in physiological processes associated with aging (U.S. EPA, 2006, 192082) may contribute to increased health effects in response to CO in this population. Older adults represent a large and growing fraction of the U.S. population, from 12.4% or 35 million people in 2000 to a projected 19.3% or 72 million people in 2030 (U.S. Census, 2000, 157064), and, as a result, are a large population that is potentially susceptible to CO-induced health effects.

5.7.2.2. Gestational Development

CO inhaled by pregnant animals quickly crosses the placental barriers and enters fetal circulation. Effects of ambient CO may be enhanced during gestation because fetal CO pharmacokinetics do not follow the same kinetics as maternal CO exposure; this contributes to the difficulty in estimating fetal COHb based on maternal levels. It has been demonstrated that human fetal Hb has a higher affinity for CO than adult Hb (Di Cera et al., 1989, 193998). Maternal and fetal COHb concentrations have been modeled as a function of time using a modified CFK equation (Hill et al., 1977, 011315). At steady-state conditions, fetal COHb has been found to be 10-15% higher than maternal COHb levels. For example, exposure to 30 ppm CO results in a steady-state maternal COHb of 5% and a fetal COHb of 5.75%. Fetal CO uptake lags behind maternal uptake for the first few hours but later may overtake the maternal values. Similarly, during washout, fetal COHb levels are maintained for longer, with a half-life of around 7.5 h versus the maternal half-life of around 4 h (Longo and Hill, 1977, 010802). In addition, maternal endogenous CO production increases during pregnancy (0.92 mL/h) due to contributions from fetal endogenous CO production (0.036 mL/h) and altered hemoglobin metabolism (Hill et al., 1977, 011315; Longo, 1970, 013922).

Epidemiologic studies provide limited evidence that in utero CO exposure is associated with changes in various birth outcomes (Section 5.4.1). CO exposure during early pregnancy was associated with an increased risk of PTB. In the studies that examined associations between CO and birth defects, maternal CO exposure was associated with an increased risk of cardiac birth defects, which is also coherent with evidence in Section 5.2 identifying the heart as a target organ for CO. There is also evidence for small reductions in birth weight (10-20 g) associated with CO exposure, generally in the first or third trimester, although the decrease does not generally translate to an increased risk of LBW or SGA. It is therefore difficult to conclude if CO is related to a small change in birth weight across all births or a marked effect in some subset of births. In addition, there is limited evidence that prenatal CO exposure is associated with an increased risk of infant mortality in the post-neonatal period.

Toxicological studies lend biological plausibility to the CO-related developmental outcomes observed in epidemiologic studies (Section 5.4.2). Associations have been observed between CO exposure in laboratory animals and decrements in birth weight as well as reduced prenatal growth. Animal toxicological studies also provide evidence for effects on the heart, including transient cardiomegaly at birth after continuous in utero CO exposure and delayed myocardial electrophysiological maturation. Evidence exists for additional developmental outcomes which have been examined in toxicological studies but not epidemiologic or human clinical studies, including behavioral abnormalities, learning and memory deficits, locomotor effects, neurotransmitter changes, and changes in the auditory system. Furthermore, exogenous CO may interact or disrupt the normal physiological roles of endogenous CO in the body. There is evidence that CO plays a role in maintaining pregnancy, controlling vascular tone, regulating hormone balance, and sustaining normal follicular maturation.

The developmental outcomes examined in the epidemiologic studies evaluated affect a substantial portion of the U.S. population. PTB and LBW have been established as strong predictors

of infant mortality and morbidity (Barker et al., 2002, 193960; Berkowitz and Papiernik, 1993, 055466; Li et al., 2003, 193965; McIntire et al., 1999, 015310). In 2004, 36.5% of all infant deaths in the U.S. were preterm-related (MacDorman et al., 2007, 193973). Vital statistics for the year 2005 in the U.S. showed that the rate for PTB was 12.7%, which has risen 20% since 1990, and the rate for LBW was 8.2%, which has risen 17% since 1990 (Martin et al., 2007, 193982). Data from the Metropolitan Atlanta Congenital Defects Program (MACDP), which is one of the most comprehensive birth defect registries in the U.S., have shown that the prevalence of congenital heart defects increased between 1968 and 1997. During 1995-1997 the rate was 90.2 per 10,000 births (0.9%) and this was an increase of 58.7 per 10,000 births above the rate during 1968-1972 (Botto et al., 2001, 192379). Cardiovascular defects are the single largest contributor to infant mortality attributable to birth defects (CDC, 1998, 193243). Between 1995 and 1997, 1 in 13 infant deaths (7.4%) was due to a congenital heart defect (Boneva et al., 2001, 193972). The combined evidence from epidemiologic and toxicological studies, along with the increasing prevalence of PTB, LBW, and cardiac birth defects in the U.S. population, indicates that critical developmental phases may be characterized by enhanced sensitivity to CO exposure.

5.7.3. Gender

COHb concentrations are generally higher in male subjects than in female subjects (Horvath et al., 1988, 012725). In addition, the COHb half-life is longer in healthy men than in women of the same age, which may be partially explained by differences in muscle mass or the slight correlation between COHb half-life and increased height (Joumard et al., 1981, 011330). The rate of decline of D_LCO with age is lower in middle-aged women than in men; however, it is similar in older adults (Neas and Schwartz, 1996, 079363). Lower rates of decline in lung diffusing capacity are consistent with the observation that women tend to be more resistant than men to altitude hypoxia (Horvath et al., 1988, 012725). Women also experience fluctuating COHb levels through the menstrual cycle when endogenous CO production doubles in the progesterone phase (0.62 mL/h versus 0.32 mL/h in estrogen phase) (Delivoria-Papadopoulos et al., 1974, 086316; Mercke and Lundh, 1976, 086309). Similarly, endogenous CO production increases during pregnancy due to contributions from fetal CO production and altered hemoglobin metabolism as described above. In an epidemiologic study investigating the association between short-term CO exposure and IHD hospital admissions (Szyszkowicz, 2007, 193793), males had higher associations than females in both the all-ages group and in those >64 yr of age. However, this limited epidemiologic evidence combined with known gender-related differences in endogenous CO production do not provide sufficient basis for determining whether CO disproportionately affects males or females.

5.7.4. Altitude

Higher altitude results in changes in a number of factors that contribute to the uptake and elimination of CO. The relationship between altitude and CO exposure has been discussed in depth in the 2000 CO AQCD (U.S. EPA, 2000, 000907) and other documents (U.S. EPA, 1978, 086321) and is reviewed in Section 4.4.2 of this ISA. In an effort to maintain proper O_2 transport and supply, physiological changes occur as compensatory mechanisms to combat the decreased barometric pressure and resulting altitude-induced hypobaric hypoxia. These changes, which include increases in BP and cardiac output and redistribution of blood from skin to organs and from blood to extravascular compartments, generally will favor increased CO uptake and COHb formation, as well as CO elimination. It has been demonstrated that breathing CO (9 ppm) at rest at altitude produces higher COHb compared to sea level (McGrath et al., 1993, 013865), whereas high-altitude exposure in combination with exercise causes a decrease in COHb levels versus similar exposure at sea level (Horvath et al., 1988, 012725). This decrease could be a shift in CO storage or suppression of COHb formation, or both. In a controlled human exposure study on the health effects of CO at altitude, Kleinman et al. (1998, 047186) observed that CO exposure and simulated high altitude reduced the time to onset of angina relative to clean-air exposure at sea level by 9% and 11%, respectively, among a group of individuals with CAD. In this study, the combined effects of altitude and CO exposure were observed to be additive, with subjects experiencing, on average, an 18% decrease in the time to onset of angina following exposure to CO and simulated altitude relative to clean air

exposure at sea level. No epidemiologic studies were identified that specifically examined the effect of altitude on health effects due to CO exposure.

Altitude also increases the baseline COHb levels by inducing endogenous CO production and has been shown to be positively associated with baseline COHb concentrations (McGrath, 1992, 001005; McGrath et al., 1993, 013865). This increase in COHb with altitude-induced hypoxia has also been associated with increases in mRNA, protein, and activity of HO-1 in rats and cells leading to enhanced endogenous CO production (Carraway et al., 2002, 026018; Chin et al., 2007, 190601). Early HH has been found to increase lung HO-1 protein and activity, whereas chronic HH induced endogenous CO production in nonpulmonary sites (Section 4.5) (Carraway et al., 2000, 021096). Whether other variables (such as an accelerated metabolism or a greater pool of Hb, transient shifts in body stores, or a change in the elimination rate of CO) play a role in increasing COHb concentrations at high altitudes has not been explored.

As the length of stay increases at high altitude, acclimatization occurs, inducing hyperventilation, polycythemia or increased red blood cell count, and increased tissue capillarity and Mb content in skeletal muscle, which could also favor increased CO uptake. Most of the initial adaptive changes gradually revert to sea-level values. However, these adaptive changes persist in people raised at high altitude even after reacclimatization to sea level (Hsia, 2002, 193857). This evidence indicates that visitors to high altitude locations may represent a potentially susceptible population for increased risk of health effects due to CO exposure.

5.7.5. Exercise

Exercise is an important determinant of CO kinetics and toxicity due to the extensive increase in gas exchange. O_2 consumption can increase more than 10-fold during exercise. Similarly, ventilation, membrane and lung diffusing capacity, pulmonary capillary blood volume, and cardiac output increase proportional to work load. The majority of these changes facilitate CO uptake and transport by increasing gas exchange efficiency. Likewise, the COHb elimination rate increases with physical activity, causing a decrease in COHb half-life (Joumard et al., 1981, 011330). The potential effects of CO on exercising individuals was demonstrated in a controlled human exposure study where healthy subjects exposed to CO achieved COHb levels of approximately 5%, which resulted in a significant decrement in exercise duration and maximal effort capability (measured by metabolic equivalent units) (Adir et al., 1999, 001026). These effects could be attributed to CO lowering the anaerobic threshold, allowing earlier fatigue of the skeletal muscles and decreasing maximal effort capability during heavy exercise. Due to the counterbalancing effects of increased rates of COHb formation and elimination, it is unclear whether individuals engaging in light to moderate exercise are a potentially susceptible population for increased health effects due to ambient CO exposure.

5.7.6. Proximity to Roadways

Individuals that spend a substantial amount of time on or near heavily traveled roadways, such as commuters and those living or working near freeways, are likely to be exposed to elevated CO concentrations, as discussed in Chapter 3. Targeted sampling studies have found CO concentrations measured at the roadside to be several-fold higher than concentrations measured a few hundred meters downwind (Baldauf et al., 2008, 191017; Zhu et al., 2002, 041553), with the shape of the concentration profile dependent on wind speed and direction. AQS monitoring data aggregated across multiple sites with no adjustment for wind conditions show somewhat higher concentrations for microscale (near-road) monitors relative to middle-scale monitors, although the ratio is lower than that observed in the roadside studies. Elevated near-road concentrations are important for residents of the estimated 17.9 million occupied homes nationwide (16.1%) that are within approximately 90 m of a freeway, railroad, or airport, according to the 2007 American Housing Survey (2008, 194013).

Studies of commuters have shown that commuting time is an important determinant of CO exposure for those traveling by car, bicycle, public transportation, and walking (Bruinen de Bruin et al., 2004, 190943; Kaur et al., 2005, 086504; Scotto Di Marco et al., 2005, 144054). In-vehicle concentrations have been measured to be several times higher than concentrations measured at fixed-site monitors not located adjacent to roadways (Bruinen de Bruin et al., 2004, 190943; Chang et al., 2000, 001276; Kaur et al., 2005, 086504; Riediker et al., 2003, 043761; Scotto Di Marco et al., 2005,

144054). Commuting is likely to be an important contributor to CO exposure for the 5.5 million U.S. worker (5%) who drive 60 min or more to work (U.S. Census Bureau, 2008, 194013). This evidence for elevated on-road and near-road CO concentrations combined with residential and commuting data indicates that the large numbers of individuals who spend a substantial amount of time on or near heavily traveled roadways are an important population that is potentially susceptible to increased health risks due to ambient CO exposure.

5.7.7. Medications and Other Substances

Endogenous CO production can be altered by medications or a number of physiological conditions that increase RBC destruction, the breakdown of hemoproteins other than Hb, and the production of bilirubin (Section 4.5). Nicotinic acid, allyl-containing compounds (acetamids and barbiturates), diphenylhydantoin, progesterone, contraceptives, and statins increase CO production. One epidemiologic study (Dales, 2004, 099036) investigated the effect of medication use on the relationship between ambient CO and HRV in individuals with CAD. The authors observed an association between short-term CO exposure and an increase in SDNN for CAD patients not taking beta blockers; however, this association did not persist in CAD patients taking beta blockers.

Compounds such as carbon disulfide and sulfur-containing chemicals (parathion and phenylthiourea) increase CO following metabolism by cytochrome p450s. The P450 system may also cause large increases in CO produced from the metabolic degradation of dihalomethanes such as methylene chloride leading to very high (>10%) COHb levels, which can be further enhanced by prior exposure to HCs or ethanol. Minor sources of endogenous CO include the auto-oxidation of phenols, photo-oxidation of organic compounds, and lipid peroxidation of cell membrane lipids. Taken together, this evidence indicates that individuals ingesting medications and other substances that enhance endogenous or metabolic CO production represent a population that is potentially susceptible to increased health effects due to additional exposure to ambient CO.

5.7.8. Summary of Susceptible Populations

Individuals with CAD represent the population most susceptible to increased risk of CO-induced health effects, based on evidence of significant decreases in the time to onset of exercise-induced angina or ST-segment changes observed in controlled human exposure studies of individuals with CAD. This is coherent with the results from epidemiologic studies that observed associations between short-term CO exposure and ED visits and HAs for IHD and related outcomes. The limited evidence from stratified analyses in epidemiologic studies, which indicates that secondary diagnoses of CHF or dysrhythmia modify associations between short-term CO exposure and IHD HAs, provides further support that individuals with cardiovascular disease represent a potentially susceptible population. Additional evidence is provided by toxicological studies that demonstrated exacerbation of cardiomyopathy and increased vascular remodeling in animal models of cardiovascular disease. Although it is not clear whether the small changes in COHb associated with ambient CO exposures result in substantially diminished O_2 delivery to tissues, the known role of CO in limiting O_2 availability provides biological plausibility for ischemia-related health outcomes following CO exposure. The continuous nature of the progression of CAD and its close relationship with other forms of cardiovascular disease suggest that a larger population than just those individuals with a prior diagnosis of CAD may be susceptible to health effects from CO exposure.

Populations potentially susceptible to CO-induced health effects also include individuals with other preexisting diseases, such as COPD or diabetes. Preliminary evidence available from controlled human exposure and epidemiologic studies suggests that individuals with obstructive lung disease may be susceptible to increased cardiovascular or respiratory effects due to CO exposure. Increased endogenous CO production and the potential for higher baseline COHb concentrations in individuals with diabetes, combined with the limited epidemiologic evidence showing cardiovascular effects, suggests that diabetics are potentially susceptible to short-term exposure to CO. Individuals with various types of anemia who have diminished O_2-carrying capacity and/or high baseline COHb levels may be more susceptible to health effects due to ambient CO exposure, although no studies were identified that evaluated specific CO-related health effects in individuals with anemia.

There is also evidence that older adults and the developing young represent populations potentially susceptible to CO-induced health effects. Epidemiologic studies provide limited evidence

from stratified analyses indicating that associations between short-term CO exposure and hospital admissions for CAD are higher among those ≥ 65 yr old than for those <65 yr. The older adult population also has a much higher prevalence of CAD than the general population as a whole, which may contribute to their increased susceptibility. Recent studies on birth outcomes have provided limited evidence of associations between in utero CO exposure and PTB, LBW and cardiac birth defects. Toxicological studies provide evidence of effects on birth weight and growth as well as development of the cardiovascular and nervous systems following prenatal exposure to CO. This evidence, combined with differences between fetal and maternal CO pharmacokinetics, indicates that critical developmental phases may be characterized by enhanced sensitivity to CO exposure.

Visitors to high-altitude locations may represent a potentially susceptible population due to changes in factors which affect the uptake and elimination of CO, although acclimatization occurs as length of stay increases. Individuals with substantial exposure to mobile source emissions, such as commuters and those living near heavily traveled roadways, represent an important population potentially susceptible to increased risk of CO-induced health effects due to elevated on-road and roadside CO concentrations.

Overall, the controlled human exposure, epidemiologic, and toxicological studies evaluated in this assessment provide evidence for increased susceptibility among multiple populations. Medical conditions that increase endogenous CO production rates may also contribute to increased susceptibility to health effects from ambient CO exposure. Although the weight of evidence varies depending on the factor being evaluated, the clearest evidence indicates that individuals with CAD are most susceptible to an increase in CO-induced health effects.

5.8. Summary

The evidence reviewed in this chapter describes recent findings regarding the health effects of ambient CO. Section 5.1 presents evidence on the mode of action of CO, including its role in limiting O_2 availability as well as its role in altered cell signaling. Evidence is presented in subsequent sections on the effect of short- and long-term exposure to CO on cardiovascular morbidity (Section 5.2), the central nervous system (Section 5.3), birth outcomes and developmental effects (Section 5.4), respiratory morbidity (Section 5.5), and mortality (Section 5.6). Potentially susceptible populations at increased risk of CO-induced health effects are discussed in Section 5.7.

Table 2-1 summarizes causal determinations for the health outcome categories reviewed in this assessment. An integrative overview of the health effects of ambient CO and uncertainties associated with interpretation of the evidence is provided in Chapter 2. The strongest evidence regarding CO-induced health effects relates to cardiovascular morbidity, and the combined evidence from controlled human exposure studies and epidemiologic studies indicates that a causal relationship is likely to exist between relevant short-term CO exposures and cardiovascular morbidity, particularly in individuals with CAD. The evidence is suggestive of a causal relationship between short-term exposure to CO and respiratory morbidity as well as between short-term CO exposure and mortality. The evidence is also suggestive of a causal relationship for birth outcomes and developmental effects following long-term exposure to CO, and for central nervous system effects linked to short- and long-term exposure to CO. The evidence indicates that there is not likely to be a causal relationship between long-term exposure to CO and mortality. For respiratory morbidity following long-term exposure to CO, the evidence was inadequate to infer a causal relationship.

References

Achouh PE; Simonet S; Fabiani JN; Verbeuren TJ (2008). Carbon monoxide induces relaxation of human internal thoracic and radial arterial grafts. Interact Cardiovasc Thorac Surg, 7: 959-963. 179918

Adams KF; Koch G; Chatterjee B; Goldstein GM; O'Neil JJ; Bromberg PA; Sheps DS; McAllister S; Price CJ; Bissette J (1988). Acute elevation of blood carboxyhemoglobin to 6% impairs exercise performance and aggravates symptoms in patients with ischemic heart disease. J Am Coll Cardiol, 12: 900-909. 012692

Aday LA (2001). At risk in America: The health and health care needs of vulnerable populations in the United States. San Francisco, CA: Jossey-Bass, Inc. 192150

Adir Y; Merdler A; Haim SB; Front A; Harduf R; Bitterman H (1999). Effects of exposure to low concentrations of carbon monoxide on exercise performance and myocardial perfusion in young healthy men. Occup Environ Med, 56: 535-538. 001026

Alderman BW; Baron AE; Savitz DA (1987). Maternal exposure to neighborhood carbon monoxide and risk of low infant birth weight. Public Health Rep, 102: 410-414. 012243

Alexandreanu IC; Lawson DM (2002). Effects of chronic administration of a heme oxygenase substrate or inhibitor on progression of the estrous cycle, pregnancy and lactation of Sprague-Dawley rats. Life Sci, 72: 153-162. 192373

Alexandreanu IC; Lawson DM (2003). Heme oxygenase in the rat anterior pituitary: Immunohistochemical localization and possible role in gonadotropin and prolactin secretion. Exp Biol Med, 228: 64-69. 193871

Allred EN; Bleecker ER; Chaitman BR; Dahms TE; Gottlieb SO; Hackney JD; Hayes D; Pagano M; Selvester RH; Walden SM; Warren J (1989). Acute effects of carbon monoxide exposure on individuals with coronary artery disease. Health Effects Institute. Boston, MA. 012697

Allred EN; Bleecker ER; Chaitman BR; Dahms TE; Gottlieb SO; Hackney JD; Pagano M; Selvester RH; Walden SM; Warren J (1989). Short-term effects of carbon monoxide exposure on the exercise performance of subjects with coronary artery disease. N Engl J Med, 321: 1426-1432. 013018

Allred EN; Bleecker ER; Chaitman BR; Dahms TE; Gottlieb SO; Hackney JD; Pagano M; Selvester RH; Walden SM; Warren J (1991). Effects of carbon monoxide on myocardial ischemia. Environ Health Perspect, 91: 89-132. 011871

Alonso JR; Cardellach F; Lopez S; Casademont J; Miro O (2003). Carbon monoxide specifically inhibits cytochrome c oxidase of human mitochondrial respiratory chain. Pharmacol Toxicol, 93: 142-146. 193882

American Lung Association (2001). Urban air pollution and health inequities: A workshop report. Environ Health Perspect, 3: 357-374. 016626

Anderson EW; Andelman RJ; Strauch JM; Fortuin NJ; Knelson JH (1973). Effect of low-level carbon monoxide exposure on onset and duration of angina pectoris: a study in ten patients with ischemic heart disease. Ann Intern Med, 79: 46-50. 023134

Andresen JJ; Shafi NI; Durante W; Bryan RM Jr (2006). Effects of carbon monoxide and heme oxygenase inhibitors in cerebral vessels of rats and mice. Am J Physiol Heart Circ Physiol, 291: H223-H230. 180449

Antonelli T; Tomasini MC; Tattoli M; Cassano T; Finetti S; Mazzoni E; Trabace L; Carratu MR; Cuomo V; Tanganelli S; Ferraro L (2006). Prenatal exposure to the cannabinoid receptor agonist WIN 55,212-2 and carbon monoxide reduces extracellular glutamate levels in primary rat cerebral cortex cell cultures. Neurochem Int, 49: 568-76. 194960

Arnedo-Pena A; Garcia-Marcos L; Carvajal Uruena I; Busquets Monge R; Morales Suarez-Varela M; Miner Canflanca I; Batlles Garrido J; Blanco Quiros A; Lopez-Silvarrey Varela A; Garcia Hernandez G; Aguinaga Ontoso I; Gonzalez Diaz C (2009). Air pollution and recent symptoms of asthma, allergic rhinitis, and atopic eczema in schoolchildren aged between 6 and 7 years. Arch Bronconeumol, 45: 224-229. 190238

Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at http://epa.gov/hero. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISAs) and the Integrated Risk Information System (IRIS).

Astrup P; Olsen HM; Trolle D; Kjeldsen K (1972). Effect of moderate carbon-monoxide exposure on fetal development. Lancet, 7789: 1220-1222. 011121

Ayres SM; Giannelli S Jr; Mueller H; Criscitiello A (1973). Myocardial and systemic vascular responses to low concentration of carboxyhemoglobin. Ann Clin Lab Sci, 3: 440-447. 193943

Baccarelli A; Zanobetti A; Martinelli I; Grillo P; Hou L; Giacomini S; Bonzini M; Lanzani G; Mannucci PM; Bertazzi PA; Schwartz J (2007). Effects of exposure to air pollution on blood coagulation. J Thromb Haemost, 5: 252-260. 090733

Bainbridge SA; Farley AE; McLaughlin BE; Graham CH; Marks GS; Nakatsu K; Brien JF; Smith GN (2002). Carbon monoxide decreases perfusion pressure in isolated human placenta. Placenta, 23: 563-569. 043161

Baldauf R; Thoma E; Khlystov A; Isakov V; Bowker G; Long T; Snow R (2008). Impacts of noise barriers on near-road air quality. Atmos Environ, 42: 7502-7507. 191017

Ballester F; Rodriguez P; Iniguez C; Saez M; Daponte A; Galan I; Taracido M; Arribas F; Bellido J; Cirarda FB; Canada A; Guillen JJ; Guillen-Grima F; Lopez E; Perez-Hoyos S; Lertxundi A; Toro S (2006). Air pollution and cardiovascular admisisons association in Spain: results within the EMECAS project. J Epidemiol Community Health, 60: 328-336. 088746

Ballester F; Tenias JM; Perez-Hoyos S (2001). Air pollution and emergency hospital admissions for cardiovascular diseases in Valencia, Spain. J Epidemiol Community Health, 55: 57-65. 013257

Barber A; Robson SC; Myatt L; Bulmer JN; Lyall F (2001). Heme oxygenase expression in human placenta and placental bed: reduced expression of placenta endothelial HO-2 in preeclampsia and fetal growth restriction. FASEB J, 15: 1158-68. 193891

Barker DJ; Eriksson JG; Forsen T; Osmond C (2002). Fetal origins of adult disease: Strength of effects and biological basis. Int J Epidemiol, 31: 1235-1239. 193960

Barnett AG; Williams GM; Schwartz J; Best TL; Neller AH; Petroeschevsky AL; Simpson RW (2006). The effects of air pollution on hospitalizations for cardiovascular disease in elderly people in Australian and New Zealand cities. Environ Health Perspect, 114: 1018-1023. 089770

Bathoorn E; Slebos DJ; Postma DS; Koeter GH; van Oosterhout AJ; van der Toorn M; Boezen HM; Kerstjens HA (2007). Anti-inflammatory effects of inhaled carbon monoxide in patients with COPD: A pilot study. Eur Respir J, 30: 1131-1137. 193963

Beard RR; Wertheim GA (1967). Behavioral impairment associated with small doses of carbon monoxide. Am J Public Health, 57: 2012-2022. 011015

Bell ML; Ebisu K; Belanger K (2007). Ambient air pollution and low birth weight in Connecticut and Massachusetts. Environ Health Perspect, 115: 1118-24. 091059

Bell ML; Peng RD; Dominici F; Samet JM (2009). Emergency admissions for cardiovascular disease and ambient levels of carbon monoxide: Results for 126 U.S. urban counties, 1999-2005. Circulation, 120: 949-955. 193780

Benagiano V; Lorusso L; Coluccia A; Tarullo A; Flace P; Girolamo F; Bosco L; Cagiano R; Ambrosi G (2005). Glutamic acid decarboxylase and GABA immunoreactivities in the cerebellar cortex of adult rat after prenatal exposure to a low concentration of carbon monoxide. Neuroscience, 135: 897-905. 180445

Benagiano V; Lorusso L; Flace P; Girolamo F; Rizzi A; Sabatini R; Auteri P; Bosco L; Cagiano R; Ambrosi G (2007). Effects of prenatal exposure to the CB-1 receptor agonist WIN 55212-2 or CO on the GABAergic neuronal systems of rat cerebellar cortex. Neuroscience, 149: 592-601. 193892

Benignus VA (1993). Importance of experimenter-blind procedure in neurotoxicology. Neurotoxicol Teratol, 15: 45-49. 013645

Benignus VA; Muller KE; Barton CN; Prah JD (1987). Effect of low level carbon monoxide on compensatory tracking and event monitoring. Neurotoxicol Teratol, 9: 227-234. 012250

Berger A; Zareba W; Schneider A; Ruckerl R; Ibald-Mulli A; Cyrys J; Wichmann HE; Peters A (2006). Runs of ventricular and supraventricular tachycardia triggered by air pollution in patients with coronary heart disease. J Occup Environ Med, 48: 1149-58. 098702

Berk PD; Rodkey FL; Blaschke TF; Collison HA; Waggoner JG (1974). Comparison of plasma bilirubin turnover and carbon monoxide production in man. J Lab Clin Med, 83: 29-37. 012386

Berkowitz GS; Papiernik E (1993). Epidemiology of preterm birth. Epidemiol Rev, 15: 414-443. 055466

Bernard N; Saintot M; Astre C; Gerber M (1998). Personal exposure to nitrogen dioxide pollution and effect on plasma antioxidants. J Lab Clin Med, 53: 122-128. 086427

Biggeri A; Baccini M; Bellini P; Terracini B (2005). Meta-analysis of the Italian studies of short-term effects of air pollution (MISA), 1990-1999. Int J Occup Environ Health, 11: 107-122. 087395

Bing O; Grundemar L; Ny L; Moller C; Heilig M (1995). Modulation of carbon monoxide production and enhanced spatial learning by tin protoporphyrin. Neuroreport, 6: 1369-1372. 079418

Boneva RS; Botto LD; Moore CA; Yang QH; Correa A; Erickson JD (2001). Mortality associated with congenital heart defects in the United States: Trends and racial disparities, 1979-1997. Circulation, 103: 2376-2381. 193972

Botto LD; Correa A; Erickson JD (2001). Racial and temporal variations in the prevalence of heart defects. Pediatrics, 107: E32. 192379

Brian JE Jr; Heistad DD; Faraci FM (1994). Effect of carbon monoxide on rabbit cerebral arteries. Stroke, 25: 639-644. 076283

Briet M; Collin C; Laurent S; Tan A; Azizi M; Agharazii M; Jeunemaitre X; Alhenc-Gelas F; Boutouyrie P (2007). Endothelial function and chronic exposure to air pollution in normal male subjects. Hypertension, 50: 970-976. 093049

Brown SD; Piantadosi CA (1992). Recovery of energy metabolism in rat brain after carbon monoxide hypoxia. J Clin Invest, 89: 666-672. 013441

Bruinen de Bruin Y; Carrer P; Jantunen M; Hänninen O; Scotto di Marco G; Kephalopoulos S; Cavallo D; Maroni M (2004). Personal carbon monoxide exposure levels: Contribution of local sources to exposures and microenvironment concentrations in Milan. J Expo Anal Environ Epidemiol, 14: 312-322. 190943

Brüne B; Ullrich V (1987). Inhibition of platelet aggregation by carbon monoxide is mediated by activation of guanylate cyclase. Mol Pharmacol, 32: 497-504. 016535

Burnett RT; Brook J; Dann T; Delocla C; Philips O; Cakmak S; Vincent R; Goldberg MS; Krewski D (2000). Association between particulate- and gas-phase components of urban air pollution and daily mortality in eight Canadian cities. Inhal Toxicol, 12: 15-39. 010273

Burnett RT; Goldberg MS (2003). Size-fractionated particulate mass and daily mortality in eight Canadian cities. Health Effects Institute. Boston, MA. 042798

Burnett RT; Smith-Doiron M; Stieb D; Raizenne ME; Brook JR; Dales RE; Leech JA; Cakmak S; Krewski D (2001). Association between ozone and hospitalization for acute respiratory diseases in children less than 2 years of age. Am J Epidemiol, 153: 444-452. 093439

Burnett RT; Stieb D; Brook JR; Cakmak S; Dales R; Raizenne M; Vincent R; Dann T (2004). Associations between short-term changes in nitrogen dioxide and mortality in Canadian cities. Arch Environ Occup Health, 59: 228-236. 086247

Bye A; Sørhaug S; Ceci M; Høydal MA; Stølen T; Heinrich G; Tjønna AE; Najjar SM; Nilsen OG; Catalucci D; Grimaldi S; Contu R; Steinshamn S; Condorelli G; Smith GL; Ellingsen O; Waldum H; Wisløff U (2008). Carbon monoxide levels experienced by heavy smokers impair aerobic capacity and cardiac contractility and induce pathological hypertrophy. Inhal Toxicol, 20: 635-646. 193777

Cagiano R; Ancona D; Cassano T; Tattoli M; Trabace L; Cuomo V (1998). Effects of prenatal exposure to low concentrations of carbon monoxide on sexual behaviour and mesolimbic dopaminergic function in rat offspring. Br J Pharmacol, 125: 909-915. 087170

Cakmak S; Dales RE; Judek S (2006). Respiratory health effects of air pollution gases: modification by education and income. Arch Environ Occup Health, 61: 5-10. 093272

Cardell L-O; Ueki IF; Stjarne P; Agusti C; Takeyama K; Linden A; Nadel JA (1998). Bronchodilatation in vivo by carbon monoxide, a cyclic GMP related messenger. Br J Pharmacol, 124: 1065-1068. 086700

Cardell LO; Lou YP; Takeyama K; Ueki IF; Lausier J; Nadel JA (1998). Carbon monoxide, a cyclic GMP-related messenger, involved in hypoxic bronchodilation in vivo. Pulm Pharmacol Ther, 11: 309-315. 011534

Carmines E; Rajendran N (2008). Evidence for carbon monoxide as the major factor contributing to lower fetal weights in rats exposed to cigarette smoke. Toxicol Sci, 102: 383. 188440

Carratu MR; Cagiano R; Desantis S; Labate M; Tattoli M; Trabace L; Cuomo V (2000). Prenatal exposure to low levels of carbon monoxide alters sciatic nerve myelination in rat offspring. Life Sci, 67: 1759-1772. 015839

Carratu MR; Cagiano R; Tattoli M; Trabace L; Borracci P; Cuomo V (2000). Prenatal exposure model simulating CO inhalation in human cigarette smokers: sphingomyelin alterations in the rat sciatic nerve. Toxicol Lett, 117: 101-106. 015935

Carratu MR; Renna G; Giustino A; De Salvia MA; Cuomo V (1993). Changes in peripheral nervous system activity produced in rats by prenatal exposure to carbon monoxide. Arch Toxicol, 67: 297-301. 013812

Carraway MS; Ghio AJ; Carter JD; Piantadosi CA (2000). Expression of heme oxygenase-1 in the lung in chronic hypoxia. Am J Physiol, 278: L806-L812. 021096

Carraway MS; Ghio AJ; Suliman HB; Carter JD; Whorton AR; Piantadosi CA (2002). Carbon monoxide promotes hypoxic pulmonary vascular remodeling. Am J Physiol, 282: L693-L702. 026018

Castillo A; Llapur CJ; Martinez T; Kisling J; Williams-Nkomo T; Coates C; Tepper RS (2006). Measurement of single breath-hold carbon monoxide diffusing capacity in healthy infants and toddlers. Pediatr Pulmonol, 41: 544-550 . 193234

Cavallin-Ståhl E; Mercke C; Lundh B (1976). Carbon monoxide production in patients with breast carcinoma. Br J Haematol, 32: 177-182. 086306

Cavallin-Ståhl E; Mercke C; Lundh B (1976). Erythropoiesis and carbon monoxide production in Hodgkin's disease. Br J Haematol, 32: 167-175. 193239

CDC (1998). Trends in infant mortality attributable to birth defects--United States, 1980-1995. MMWR Morb Mortal Wkly Rep, 47: 773-778. 193243

Cella M; Farina MG; Sarmiento MIK; Chianelli M; Rosenstein RE; Franchi AM (2006). Heme oxygenase-carbon monoxide (HO-CO) system in rat uterus : Effect of sexual steroids and prostaglandins. J Steroid Biochem Mol Biol, 99: 59-66 . 193240

Chan C-C; Chuang K-J; Chien L-C; Chen W-J; Chang W-T (2006). Urban air pollution and emergency admissions for cerebrovascular diseases in Taipei, Taiwan. Eur Heart J, 27: 1238-1244. 090193

Chan C-C; Chuang K-J; Su T-C; Lin L-Y (2005). Association between nitrogen dioxide and heart rate variability in a susceptible population. Eur J Cardiovasc Prev Rehabil, 12: 580-586. 088988

Chang C-C; Tsai S-S; Ho S-C; Yang C-Y (2005). Air pollution and hospital admissions for cardiovascular disease in Taipei, Taiwan. Environ Res, 98: 114-119. 080086

Chang L-T; Koutrakis P; Catalano PJ; Suh HH (2000). Hourly personal exposures to fine particles and gaseous pollutants--results from Baltimore, Maryland. J Air Waste Manag Assoc, 50: 1223-1235. 001276

Chen GH; Kong J; Reinhard K; Fechter LD (2001). NMDA receptor blockage protects against permanent noise-induced hearing loss but not its potentiation by carbon monoxide . Hear Res, 154: 108-115. 193985

Chen L; Yang W; Jennison BL; Goodrich A; Omaye ST (2002). Air pollution and birth weight in northern Nevada, 1991-1999. Inhal Toxicol, 14: 141-157. 024945

Chen P-C; Lai Y-M; Chan C-C; Hwang J-S; Yang C-Y; Wang J-D (1999). Short-term effect of ozone on the pulmonary function of children in primary school. Environ Health Perspect, 107: 921-925. 011149

Cheng C; Noordeloos AM; Jeney V; Soares MP; Moll F; Pasterkamp G; Serruys PW; Duckers HJ (2009). Heme oxygenase 1 determines atherosclerotic lesion progression into a vulnerable plaque. Circulation, 119: 3017-3027. 193775

Chevalier RB; Krumholz RA; Ross JC (1966). Reaction of nonsmokers to carbon monoxide inhalation: cardiopulmonary responses at rest and during exercise. JAMA, 198: 1061-1064. 010641

Chin BY; Jiang G; Wegiel B; Wang HJ; Macdonald T; Zhang XC; Gallo D; Cszimadia E; Bach FH; Lee PJ; Otterbein LE (2007). Hypoxia-inducible factor 1alpha stabilization by carbon monoxide results in cytoprotective preconditioning. PNAS, 104: 5109-5114. 190601

Chuang KJ; Coull BA; Zanobetti A; Suh H; Schwartz J; Stone PH; Litonjua A; Speizer FE; Gold DR (2008). Particulate Air Pollution as a Risk Factor for ST-Segment Depression in Patients With Coronary Artery Disease. Circulation, 118: 1314-1320. 155731

Chung Y; Huang SJ; Glabe A; Jue T (2006). Implication of CO inactivation on myoglobin function. Am J Physiol Lung Cell Mol Physiol, 290: 1616-1624. 193987

Coburn RF; Williams WJ; Kahn SB (1966). Endogenous carbon monoxide production in patients with hemolytic anemia. J Clin Invest, 45: 460-468. 010984

Coceani F; Breen CA; Lees JG; Falck JR; Olley PM (1988). Further evidence implicating a cytochrome P-450-mediated reaction in the contractile tension of the lamb ductus arteriosus. Circ Res, 62: 471-477. 040493

Cronje FJ; Carraway MS; Freiberger JJ; Suliman HB; Piantadosi CA (2004). Carbon monoxide actuates O2-limited heme degradation in the rat brain. Free Radic Biol Med, 37: 1802-1812. 180440

D'Amico G; Lam F; Hagen T; Moncada S (2006). Inhibition of cellular respiration by endogenously produced carbon monoxide. J Cell Sci, 119: 2291-2298. 193992

D'Ippoliti D; Forastiere F; Ancona C; Agabiti N; Fusco D; Michelozzi P; Perucci CA (2003). Air pollution and myocardial infarction in Rome: a case-crossover analysis. Epidemiology, 14: 528-535. 074311

Dales R (2004). Ambient carbon monoxide may influence heart rate variability in subjects with coronary artery disease. J Occup Environ Med, 46: 1217-1221. 099036

Davies DM; Smith DJ (1980). Electrocardiographic changes in healthy men during continuous low-level carbon monoxide exposure. Environ Res, 21: 197-206. 011288

Davies RF; Topping DL; Turner DM (1976). The effect of intermittent carbon monoxide exposure on experimental atherosclerosis in the rabbit. Atherosclerosis, 24: 527-536. 010660

Deedwania PC; Stein PK; Koren A; Mukherjee R; Pitt B (2005). Decreased heart rate variability is an independent predictor of sudden cardiac death in post-ML heart failure: Results of the EPHESUS arrhythmia and heart-rate variability analysis. In JT Dipiro (Ed.),Pharmacotherapy: A Pathophysiological Approach (pp. 3029). New York City: McGraw-Hill. 195134

Delfino RJ: Staimer N; Tjoa T; Gillen DL; Polidori A; Arhami M; Kleinman MT; Vaziri ND; Longhurst J; Sioutas C (2009). Air pollution exposures and circulating biomarkers of effect in a susceptible population: clues to potential causal component mixtures and mechanisms. Environ Health Perspect, 117: 1232-1238. 200844

Delfino RJ; Gone H; Linn WS; Pellizzari ED; Hu Y (2003). Asthma symptoms in Hispanic children and daily ambient exposures to toxic and criteria air pollutants. Environ Health Perspect, 111: 647-656. 050460

Delfino RJ; Staimer N; Tjoa T; Polidori A; Arhami M; Gillen DL; Kleinman MT; Vaziri ND; Longhurst J; Zaldivar F; Sioutas C (2008). Circulating biomarkers of inflammation, antioxidant activity, and platelet activation are associated with primary combustion aerosols in subjects with coronary artery disease. Environ Health Perspect, 116: 898-906. 156390

Delivoria-Papadopoulos M; Coburn RF; Forster RE (1974). Cyclic variation of rate of carbon monoxide production in normal women. J Appl Physiol, 36: 49-51. 086316

Denschlag D; Marculescu R; Unfried G; Hefler LA; Exner M; Hashemi A; Riener EK; Keck C; Tempfer CB; Wagner O (2004). The size of a microsatellite polymorphism of the haem oxygenase 1 gene is associated with idiopathic recurrent miscarriage. Mol Hum Reprod, 10: 211-4. 193894

De Hartog JJ; Hoek G; Peters A; Timonen KL; Ibald-Mulli A; Brunekreef B; Heinrich J; Tiittanen P; Van Wijnen JH; Kreyling W; Kulmala M; Pekkanen J (2003). Effects of fine and ultrafine particles on cardiorespiratory symptoms in elderly subjects with coronary heart disease: the ULTRA study. Am J Epidemiol, 157: 613-623. 001061

De Jong MJ; Randall DC (2005). Heart rate variability analysis in the assessment of autonomic function in heart failure. J Cardiovasc Nurs, 20: 186-195; quiz 196-197. 193996

De Leon SF; Thurston GD; Ito K (2003). Contribution of respiratory disease to nonrespiratory mortality associations with air pollution. Am J Respir Crit Care Med, 167: 1117-1123. 055688

De Luca A; Pierno S; Tricarico D; Carratu MR; Cagiano R; Cuomo V; Camerino DC (1996). Developmental changes of membrane electrical properties of rat skeletal muscle fibers produced by prenatal exposure to carbon monoxide. Environ Toxicol Pharmacol, 2: 213-221. 080911

De Salvia MA; Cagiano R; Carratu MR; Di Giovanni V; Trabace L; Cuomo V (1995). Irreversible impairment of active avoidance behavior in rats prenatally exposed to mild concentrations of carbon monoxide. Psychopharmacology, 122: 66-71. 079441

Di Cera E; Doyle ML; Morgan MS; De Cristofaro R; Landolfi R; Bizzi B; Castagnola M; Gill SJ (1989). Carbon monoxide and oxygen binding to human hemoglobin F0. Biochemistry, 28: 2631-2638. 193998

Di Giovanni V; Cagiano R; De Salvia MA; Giustino A; Lacomba C; Renna G; Cuomo V (1993). Neurobehavioral changes produced in rats by prenatal exposure to carbon monoxide. Brain Res, 616: 126-131. 013822

Dockery DW; Luttmann-Gibson H; Rich DQ; Link MS; Mittleman MA; Gold DR; Koutrakis P; Schwartz JD; Verrier RL (2005). Association of air pollution with increased incidence of ventricular tachyarrhythmias recorded by implanted cardioverter defibrillators. Environ Health Perspect, 113: 670-674. 078995

Dominici F; McDermott A; Daniels M; Zeger SL; Samet JM (2003). Mortality among residents of 90 cities. In: Revised analyses of time-series studies of air pollution and health. Health Effects Institute. Boston, MA. HEI Special Report. http://www.healtheffects.org/Pubs/TimeSeries.pdf. 056116

Dominici F; McDermott A; Daniels M; Zeger SL; Samet JM (2005). Revised analyses of the national morbidity, mortality, and air pollution study: mortality among residents of 90 cities. J Toxicol Environ Health A Curr Iss, 68: 1071-1092. 087912

Dominici F; McDermott A; Zeger SL; Samet JM (2002). On the use of generalized additive models in time-series studies of air pollution and health. Am J Epidemiol, 156: 193-203. 030458

Drinkwater BL; Raven PB; Horvath SM; Gliner JA; Ruhling RO; Bolduan NW; Taguchi S (1974). Air pollution, exercise, and heat stress. Arch Environ Occup Health, 28: 177-181. 041332

Dubuis E; Gautier M; Melin A; Rebocho M; Girardin C; Bonnet P; Vandier C (2002). Chronic carbon monoxide enhanced IbTx-sensitive currents in rat resistance pulmonary artery smooth muscle cells. Am J Physiol Lung Cell Mol Physiol, 283: L120-L129. 193911

Dubuis E; Gautier M; Melin A; Rebocho M; Girardin C; Bonnet P; Vandier C (2003). Chronic carbon monoxide exposure of hypoxic rats increases in vitro sensitivity of pulmonary artery smooth muscle. Can J Physiol Pharmacol, 81: 711-719. 180439

Durante W; Johnson FK; Johnson RA (2006). Role of carbon monoxide in cardiovascular function. J Cell Mol Med, 10: 672-686. 193778

Dyer R; Eccles U; Swartzwelder H; Fechter L; Annau Z (1979). Prenatal carbon monoxide and adult evoked potentials in rats. J Environ Sci Health C Environ Carcinog Ecotoxicol Rev, 13: 107-120. 190994

Ekblom B; Huot R (1972). Response to submaximal and maximal exercise at different levels of carboxyhemoglobin. Acta Physiol, 86: 474-482. 010886

Farrugia G; Irons WA; Rae JL; Sarr MG; Szurszewski JH (1993). Activation of whole cell currents in isolated human jejunal circular smooth muscle cells by carbon monoxide. Am J Physiol, 264: G1184-G1189. 013826

Favory R; Lancel S; Tissier S; Mathieu D; Decoster B; Neviere R (2006). Myocardial dysfunction and potential cardiac hypoxia in rats induced by carbon monoxide inhalation. Am J Respir Crit Care Med, 174: 320-325. 184462

Fechter LD; Annau Z (1977). Toxicity of mild prenatal carbon monoxide exposure. Science, 197: 680-682. 010688

Fechter LD; Annau Z (1980). Prenatal carbon monoxide exposure alters behavioral development. Neurotoxicol Teratol, 2: 7-11. 011295

Fechter LD; Chen GD; Rao D (2002). Chemical Asphyxiants and Noise. Noise Health, 4: 49-61. 193926

Fechter LD; Karpa MD; Proctor B; Lee AG; Storm JE (1987). Disruption of neostriatal development in rats following perinatal exposure to mild, but chronic carbon monoxide. Neurotoxicol Teratol, 9: 277-281. 012259

Fechter LD; Liu Y; Pearce TA (1997). Cochlear protection from carbon monoxide exposure by free radical blockers in the guinea pig. Toxicol Appl Pharmacol, 142: 47-55. 081322

Fechter LD; Thakur M; Miller B; Annau Z; Srivastava U (1980). Effects of prenatal carbon monoxide exposure on cardiac development. Toxicol Appl Pharmacol, 56: 370-375. 011294

Fischer PH; Steerenberg PA; Snelder JD; Van Loveren H; Van Amsterdam JGC (2002). Association between exhaled nitric oxide, ambient air pollution and respiratory health in school children. Int Arch Occup Environ Health, 75: 348-353. 025731

Fisher AB; Hyde RW; Baue AE; Reif JS; Kelly DF (1969). Effect of carbon monoxide on function and structure of the lung. J Appl Physiol, 26: 4-12. 012381

Fodor GG; Winneke G (1972). Effect of low CO concentrations on resistance to monotony and on psychomotor capacity. Gefahrst Reinhalt Luft, 32: 46-54. 011041

Fried PA; Watkinson B; Gray R (1998). Differential effects on cognitive functioning in 9- to 12-year olds prenatally exposed to cigarettes and marihuana. Neurotoxicol Teratol, 20: 293-306. 190210

Fried PA; Watkinson B; Gray R (2003). Differential effects on cognitive functioning in 13- to 16-year-olds prenatally exposed to cigarettes and marihuana. Neurotoxicol Teratol, 25: 427-436. 190209

Fung KY; Luginaah I; Gorey KM; Webster G (2005). Air pollution and daily hospital admissions for cardiovascular diseases in Windsor, Ontario. Can J Public Health, 96: 29-33. 074322

Gautier M; Antier D; Bonnet P; Le Net JL; Hanton G; Eder V (2007). Continuous inhalation of carbon monoxide induces right ventricle ischemia and dysfunction in rats with hypoxic pulmonary hypertension. Am J Physiol Heart Circ Physiol, 293: H1046-52. 096471

Ghio AJ; Stonehuerner JG; Dailey LA; Richards JH; Madden MD; Deng Z; Nguyen NB; Callaghan KD; Yang F; Piantadosi CA (2008). Carbon monoxide reversibly alters iron homeostasis and respiratory epithelial cell function. Am J Respir Cell Mol Biol, 38: 715-723. 096321

Gilboa SM; Mendola P; Olshan AF; Langlois PH; Savitz DA; Loomis D; Herring AH; Fixler DE (2005). Relation between ambient air quality and selected birth defects, seven county study, Texas, 1997-2000. Am J Epidemiol, 162: 238-252. 087892

Giustino A; Cagiano R; Carratu MR; Cassano T; Tattoli M; Cuomo V (1999). Prenatal exposure to low concentrations of carbon monoxide alters habituation and non-spatial working memory in rat offspring. Brain Res, 844: 201-205. 011538

Giustino A; Cagiano R; Carratu MR; De Salvia MA; Panaro MA; Jirillo E; Cuomo V (1993). Immunological changes produced in rats by prenatal exposure to carbon monoxide. Basic Clin Pharmacol Toxicol, 73: 274-278. 013833

Giustino A; Carratu MR; Brigiani GS; De Salvia MA; Pellegrino NM; Steardo L; Jirillo E; Cuomo V (1994). Changes in the frequency of splenic immunocompetent cells in rats exposed to carbon monoxide during gestation. Immunopharmacol Immunotoxicol, 16: 281-292. 076343

Glabe A; Chung Y; Xu D; Jue T (1998). Carbon monoxide inhibition of regulatory pathways in myocardium. Am J Physiol, 274: H2143-2151. 086704

Gold DR; Litonjua A; Schwartz J; Lovett E; Larson A; Nearing B; Allen G; Verrier M; Cherry R; Verrier R (2000). Ambient pollution and heart rate variability. Chest, 101: 1267-1273. 011432

Gold DR; Litonjua AA; Zanobetti A; Coull BA; Schwartz J; MacCallum G; Verrier RL; Nearing BD; Canner MJ; Suh H; Stone PH (2005). Air pollution and ST-segment depression in elderly subjects. Environ Health Perspect, 113: 883-887. 087558

Goldberg MS; Burnett RT; Valois M-F; Flegel K; Bailar JC III; Brook J; Vincent R; Radon K (2003). Associations between ambient air pollution and daily mortality among persons with congestive heart failure. Environ Res, 91: 8-20. 035202

Goldberg MS; Giannetti N; Burnett RT; Mayo NE; Valois MF; Brophy JM (2008). A panel study in congestive heart failure to estimate the short-term effects from personal factors and environmental conditions on oxygen saturation and pulse rate. Occup Environ Med, 65: 659-666. 180380

Goss CH; Newsom SA; Schildcrout JS; Sheppard L; Kaufman JD (2004). Effect of ambient air pollution on pulmonary exacerbations and lung function in cystic fibrosis. Am J Respir Crit Care Med, 169: 816-821. 055624

Gouveia N; Bremner SA; Novaes HMD (2004). Association between ambient air pollution and birth weight in Sao Paulo, Brazil. J Epidemiol Community Health, 58: 11-17. 055613

Grover TR; Rairigh RL; Zenge JP; Abman SH; Kinsella JP (2000). Inhaled carbon monoxide does not cause pulmonary vasodilation in the late-gestation fetal lamb. Am J Physiol Lung Cell Mol Physiol, 278: L779-84. 097088

Gryparis A; Forsberg B; Katsouyanni K; Analitis A; Touloumi G; Schwartz J; Samoli E; Medina S; Anderson HR; Niciu EM; Wichmann HE; Kriz B; Kosnik M; Skorkovsky J; Vonk JM; Dortbudak Z (2004). Acute effects of ozone on mortality from the "Air pollution and health: a European approach" project. Am J Respir Crit Care Med, 170: 1080-1087. 057276

Guo YL; Lin Y-C; Sung F-C; Huang S-L; Ko Y-C; Lai J-S; Su H-J; Shaw C-K; Lin R-S; Dockery DW (1999). Climate, traffic-related air pollutants, and asthma prevalence in middle-school children in Taiwan. Environ Health Perspect, 107: 1001-1006. 010937

Ha E-H; Hong Y-C; Lee B-E; Woo B-H; Schwartz J; Christiani DC (2001). Is air pollution a risk factor for low birth weight in Seoul? Epidemiology, 12: 643-648. 019390

Ha E-H; Lee J-T; Kim H; Hong Y-C; Lee (2003). Infant susceptibility of mortality to air pollution in Seoul, South Korea. Pediatrics, 111: 284-290. 042552

Hajat S; Armstrong B; Wilkinson P; Busby A; Dolk H (2007). Outdoor air pollution and infant mortality: Analysis of daily time-series data in 10 English cities. J Epidemiol Community Health, 61: 719-722. 093276

Hampson NB; Weaver LK (2007). Carbon monoxide poisoning: a new incidence for an old disease. Undersea Hyperb Med, 34: 163-168. 190272

Hanada A; Sander M; González-Alonso J (2003). Human skeletal muscle sympathetic nerve activity, heart rate and limb haemodynamics with reduced blood oxygenation and exercise. J Physiol, 551: 635-647. 193915

Harada T; Koi H; Kubota T; Aso T (2004). Haem oxygenase augments porcine granulosa cell apoptosis in vitro. J Endocrinol, 181: 191-205. 193920

Hausberg M; Somers VK (1997). Neural circulatory responses to carbon monoxide in healthy humans. Hypertension, 29: 1114-1118. 083450

Hawkins RD; Zhuo M; Arancio O (1994). Nitric oxide and carbon monoxide as possible retrograde messengers in hippocampal long-term potentiation. Dev Neurobiol, 25: 652-665. 076503

Henrotin JB; Besancenot JP; Bejot Y; Giroud M (2007). Short-term effects of ozone air pollution on ischaemic stroke occurrence: A case-crossover analysis from a 10-year population-based study in Dijon, France. Occup Environ Med, 64: 439-445. 093270

Hermans RH; McGivern RF; Chen W; Longo LD (1993). Altered adult sexual behavior in the male rat following chronic prenatal hypoxia. Neurotoxicol Teratol, 15: 353-63. 190510

Hill EP; Hill JR; Power GG; Longo LD (1977). Carbon monoxide exchanges between the human fetus and mother: A mathematical model. Am J Physiol, 232: H311-H323. 011315

Hirsch T; Weiland SK; Von Mutius E; Safeca AF; Grafe H; Csaplovics E; Duhme H; Keil U; Leupold W (1999). Inner city air pollution and respiratory health and atopy in children. Eur Respir J, 14: 669-677. 003537

Hoek G (2003). Daily mortality and air pollution in The Netherlands. Health Effects Institute. Boston, MA. 042818

Hoek G; Brunekreef B; Fischer P; Van Wijnen J (2001). The association between air pollution and heart failure, arrhythmia, embolism, thrombosis, and other cardiovascular causes of death in a time series study. Epidemiology, 12: 355-357. 016550

Hoek G; Brunekreef B; Verhoeff A; Van Wijnen J; Fischer P (2000). Daily mortality and air pollution in the Netherlands. J Air Waste Manag Assoc, 50: 1380-1389. 010350

Holguin F; Tellez-Rojo MM; Hernandez M; Cortez M; Chow JC; Watson JG; Mannino D; Romieu I (2003). Air pollution and heart rate variability among the elderly in Mexico City. Epidemiology, 14: 521-527. 057326

Horvath SM; Bedi JF; Wagner JA; Agnew JW (1988). Maximal aerobic capacity at several ambient concentrations of carbon monoxide at several altitudes. J Appl Physiol, 65: 2696-2708. 012725

Horvath SM; Dahms TE; O'Hanlon JF (1971). Carbon monoxide and human vigilance: A deleterious effect of present urban concentrations. Arch Environ Occup Health, 23: 343-347. 011075

Horvath SM; Raven PB; Dahms TE; Gray DJ (1975). Maximal aerobic capacity at different levels of carboxyhemoglobin. J Appl Physiol, 38: 300-303. 010887

Hosseinpoor AR; Forouzanfar MH; Yunesian M; Asghari F; Naieni KH; Farhood D (2005). Air pollution and hospitalization due to angina pectoris in Tehran, Iran: A time-series study. Environ Res, 99: 126-131. 087413

Hsia CC (2002). Recruitment of lung diffusing capacity: Update of concept and application. Chest, 122: 1774-1783. 193857

Huikuri HV; Jokinen V; Syvanne M; Nieminen MS; Airaksinen KEJ; Ikaheimo MJ; Koistinen JM; Kauma H; Kesaniemi AY; Majahalme S; Niemela KO; Frick MH (1999). Heart rate variability and progression of coronary atherosclerosis. Arterioscler Thromb Vasc Biol, 19: 1979-1985. 184464

Hutcheon JA; Platt RW (2008). The missing data problem in birth weight percentiles and thresholds for "small-for-gestational-age". Am J Epidemiol, 167: 786-792. 193795

Huynh M; Woodruff TJ; Parker JD; Schoendorf KC (2006). Relationships between air pollution and preterm birth in California. Paediatr Perinat Epidemiol, 20: 454-461. 091240

Hwang B-F; Jaakkola JJK; Lee Y-L; Lin Y-C; Guo Y-LL (2006). Relation between air pollution and allergic rhinitis in Taiwanese schoolchildren. Respir Res, 7: 23. 088971

Hwang B-F; Lee Y-L; Lin Y-C; Jaakkola JJK; Guo YL (2005). Traffic related air pollution as a determinant of asthma among Taiwanese school children. Thorax, 60: 467-473. 089454

Hwang BF; Jaakkola JJ (2008). Ozone and other air pollutants and the risk of oral clefts. Environ Health Perspect, 116: 1411-1415. 193794

Ibald-Mulli A; Stieber J; Wichmann H-E; Koenig W; Peters A (2001). Effects of air pollution on blood pressure: A population-based approach. Am J Public Health, 91: 571-577. 016030

Ibald-Mulli A; Timonen KL; Peters A; Heinrich J; Wolke G; Lanki T; Buzorius G; Kreyling WG; De Hartog J; Hoek G; Ten Brink HM; Pekkanen J (2004). Effects of particulate air pollution on blood pressure and heart rate in subjects with cardiovascular disease: a multicenter approach. Environ Health Perspect, 112: 369-377. 087415

Iheagwara KN; Thom SR; Deutschman CS; Levy RJ (2007). Myocardial cytochrome oxidase activity is decreased following carbon monoxide exposure. Biochim Biophys Acta, 1772: 1112-1116. 193861

Imai T; Morita T; Shindo T; Nagai R; Yazaki Y; Kurihara H; Suematsu M; Katayama S (2001). Vascular smooth muscle cell-directed overexpression of heme oxygenase-1 elevates blood pressure through attenuation of nitric oxide-induced vasodilation in mice. Circ Res, 89: 55-62. 193864

Ischiropoulos H; Beers MF; Ohnishi ST; Fisher D; Garner SE; Thom SR (1996). Nitric oxide production and perivascular tyrosine nitration in brain after carbon monoxide poisoning in the rat. J Clin Invest, 97: 2260-2267. 079491

Ito K; Thurston GD; Silverman RA (2007). Characterization of PM2.5, gaseous pollutants, and meteorological interactions in the context of time-series health effects models. J Expo Sci Environ Epidemiol, 17 Suppl 2: S45-S60. 156594

Jalaludin B; Mannes T; Morgan G; Lincoln D; Sheppeard V; Corbett S (2007). Impact of ambient air pollution on gestational age is modified by season in Sydney, Australia. Environ Health, 6: 16. 156601

Jalaludin B; Morgan G; Lincoln D; Sheppeard V; Simpson R; Corbett S (2006). Associations between ambient air pollution and daily emergency department attendances for cardiovascular disease in the elderly (65+ years), Sydney, Australia. J Expo Sci Environ Epidemiol, 16: 225-237. 189416

Jerrett M; Burnett RT; Willis A; Krewski D; Goldberg MS; DeLuca P; Finkelstein N (2003). Spatial analysis of the air pollution-mortality relationship in the context of ecologic confounders. J Toxicol Environ Health A Curr Iss, 66: 1735-1777. 087380

Johnson FK; Durante W; Peyton KJ; Johnson RA (2003). Heme oxygenase inhibitor restores arteriolar nitric oxide function in Dahl rats. Hypertension, 41: 149-155. 193868

Johnson FK; Durante W; Peyton KJ; Johnson RA (2004). Heme oxygenase-mediated endothelial dysfunction in DOCA-salt, but not in spontaneously hypertensive, rat arterioles. Am J Physiol Heart Circ Physiol, 286: 1681-1687. 193870

Johnson FK; Johnson RA (2003). Carbon monoxide promotes endothelium-dependent constriction of isolated gracilis muscle arterioles. Am J Physiol, 285: R536-R541. 053611

Johnson FK; Johnson RA; Durante W; Jackson KE; Stevenson BK; Peyton KJ (2006). Metabolic syndrome increases endogenous carbon monoxide production to promote hypertension and endothelial dysfunction in obese Zucker rats. Am J Physiol Regul Integr Comp Physiol, 290: 601-608. 193874

Joumard R; Chiron M; Vidon R; Maurin M; Rouzioux J-M (1981). Mathematical models of the uptake of carbon monoxide on hemoglobin at low carbon monoxide levels. Environ Health Perspect, 41: 277-289. 011330

Kanten WE; Penney DG; Francisco K; Thill JE (1983). Hemodynamic responses to acute carboxyhemoglobinemia in the rat. Am J Physiol, 244: H320-H327. 011333

Karr C; Lumley T; Schreuder A; Davis R; Larson T; Ritz B; Kaufman J (2007). Effects of subchronic and chronic exposure to ambient air pollutants on infant bronchiolitis. Am J Epidemiol, 165: 553-560. 090719

Karr C; Lumley T; Shepherd K; Davis R; Larson T; Ritz B; Kaufman J (2006). A case-crossover study of wintertime ambient air pollution and infant bronchiolitis. Environ Health Perspect, 114: 277-281. 088751

Katoue MG; Khan I; Oriowo MA (2005). Increased expression and activity of heme oxygenase-2 in pregnant rat aorta is not involved in attenuated vasopressin-induced contraction. Naunyn Schmiedebergs Arch Pharmacol, 372: 220-7. 193896

Katsouyanni K; Touloumi G; Samoli E; Gryparis A; Le Tertre A; Monopolis Y; Rossi G; Zmirou D; Ballester F; Boumghar A; Anderson HR; Wojtyniak B; Paldy A; Braunstein R; Pekkanen J; Schindler C; Schwartz J (2001). Confounding and effect modification in the short-term effects of ambient particles on total mortality: results from 29 European cities within the APHEA2 project. Epidemiology, 12: 521-531. 019008

Kaur S; Nieuwenhuijsen M; Colvile R (2005). Personal exposure of street canyon intersection users to PM2.5, ultrafine particle counts and carbon monoxide in central London, UK. Atmos Environ, 39: 3629-3641. 086504

Kim HP; Wang X; Nakao A; Kim SI; Murase N; Choi ME; Ryter SW; Choi AM (2005). Caveolin-1 expression by means of p38beta mitogen-activated protein kinase mediates the antiproliferative effect of carbon monoxide. PNAS, 102: 11319-11324. 193959

Kim HS; Loughran PA; Rao J; Billar TR; Zuckerbraun BS (2008). Carbon monoxide activates NF-kappaB via ROS generation and Akt pathways to protect against cell death of hepatocytes. Am J Physiol Gastrointest Liver Physiol, 295: G146-G152. 193961

Kingdom JC; Kaufmann P (1997). Oxygen and placental villous development: origins of fetal hypoxia. Placenta, 18: 613-21; discussion 623-6. 193897

Kinney HC; Filiano JJ; Sleeper LA; Mandell F; Valdes-Dapena M; White WF (1995). Decreased muscarinic receptor binding in the arcuate nucleus in sudden infant death syndrome. Science, 269: 1446-1450. 193898

Kizakevich PN; McCartney ML; Hazucha MJ; Sleet LH; Jochem WJ; Hackney AC; Bolick K (2000). Noninvasive ambulatory assessment of cardiac function in healthy men exposed to carbon monoxide during upper and lower body exercise. Eur J Appl Physiol, 83: 7-16. 052691

Klasner AE; Smith SR; Thompson MW; Scalzo AJ (1998). Carbon monoxide mass exposure in a pediatric population. Acad Emerg Med, 5: 992-996. 087196

Klausen K; Rasmussen B; Gjellerod H; Madsen H; Petersen E (1968). Circulation, metabolism and ventilation during prolonged exposure to carbon monoxide and to high altitude. Scand J Clin Lab Invest, 103: 26-38. 193936

Kleeberger SR; Ohtsuka Y (2005). Gene-particulate matter-health interactions. Toxicol Appl Pharmacol, 207: S276-S281. 130489

Kleinman MT; Davidson DM; Vandagriff RB; Caiozzo VJ; Whittenberger JL (1989). Effects of short-term exposure to carbon monoxide in subjects with coronary artery disease. Arch Environ Occup Health, 44: 361-369. 012696

Kleinman MT; Leaf DA; Kelly E; Caiozzo V; Osann K; O'Niell T (1998). Urban angina in the mountains: effects of carbon monoxide and mild hypoxemia on subjects with chronic stable angina. Arch Environ Occup Health, 53: 388-397. 047186

Klemm RJ; Lipfert FW; Wyzga RE; Gust C (2004). Daily mortality and air pollution in Atlanta: two years of data from ARIES. Inhal Toxicol, 16 Suppl 1: 131-141. 056585

Knuckles TL; Lund AK; Lucas SN; Campen MJ (2008). Diesel exhaust exposure enhances venoconstriction via uncoupling of eNOS. Toxicol Appl Pharmacol, 230: 346-351. 191987

Koehler RC; Jones MD Jr; Traystman RJ (1982). Cerebral circulatory response to carbon monoxide and hypoxic hypoxia in the lamb. Am J Physiol, 243: H27-H32. 011341

Kohsaka A; Watanobe H; Kakizaki Y; Suda T (1999). A comparative study of the effects of nitric oxide and carbon monoxide on the in vivo release of gonadotropin-releasing hormone and neuropeptide Y from rat hypothalamus during the estradiol-induced luteinizing hormone surge: estimation by push-pull perfusion. Neuroendocrinology, 69: 245-253. 191000

Koike A; Wasserman K; Armon Y; Weiler-Ravell D (1991). The work-rate-dependent effect of carbon monoxide on ventilatory control during exercise. Respir Physiol Neurobiol, 85: 169-183. 013500

Koken PJM; Piver WT; Ye F; Elixhauser A; Olsen LM; Portier CJ (2003). Temperature, air pollution, and hospitalization for cardiovascular diseases among elderly people in Denver. Environ Health Perspect, 111: 1312-1317. 049466

Korres S; Riga M; Balatsouras D; Papadakis C; Kanellos P; Ferekidis E (2007). Influence of smoking on developing cochlea: Does smoking during pregnancy affect the amplitudes of transient evoked otoacoustic emissions in newborns? Int J Pediatr Otorhinolaryngol, 71: 781-786. 190908

Kotsch K; Francuski M; Pascher A; Klemz R; Seifert M; Mittler J; Schumacher G; Buelow R; Volk HD; Tullius SG; Neuhaus P; Pratschke J (2006). Improved long-term graft survival after HO-1 induction in brain-dead donors. Am J Transplant, 6: 477-86. 193899

Kreider JC; Blumberg MS (2005). Geotaxis and beyond: Commentary on Motz and Alberts. Neurotoxicol Teratol, 27: 529-533. 193944

Krewski D; Burnett RT; Goldberg MS; Hoover K; Siemiatycki J; Jerrett M; Abrahamowicz M; White WH (2000). Reanalysis of the Harvard Six Cities study and the American Cancer Society study of particulate air pollution and mortality. Health Effects Institute. Cambridge, MA.http://pubs.healtheffects.org/view.php?id=6. 012281

Krewski D; Jerrett M; Burnett RT; Ma R; Hughes E; Shi Y; Turner MC; Pope AC III; Thurston G; Calle EE; Thun MJ (2009). Extended follow-up and spatial analysis of the American Cancer Society study linking particulate air pollution and mortality. Health Effects Institute. Cambridge, MA. Report Nr. 140. 191193

Kunzli N; Tager IB (1997). The semi-individual study in air pollution epidemiology: a valid design as compared to ecologic studies. Environ Health Perspect, 105: 1078-1083. 086180

Lagorio S; Forastiere F; Pistelli R; Iavarone I; Michelozzi P; Fano V; Marconi A; Ziemacki G; Ostro BD (2006). Air pollution and lung function among susceptible adult subjects: a panel study. Environ Health, 5: 11. 089800

Lamar CA; Mahesh VB; Brann DW (1996). Regulation of gonadotropin-releasing hormone (GnRH) secretion by heme molecules: a regulatory role for carbon monoxide? Endocrinology, 137: 790-793. 078819

Lanki T; Pekkanen J; Aalto P; Elosua R; Berglind N; D'Ippoliti D; Kulmala M; Nyberg F; Peters A; Picciotto S; Salomaa V; Sunyer J; Tiittanen P; Von Klot S; Forastiere F; for the HEAPSS Study Group (2006). Associations of traffic-related air pollutants with hospitalisation for first acute myocardial infarction: the HEAPSS study. Occup Environ Med, 63: 844-851. 089788

Lee BE; Ha EH; Park HS; Kim YJ; Hong YC; Kim H; Lee JT (2003). Exposure to air pollution during different gestational phases contributes to risks of low birth weight. Hum Reprod, 18: 638-643. 043202

Lee I-M; Tsai S-S; Chang C-C; Ho C-K; Yang C-Y (2007). Air pollution and hospital admissions for chronic obstructive pulmonary disease in a tropical city: Kaohsiung, Taiwan. Inhal Toxicol, 19: 393-398. 090707

Lee JT; Kim H; Cho YS; Hong YC; Ha EH; Park H (2003). Air pollution and hospital admissions for ischemic heart diseases among individuals 64+ years of age residing in Seoul, Korea. Arch Environ Health, 58: 617-623. 095552

Lee Y-L; Shaw C-K; Su H-J; Lai J-S; Ko Y-C; Huang S-L; Sung F-C; Guo Y-L (2003). Climate, traffic-related air pollutants and allergic rhinitis prevalence in middle-school children in Taiwan. Eur Respir J, 21: 964-970. 049201

Leem J-H; Kaplan BM; Shim YK; Pohl HR; Gotway CA; Bullard SM; Rogers JF; Smith MM; Tylenda CA (2006). Exposures to air pollutants during pregnancy and preterm delivery. Environ Health Perspect, 114: 905-910. 089828

Levy D; Lumley T; Sheppard L; Kaufman J; Checkoway H (2001). Referent selection in case-crossover analyses of acute health effects of air pollution. Epidemiology, 12: 186-192. 017172

Levy D; Sheppard L; Checkoway H; Kaufman J; Lumley T; Koenig J; Siscovick D (2001). A case-crossover analysis of particulate matter air pollution and out-of-hospital primary cardiac arrest. Epidemiology, 12: 193-199. 017171

Li CI; Daling JR; Emanuel I (2003). Birthweight and risk of overall and cause-specific childhood mortality. Paediatr Perinat Epidemiol, 17: 164-170. 193965

Liao D; Duan Y; Whitsel EA; Zheng Z-J; Heiss G; Chinchilli VM; Lin H-M (2004). Association of higher levels of ambient criteria pollutants with impaired cardiac autonomic control: a population-based study. Am J Epidemiol, 159: 768-777. 056590

Liao D; Heiss G; Chinchilli VM; Duan Y; Folsom AR; Lin HM; Salomaa V (2005). Association of criteria pollutants with plasma hemostatic/inflammatory markers: a population-based study. J Expo Sci Environ Epidemiol, 15: 319-328. 088677

Lin C-M; Li C-Y; Mao I-F (2004). Increased risks of term low-birth-weight infants in a petrochemical industrial city with high air pollution levels. Arch Environ Occup Health, 59: 663-668. 089827

Lin CA; Pereira LAA; Nishioka DC; Conceicao GMS; Graga ALF; Saldiva PHN (2004). Air pollution and neonatal deaths in Sao Paulo, Brazil. Braz J Med Biol Res, 37: 765-770. 095787

Lin H; McGrath JJ (1988). Carbon monoxide effects on calcium levels in vascular smooth muscle. Life Sci, 43: 1813-1816. 012773

Lin M; Chen Y; Burnett RT; Villeneuve PJ; Krewski D (2003). Effect of short-term exposure to gaseous pollution on asthma hospitalisation in children: a bi-directional case-crossover analysis. J Epidemiol Community Health, 57: 50-55. 042549

Lin M; Chen Y; Villeneuve PJ; Burnett RT; Lemyre L; Hertzman C; McGrail KM; Krewski D (2004). Gaseous air pollutants and asthma hospitalization of children with low household income in Vancouver, British Columbia, Canada. Am J Epidemiol, 159: 294-303. 055600

Lin M; Stieb DM; Chen Y (2005). Coarse particulate matter and hospitalization for respiratory infections in children younger than 15 years in Toronto: a case-crossover analysis. Pediatrics, 116: 235-240. 087828

Linn WS; Szlachcic Y; Gong H Jr; Kinney PL; Berhane KT (2000). Air pollution and daily hospital admissions in metropolitan Los Angeles. Environ Health Perspect, 108: 427-434. 002839

Lipfert FW; Baty JD; Miller JP; Wyzga RE (2006). PM2.5 constituents and related air quality variables as predictors of survival in a cohort of U.S. military veterans. Inhal Toxicol, 18: 645-657. 088756

Lipfert FW; Morris SC (2002). Temporal and spacial relationships between age-specific mortality and ambient air quality in the United States: preliminary results for counties, 1960-97. Occup Environ Med, 59: 156-174. 019217

Lipfert FW; Perry HM Jr; Miller JP; Baty JD; Wyzga RE; Carmody SE (2000). The Washington University-EPRI veterans' cohort mortality study: preliminary results. Inhal Toxicol, 4: 41-73. 004087

Lipfert FW; Wyzga RE; Baty JD; Miller JP (2006). Traffic density as a surrogate measure of environmental exposures in studies of air pollution health effects: long-term mortality in a cohort of US veterans. Atmos Environ, 40: 154-169. 088218

Liu S; Krewski D; Shi Y; Chen Y; Burnett R (2007). Association between maternal exposure to ambient air pollutants during pregnancy and fetal growth restriction. J Expo Sci Environ Epidemiol, 17: 426-432. 090429

Liu S; Krewski D; Shi Y; Chen Y; Burnett RT (2003). Association between gaseous ambient air pollutants and adverse pregnancy outcomes in Vancouver, Canada. Environ Health Perspect, 111: 1773-1778. 089548

Liu Y; Fechter LD (1995). MK-801 protects against carbon monoxide-induced hearing loss. Toxicol Appl Pharmacol, 132: 196-202. 076524

Ljungman P; Bellander T; Schneider A; Breitner S; Forastiere F; Hampel R; Illig T; Jacquemin B; Katsouyanni K; von Klot S (2009). Modification of the interleukin-6 response to air pollution by interleukin-6 and fibrinogen polymorphisms. Environ Health Perspect, 117: 1373-1379. 191983

Loennechen JP; Beisvag V; Arbo I; Waldum HL; Sandvik AK; Knardahl S; Ellingsen O (1999). Chronic carbon monoxide exposure in vivo induces myocardial endothelin-1 expression and hypertrophy in rat. Pharmacol Toxicol, 85: 192-197. 011549

Longo LD (1970). Carbon monoxide in the pregnant mother and fetus and its exchange across the placenta. Ann N Y Acad Sci, 174: 313-341. 013922

Longo LD; Hill EP (1977). Carbon monoxide uptake and elimination in fetal and maternal sheep. Am J Physiol, 232: H324-H330. 010802

Longo M; Jain V; Vedernikov YP; Saade GR; Goodrum L; Facchinetti F; Garfield RE (1999). Effect of nitric oxide and carbon monoxide on uterine contractility during human and rat pregnancy. Am J Obstet Gynecol, 181: 981-988. 011548

Lopez I; Acuna D; Webber DS; Korsak RA; Edmond J (2003). Mild carbon monoxide exposure diminishes selectively the integrity of the cochlea of the developing rat. J Neurosci Res, 74: 666-75. 193901

Lopez IA; Acuna D; Beltran-Parrazal L; Espinosa-Jeffrey A; Edmond J (2008). Oxidative stress and the deleterious consequences to the rat cochlea after prenatal chronic mild exposure to carbon monoxide in air. Neuroscience, 151: 854-867. 097343

Lund AK; Knuckles TL; Obot Akata C; Shohet R; McDonald JD; Gigliotti A; Seagrave JC; Campen MJ (2007). Gasoline exhaust emissions induce vascular remodeling pathways involved in atherosclerosis. Toxicol Sci, 95: 485-94. 125741

Lund AK; Lucero J; Lucas S; Madden MC; McDonald JD; Seagrave JC; Knuckles TL; Campen MJ (2009). Vehicular emissions induce vascular MMP-9 expression and activity associated with endothelin-1 mediated pathways. Arterioscler Thromb Vasc Biol, 29: 511-517. 180257

Lyall F; Barber A; Myatt L; Bulmer JN; Robson SC (2000). Hemeoxygenase expression in human placenta and placental bed implies a role in regulation of trophoblast invasion and placental function. FASEB J, 14: 208-19. 193902

MacDorman MF; Callaghan WM; Mathews TJ; Hoyert DL; Kochanek KD (2007). Trends in preterm-related infant mortality by race and ethnicity, United States 1999-2004. Int J Health Serv, 37: 635-641. 193973

MacMillan V (1975). Regional cerebral blood flow of the rat in acute carbon monoxide intoxication. Can J Physiol Pharmacol, 53: 644-650. 012909

Mactutus CF; Fechter LD (1984). Prenatal exposure to carbon monoxide: learning and memory deficits. Science, 223: 409-411. 011355

Mactutus CF; Fechter LD (1985). Moderate prenatal carbon monoxide exposure produces persistent, and apparently permanent, memory deficits in rats. Teratology, 31: 1-12. 011536

Maheswaran R; Haining RP; Brindley P; Law J; Pearson T; Fryers PR; Wise S; Campbell MJ (2005). Outdoor air pollution and stroke in Sheffield, United Kingdom: A small-area level geographical study. Stroke, 36: 239-243. 088683

Maisonet M; Bush TJ; Correa A; Jaakkola JJK (2001). Relation between ambient air pollution and low birth weight in the northeastern United States. Environ Health Perspect, 1093: 351-356. 016624

Mann JK; Tager IB; Lurmann F; Segal M; Quesenberry CP Jr; Lugg MM; Shan J; Van den Eeden SK (2002). Air pollution and hospital admissions for ischemic heart disease in persons with congestive heart failure or arrhythmia. Environ Health Perspect, 110: 1247-1252. 036723

Mannes T; Jalaludin B; Morgan G; Lincoln D; Sheppeard V; Corbett S (2005). Impact of ambient air pollution on birth weight in Sydney, Australia. Occup Environ Med, 62: 524-530. 087895

Marthan R; Castaing Y; Manier G; Guenard H (1985). Gas exchange alterations in patients with chronic obstructive lung disease. Chest, 87: 470-475. 086334

Martin JA; Hamilton BE; Sutton PD; Ventura SJ; Menacker F; Kirmeyer S; Munson ML (2007). Births: Final data for 2005. National Center for Health Statistics. Hyattsville, MD. 193982

Mayr FB; Spiel A; Leitner J; Marsik C; Germann P; Ullrich R; Wagner O; Jilma B (2005). Effects of carbon monoxide inhalation during experimental endotoxemia in humans. Am J Respir Crit Care Med, 171: 354-360. 193984

McGrath JJ (1992). Effects of altitude on endogenous carboxyhemoglobin levels. J Toxicol Environ Health, 35: 127-133. 001005

McGrath JJ; Schreck RM; Lee PS (1993). Carboxyhemoglobin levels in humans: Effects of altitude. Inhal Toxicol, 5: 241-249. 013865

McGregor HP; Westcott K; Walker DW (1998). The effect of prenatal exposure to carbon monoxide on breathing and growth of the newborn guinea pig. Pediatr Res, 43: 126-131. 085342

McIntire DD; Bloom SL; Casey BM; Leveno KJ (1999). Birth weight in relation to morbidity and mortality among newborn infants. N Engl J Med, 340: 1234-1238. 015310

McLaughlin BE; Lash GE; Smith GN; Marks GS; Nakatsu K; Graham CH; Brien JF (2003). Heme oxygenase expression in selected regions of term human placenta. Exp Biol Med, 228: 564-567. 193827

Medeiros A; Gouveia N (2005). Relacao entre baixo peso ao nascer e a poluicao do ar no Municipio de Sao Paulo [Relationship between low birthweight and air pollution in the city of Sao Paulo, Brazil]. Rev Saude Publica, 39: 965-972. 089824

Meilin S; Rogatsky GG; Thom SR; Zarchin N; Guggenheimer-Furman E; Mayevsky A (1996). Effects of carbon monoxide on the brain may be mediated by nitric oxide. J Appl Physiol, 81: 1078-1083. 079919

Melin A; Bonnet P; Eder V; Antier D; Obert P; Fauchier L (2005). Direct implication of carbon monoxide in the development of heart failure in rats with cardiac hypertrophy subjected to air pollution. Cardiovasc Toxicol, 5: 311-320. 193833

Melin A; Obert P; Rebocho M; Bonnet P (2002). Cardiac morphology and function following long-term exposure to carbon monoxide at high altitude in rats. J Toxicol Environ Health A Curr Iss, 65: 1981-1998. 037502

Meng YY; Wilhelm M; Rull RP; English P; Ritz B (2007). Traffic and outdoor air pollution levels near residences and poorly controlled asthma in adults. Ann Allergy Asthma Immunol, 98: 455-463. 093275

Mercke C; Lundh B (1976). Erythrocyte filterability and heme catabolism during the menstrual cycle. Ann Intern Med, 85: 322-324. 086309

Mereu G; Cammalleri M; Fà M; Francesconi W; Saba P; Tattoli M; Trabace L; Vaccari A; Cuomo V (2000). Prenatal exposure to a low concentration of carbon monoxide disrupts hippocampal long-term potentiation in rat offspring. J Pharmacol Exp Ther, 294: 728-734. 193838

Merriam-Webster (2009). Merriam-Webster on-line. Retrieved 15-JUN-09, from http://www.merriam-webster.com/medical/susceptible; http://www.merriam-webster.com/medical/vulnerable. 192146

Metzger KB; Klein M; Flanders WD; Peel JL; Mulholland JA; Langberg JJ; Tolbert PE (2007). Ambient air pollution and cardiac arrhythmias in patients with implantable defibrillators. Epidemiology, 18: 585-592. 092856

Metzger KB; Tolbert PE; Klein M; Peel JL; Flanders WD; Todd KH; Mulholland JA; Ryan PB; Frumkin H (2004). Ambient air pollution and cardiovascular emergency department visits. Epidemiology, 15: 46-56. 044222

Meyer J; Prien T; Van Aken H; Bone H-G; Waurick R; Theilmeier G; Booke M (1998). Arterio-venous carboxyhemoglobin difference suggests carbon monoxide production by human lungs. Biochem Biophys Res Commun, 244: 230-232. 047530

Miller KA; Siscovick DS; Sheppard L; Shepherd K; Sullivan JH; Anderson GL; Kaufman JD (2007). Long-term exposure to air pollution and incidence of cardiovascular events in women. N Engl J Med, 356: 447-458. 090130

Min JY; Paek D; Cho SI; Min KB (2009). Exposure to environmental carbon monoxide may have a greater negative effect on cardiac autonomic function in people with metabolic syndrome. Sci Total Environ, 407: 4807-4811. 199514

Montagnani M; Serio M; Potenza MA; Mansi G; De Salvia MA; Cagiano R; Cuomo V; Mitolo-Chieppa D (1996). Prenatal exposure to carbon monoxide and vascular responsiveness of rat resistance vessels. Life Sci, 59: 1553-1561. 080902

Moolgavkar SH (2000). Air pollution and hospital admissions for chronic obstructive pulmonary disease in three metropolitan areas in the United States. Inhal Toxicol, 12: 75-90. 010274

Moolgavkar SH (2003). Air pollution and daily deaths and hospital admissions in Los Angeles and Cook counties. Health Effects Institute. Boston, MA. 042864

Moon JS; Kim YS; Kim JH; Son BS; Kim DS; Yang W (2009). Respiratory health effects among schoolchildren and their relationship to air pollutants in Korea. Int J Environ Health Res, 19: 31-48. 190297

Morita T; Mitsialis SA; Koike H; Liu Y; Kourembanas S (1997). Carbon monoxide controls the proliferation of hypoxic vascular smooth muscle cells. J Biol Chem, 272: 32,804-32,809. 085345

Morse CI; Pritchard LJ; Wust RC; Jones DA; Degens H (2008). Carbon monoxide inhalation reduces skeletal muscle fatigue resistance. Eur Phys J A, 192: 397-401. 097980

Mortimer K; Neugebauer R; Lurmann F; Alcorn S; Balmes J; Tager I (2008). Air pollution and pulmonary function in asthmatic children: Effects of prenatal and lifetime exposures. Epidemiology, 19: 550-557. 122163

Mortimer K; Neugebauer R; Lurmann F; Alcorn S; Balmes J; Tager I (2008). Early-Lifetime exposure to air pollution and allergic sensitization in children with asthma. J Asthma, 45: 874-881. 187280

Naik JS; Walker BR (2003). Heme oxygenase-mediated vasodilation involves vascular smooth muscle cell hyperpolarization. Am J Physiol Heart Circ Physiol, 285: 220-228. 193852

Ndisang JF; Tabien HE; Wang R (2004). Carbon monoxide and hypertension. Am J Hypertens, 22: 1057-1074. 180425

Neas LM; Schwartz J (1996). The determinants of pulmonary diffusing capacity in a national sample of US adults. Am J Respir Crit Care Med, 153: 656-664. 079363

Neggers YH; Singh J (2006). Zinc supplementation to protein-deficient diet in CO-exposed mice decreased fetal mortality and malformation. Biol Trace Elem Res, 114: 269-279. 193964

O'Connor GT; Neas L; Vaughn B; Kattan M; Mitchell H; Crain EF; Evans R 3rd; Gruchalla R; Morgan W; Stout J; Adams GK; Lippmann M (2008). Acute respiratory health effects of air pollution on children with asthma in US inner cities. J Allergy Clin Immunol, 121: 1133-1139. 156818

Otto DA; Benignus VA; Prah JD (1979). Carbon monoxide and human time discrimination: Failure to replicate Beard-Wertheim experiments. Aviat Space Environ Med, 50: 40-43. 010863

Park JW; Lim YH; Kyung SY; An CH; Lee SP; Jeong SH; Ju S-Y (2005). Effects of ambient particulate matter on peak expiratory flow rates and respiratory symptoms of asthmatics during Asian dust periods in Korea. Respirology, 10: 470-476. 088673

Park SK; O'Neill MS; Vokonas PS; Sparrow D; Schwartz J (2005). Effects of air pollution on heart rate variability: The VA normative aging study. Environ Health Perspect, 113: 304-309. 057331

Parker JD; Woodruff TJ; Basu R; Schoendorf KC (2005). Air pollution and birth weight among term infants in California. Pediatrics, 115: 121-128. 087462

Patel AP; Moody JA; Handy RD; Sneyd JR (2003). Carbon monoxide exposure in rat heart: glutathione depletion is prevented by antioxidants. Biochem Biophys Res Commun, 302: 392-396. 043155

Peel JL; Metzger KB; Klein M; Flanders WD; Mulholland JA; Tolbert PE (2007). Ambient air pollution and cardiovascular emergency department visits in potentially sensitive groups. Am J Epidemiol, 165: 625-633. 090442

Peel JL; Tolbert PE; Klein M; Metzger KB; Flanders WD; Knox T; Mulholland JA; Ryan PB; Frumkin H (2005). Ambient air pollution and respiratory emergency department visits. Epidemiology, 16: 164-174. 056305

Pekkanen J; Brunner EJ; Anderson HR; Tiittanen P; Atkinson RW (2000). Daily concentrations of air pollution and plasma fibrinogen in London. Occup Environ Med, 57: 818-822. 013250

Penn A; Currie J; Snyder C (1992). Inhalation of carbon monoxide does not accelerate arteriosclerosis in cockerels. Eur J Clin Pharmacol, 228: 155-164. 013728

Penney DG (1988). A review: Hemodynamic response to carbon monoxide. Environ Health Perspect, 77: 121-130. 012519

Penney DG; Baylerian MS; Thill JE; Fanning CM; Yedavally S (1982). Postnatal carbon monoxide exposure: immediate and lasting effects in the rat. Am J Physiol, 243: H328-H339. 011387

Penney DG; Baylerian MS; Thill JE; Yedavally S; Fanning CM (1983). Cardiac response of the fetal rat to carbon monoxide exposure. Am J Physiol, 244: H289-H297. 011385

Penney DG; Davidson SB; Gargulinski RB; Caldwell-Ayre TM (1988). Heart and lung hypertrophy, changes in blood volume, hematocrit and plasma renin activity in rats chronically exposed to increasing carbon monoxide concentrations. J Appl Toxicol, 8: 171-178. 012521

Penney DG; Stryker AE; Baylerian MS (1984). Persistent cardiomegaly induced by carbon monoxide and associated tachycardia. J Appl Physiol, 56: 1045-1052. 011567

Penttinen P; Timonen KL; Tiittanen P; Mirme A; Ruuskanen J; Pekkanen J (2001). Ultrafine particles in urban air and respiratory health among adult asthmatics. Eur Respir J, 17: 428-435. 030335

Pereira Filho MA; Pereira LAA; Arbex FF; Arbex M; Conceição GM; Santos UP; Lopes AC; Saldiva PHN; Braga ALF; Cendon S (2008). Effect of air pollution on diabetes and cardiovascular diseases in São Paulo, Brazil. Braz J Med Biol Res, 41: 526-532. 190260

Peters A; Dockery DW; Muller JE; Mittleman MA (2001). Increased particulate air pollution and the triggering of myocardial infarction. Circulation, 103: 2810-2815. 016546

Peters A; Liu E; Verrier RL; Schwartz J; Gold DR; Mittleman M; Baliff J; Oh JA; Allen G; Monahan K; Dockery DW (2000). Air pollution and incidence of cardiac arrhythmia. Epidemiology, 11: 11-17. 011347

Peters A; Perz S; Doring A; Stieber J; Koenig W; Wichmann H-E (1999). Increases in heart rate during an air pollution episode. Am J Epidemiol, 150: 1094-1098. 011554

Peters JM; Avol E; Navidi W; London SJ; Gauderman WJ; Lurmann F; Linn WS; Margolis H; Rappaport E; Gong H Jr; Thomas DC (1999). A study of twelve southern California communities with differing levels and types of air pollution I Prevalence of respiratory morbidity. Am J Respir Crit Care Med, 159: 760-767. 087243

Petersen LC (1977). The effect of inhibitors on the oxygen kinetics of cytochrome c oxidase. Biochim Biophys Acta, 460: 299-307. 193764

Piantadosi CA (2002). Biological chemistry of carbon monoxide. Antioxid Redox Signal, 4: 259-270. 037463

Piantadosi CA (2008). Carbon monoxide, reactive oxygen signaling, and oxidative stress. Free Radic Biol Med, 45: 562-569. 180423

Piantadosi CA; Carraway MS; Suliman HB (2006). Carbon monoxide, oxidative stress, and mitochondrial permeability pore transition. Free Radic Biol Med, 40: 1332-1339. 180424

Piantadosi CA; Zhang J; Demchenko IT (1997). Production of hydroxyl radical in the hippocampus after CO hypoxia or hypoxic hypoxia in the rat. Free Radic Biol Med, 22: 725-732. 081326

Pleis JR; Lucas JW (2009). Summary health statistics for US adults: National Health Interview Survey, 2007. National Center for Health Statistics, Centers for Disease Control and Prevention, U.S. Department of Health and Human Services . Hyattsville, Maryland. Series 10, Number 240; (PHS) 2009?1568. http://www.cdc.gov/nchs/data/series/sr_10/sr10_240.pdf. 202833

Pope CA III; Burnett RT; Thun MJ; Calle EE; Krewski D; Ito K; Thurston GD (2002). Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. JAMA, 287: 1132-1141. 024689

Pope CA III; Thun MJ; Namboodiri MM; Dockery DW; Evans JS; Speizer FE; Heath CW Jr (1995). Particulate air pollution as a predictor of mortality in a prospective study of US adults. Am J Respir Crit Care Med, 151: 669-674. 045159

Prigge E; Hochrainer D (1977). Effects of carbon monoxide inhalation on erythropoiesis and cardiac hypertrophy in fetal rats. Toxicol Appl Pharmacol, 42: 225-228. 012326

Putz VR; Johnson BL; Setzer JV (1979). A comparative study of the effects of carbon monoxide and methylene chloride on human performance. J Environ Pathol Toxicol Oncol, 2: 97-112. 023137

Rabinovitch N; Zhang LN; Murphy JR; Vedal S; Dutton SJ; Gelfand EW (2004). Effects of wintertime ambient air pollutants on asthma exacerbations in urban minority children with moderate to severe disease. J Allergy Clin Immunol, 114: 1131-1137. 096753

Rajendra Acharya U; Paul Joseph K; Kannathal N; Lim CM; Suri JS (2006). Heart rate variability: A review. Med Biol Eng Comput, 44: 1031-1051. 193787

Ranzi A; Gambini M; Spattini A; Galassi C; Sesti D; Bedeschi M; Messori A; Baroni A; Cavagni G; Lauriola P (2004). Air pollution and respiratory status in asthmatic children: Hints for a locally based preventive strategy AIRE study. Eur J Epidemiol, 19: 567-576. 089500

Raub JA; Benignus VA (2002). Carbon monoxide and the nervous system. Neurosci Biobehav Rev, 26: 925-940. 041616

Raven PB; Drinkwater BL; Ruhling RO; Bolduan N; Taguchi S; Gliner J; Horvath SM (1974). Effect of carbon monoxide and peroxyacetyl nitrate on man's maximal aerobic capacity. J Appl Physiol, 36: 288-293. 041340

Ren X; Dorrington KL; Robbins PA (2001). Respiratory control in humans after 8 h of lowered arterial PO2, hemodilution, or carboxyhemoglobinemia. J Appl Physiol, 90: 1189-1195. 193850

Resch H; Zawinka C; Weigert G; Schmetterer L; Garhofer G (2005). Inhaled carbon monoxide increases retinal and choroidal blood flow in healthy humans. Invest Ophthalmol Vis Sci, 46: 4275-4280. 193853

Rich DQ; Kim MH; Turner JR; Mittleman MA; Schwartz J; Catalano PJ; Dockery DW (2006). Association of ventricular arrhythmias detected by implantable cardioverter defibrillator and ambient air pollutants in the St Louis, Missouri metropolitan area. Occup Environ Med, 63: 591-596. 089814

Rich DQ; Schwartz J; Mittleman MA; Link M; Luttmann-Gibson H; Catalano PJ; Speizer FE; Dockery DW (2005). Association of short-term ambient air pollution concentrations and ventricular arrhythmias. Am J Epidemiol, 161: 1123-1132. 079620

Rich KE; Petkau J; Vedal S; Brauer M (2004). A case-crossover analysis of particulate air pollution and cardiac arrhythmia in patients with implantable cardioverter defibrillators. Inhal Toxicol, 16: 363-372. 055631

Riediker M; Williams R; Devlin R; Griggs T; Bromberg P (2003). Exposure to particulate matter, volatile organic compounds, and other air pollutants inside patrol cars. Environ Sci Technol, 37: 2084-2093. 043761

Riojas-Rodriguez H; Escamilla-Cejudo JA; Gonzalez-Hermosillo JA; Tellez-Rojo MM; Vallejo M; Santos-Burgoa C; Rojas-Bracho L (2006). Personal PM2.5 and CO exposures and heart rate variability in subjects with known ischemic heart disease in Mexico City. J Expo Sci Environ Epidemiol, 16: 131-137. 156913

Ritz B; Wilhelm M; Hoggatt KJ; Ghosh JK (2007). Ambient air pollution and preterm birth in the environment and pregnancy outcomes study at the University of California, Los Angeles. Am J Epidemiol, 166: 1045-1052. 096146

Ritz B; Wilhelm M; Zhao Y (2006). Air pollution and infant death in southern California, 1989-2000. Pediatrics, 118: 493-502. 089819

Ritz B; Yu F (1999). The effect of ambient carbon monoxide on low birth weight among children born in southern California between 1989 and 1993. Environ Health Perspect, 107: 17-25. 086976

Ritz B; Yu F; Chapa G; Fruin S (2000). Effect of air pollution on preterm birth among children born in Southern California between 1989 and 1993. Epidemiology, 11: 502-511. 012068

Ritz B; Yu F; Fruin S; Chapa G; Shaw GM; Harris JA (2002). Ambient air pollution and risk of birth defects in Southern California. Am J Epidemiol, 155: 17-25. 023227

Rodriguez C; Tonkin R; Heyworth J; Kusel M; De Klerk N; Sly PD; Franklin P; Runnion T; Blockley A; Landau L; Hinwood AL (2007). The relationship between outdoor air quality and respiratory symptoms in young children. Int J Environ Health Res, 17: 351-360 . 092842

Rosenlund M; Bellander T; Nordquist T; Alfredsson L (2009). Traffic-generated air pollution and myocardial infarction. Epidemiology, 20: 265-71. 190309

Rosenlund M; Berglind N; Pershagen G; Hallqvist J; Jonson T; Bellander T (2006). Long-term exposure to urban air pollution and myocardial infarction. Epidemiology, 17: 383-390. 089796

Roth RA Jr; Rubin RJ (1976). Comparison of the effect of carbon monoxide and of hypoxic hypoxia I In vivo metabolism, distribution and action of hexobarbital. J Pharmacol Exp Ther, 199: 53-60. 012703

Roth RA Jr; Rubin RJ (1976). Comparison of the effect of carbon monoxide and of hypoxic hypoxia. II. Hexobarbital metabolism in the isolated, perfused rat liver. J Pharmacol Exp Ther, 199: 61-66. 012420

Ruckerl R; Greven S; Ljungman P; Aalto P; Antoniades C; Bellander T; Berglind N; Chrysohoou C; Forastiere F; Jacquemin B; von Klot S; Koenig W; Kuchenhoff H; Lanki T; Pekkanen J; Perucci CA; Schneider A; Sunyer J; Peters A (2007). Air pollution and inflammation (interleukin-6, C-reactive protein, fibrinogen) in myocardial infarction survivors. Environ Health Perspect, 115: 1072-1080. 156931

Ruckerl R; Ibald-Mulli A; Koenig WSchneider A; Woelke G; Cyrys J; Heinrich J; Marder V; Frampton M; Wichmann HE; Peters A (2006). Air pollution and markers of inflammation and coagulation in patients with coronary heart disease. Environ Health Perspect, 173: 432-441. 088754

Rudez G; Janssen NA; Kilinc E; Leebeek FW; Gerlofs-Nijland ME; Spronk HM; ten Cate H; Cassee FR; de Maat MP (2009). Effects of ambient air pollution on hemostasis and inflammation. Environ Health Perspect, 117: 995-1001. 193783

Ryter SW; Alam J; Choi AMK (2006). Heme oxygenase-1/carbon monoxide: From basic science to therapeutic applications. Physiol Rev, 86: 583-650. 193765

Salam MT; Millstein J; Li Y-F; Lurmann FW; Margolis HG; Gilliland FD (2005). Birth outcomes and prenatal exposure to ozone, carbon monoxide, and particulate matter: results from the Children's Health Study. Environ Health Perspect, 113: 1638-1644. 087885

Samet JM; Zeger SL; Dominici F; Curriero F; Coursac I; Dockery DW; Schwartz J; Zanobetti A (2000). The National Morbidity, Mortality, and Air Pollution Study. Part II: Morbidity and mortality from air pollution in the United States. 156939

Samoli E; Touloumi G; Schwartz J; Anderson HR; Schindler C; Forsberg B; Vigotti MA; Vonk J; Kosnik M; Skorkovsky J; Katsouyanni K (2007). Short-term effects of carbon monoxide on mortality: An analysis within the APHEA project. Environ Health Perspect, 115: 1578-1583. 098420

Sarnat SE; Suh HH; Coull BA; Schwartz J; Stone PH; Gold DR (2006). Ambient particulate air pollution and cardiac arrhythmia in a panel of older adults in Steubenville, Ohio. Occup Environ Med, 63: 700-706. 090489

Sartiani L; Cerbai E; Lonardo G; DePaoli P; Tattoli M; Cagiano R; Carratu M; Cuomo V; Mugelli A (2004). Prenatal exposure to carbon monoxide affects postnatal cellular electrophysiological maturation of the rat heart: a potential substrate for arrhythmogenesis in infancy. Circulation, 109-: 419-423. 190898

Scharte M; von Ostrowski TA; Daudel F; Freise H; Van Aken H; Bone HG (2006). Endogenous carbon monoxide production correlates weakly with severity of acute illness. Eur J Anaesthesiol, 23: 117-122. 194115

Schildcrout JS; Sheppard L; Lumley T; Slaughter JC; Koenig JQ; Shapiro GG (2006). Ambient air pollution and asthma exacerbations in children: An eight-city analysis. Am J Epidemiol, 164: 505-517. 089812

Schwartz J; Litonjua A; Suh H; Verrier M; Zanobetti A; Syring M; Nearing B; Verrier R; Stone P; MacCallum G; Speizer FE; Gold DR (2005). Traffic related pollution and heart rate variability in a panel of elderly subjects. Thorax, 60: 455-461. 074317

Schwetz BA; Smith FA; Leong BKJ; Staples RE (1979). Teratogenic potential of inhaled carbon monoxide in mice and rabbits. Teratology, 19: 385-391. 011855

Scotto Di Marco G; Kephalopoulos S; Ruuskanen J; Jantunen M (2005). Personal carbon monoxide exposure in Helsinki, Finland. Atmos Environ, 39: 2697-2707. 144054

Shaoqing Y; Ruxin Z; Yinjian C; Jianqiu C; Chunsheng Z; Jiangfeng T; Genhong L (2008). Possible contribution of endogenous carbon monoxide to the development of allergic rhinitis in guinea pigs. J Inflamm, 5: 23. 192384

Sheps DS; Adams KF Jr; Bromberg PA; Goldstein GM; O'Neil JJ; Horstman D; Koch G (1987). Lack of effect of low levels of carboxyhemoglobin on cardiovascular function in patients with ischemic heart disease. Arch Environ Occup Health, 42: 108-116. 012212

Sheps DS; Herbst MC; Hinderliter AL; Adams KF; Ekelund LG; O'Neil JJ; Goldstein GM; Bromberg PA; Dalton JL; Ballenger MN; Davis SM; Koch GG (1990). Production of arrhythmias by elevated carboxyhemoglobin in patients with coronary artery disease. Ann Intern Med, 113: 343-351. 013286

Silkoff PE; Zhang L; Dutton S; Langmack EL; Vedal S; Murphy J; Make B (2005). Winter air pollution and disease parameters in advanced chronic obstructive pulmonary disease panels residing in Denver, Colorado. J Allergy Clin Immunol, 115: 337-344. 087471

Sinclair AH; Tolsma D (2004). Associations and lags between air pollution and acute respiratory visits in an ambulatory care setting: 25-month results from the aerosol research and inhalation epidemiological study. J Air Waste Manag Assoc, 54: 1212-1218. 088696

Singh J (1986). Early behavioral alterations in mice following prenatal carbon monoxide exposure. Neurotoxicology, 7: 475-481. 012827

Singh J (2003). Gastroschisis is caused by the combination of carbon monoxide and protein-zinc deficiencies in mice. Birth Defects Res B Dev Reprod Toxicol, 68: 355-362. 053624

Singh J (2006). Interaction of maternal protein and carbon monoxide on pup mortality in mice: implications for global infant mortality. Birth Defects Res B Dev Reprod Toxicol, 77: 216-26. 190512

Singh J; Aggison L Jr; Moore-Cheatum L (1993). Teratogenicity and developmental toxicity of carbon monoxide in protein-deficient mice. Teratology, 48: 149-159. 013892

Singh J; Scott LH (1984). Threshold for carbon monoxide induced fetotoxicity. Teratology, 30: 253-257. 011409

Singh J; Smith CB; Moore-Cheatum L (1992). Additivity of protein deficiency and carbon monoxide on placental carboxyhemoglobin in mice. Am J Obstet Gynecol, 167: 843-846. 013759

Slaughter JC; Kim E; Sheppard L; Sullivan JH; Larson TV; Claiborn C (2005). Association between particulate matter and emergency room visits, hospital admissions and mortality in Spokane, Washington. J Expo Sci Environ Epidemiol, 15: 153-159. 073854

Slaughter JC; Lumley T; Sheppard L; Koenig JQ; Shapiro GG (2003). Effects of ambient air pollution on symptom severity and medication use in children with asthma. Ann Allergy Asthma Immunol, 91: 346-353. 086294

Solanki DL; McCurdy PR; Cuttitta FF; Schechter GP (1988). Hemolysis in sickle cell disease as measured by endogenous carbon monoxide production: A preliminary report. Am J Clin Pathol, 89: 221-225. 012426

Song R; Mahidhara RS; Liu F; Ning W; Otterbein LE; Choi AMK (2002). Carbon monoxide inhibits human airway smooth muscle cell proliferation via mitogen-activated protein kinase pathway. Am J Respir Cell Mol Biol, 27: 603-610. 037531

Sorhaug S; Steinshamn S; Nilsen OG; Waldum HL (2006). Chronic inhalation of carbon monoxide: Effects on the respiratory and cardiovascular system at doses corresponding to tobacco smoking. Toxicology, 228: 280-290. 180414

Steinvil A; Kordova-Biezuner L; Shapira I; Berliner S; Rogowski O (2008). Short-term exposure to air pollution and inflammation-sensitive biomarkers. Environ Res, 106: 51-61. 188893

Stevens CF; Wang Y (1993). Reversal of long-term potentiation by inhibitors of haem oxygenase. Nature, 364: 147-149. 188458

Stewart RD; Newton PE; Hosko MJ; Peterson JE (1973). Effect of carbon monoxide on time perception. Arch Environ Occup Health, 27: 155-160. 093412

Stewart RD; Peterson JE; Fisher TN; Hosko MJ; Baretta ED; Dodd HC; Herrmann AA (1973). Experimental human exposure to high concentrations of carbon monoxide. Arch Environ Occup Health, 26: 1-7. 012428

Stieb DM; Judek S; Burnett RT (2002). Meta-analysis of time-series studies of air pollution and mortality: effects of gases and particles and the influence of cause of death, age, and season. J Air Waste Manag Assoc, 52: 470-484. 025205

Stieb DM; Judek S; Burnett RT (2003). Meta-analysis of time-series studies of air pollution and mortality: Update in relation to the use of generalized additive models. J Air Waste Manag Assoc, 53: 258-261. 056908

Stockard-Sullivan JE; Korsak RA; Webber DS; Edmond J (2003). Mild carbon monoxide exposure and auditory function in the developing rat. J Neurosci Res, 74: 644-654. 190947

Stone JR; Marletta MA (1994). Soluble guanylate cyclase from bovine lung: Activation with nitric oxide and carbon monoxide and spectral characterization of the ferrous and ferric states. Biochemistry, 33: 5636-5640. 076455

Storm JE; Fechter LD (1985). Alteration in the postnatal ontogeny of cerebellar norepinephrine content following chronic prenatal carbon monoxide. J Neurochem, 45: 965-969. 011653

Storm JE; Fechter LD (1985). Prenatal carbon monoxide exposure differentially affects postnatal weight and monoamine concentration of rat brain regions. Toxicol Appl Pharmacol, 81: 139-146. 011652

Storm JE; Valdes JJ; Fechter LD (1986). Postnatal alterations in cerebellar GABA content, GABA uptake and morphology following exposure to carbon monoxide early in development. Dev Neurosci, 8: 251-261. 012136

Strickland MJ; Klein M; Correa A; Reller MD; Mahle WT; Riehle-Colarusso TJ; Botto LD; Flanders WD; Mulholland JA; Siffel C; Marcus M; Tolbert PE (2009). Ambient air pollution and cardiovascular malformations in Atlanta, Georgia, 1986-2003. Am J Epidemiol, 169: 1004-14. 190324

Stupfel M; Bouley G (1970). Physiological and biochemical effects on rats and mice exposed to small concentrations of carbon monoxide for long periods. Ann N Y Acad Sci, 174: 342-368. 010557

Styka PE; Penney DG (1978). Regression of carbon monoxide-induced cardiomegaly. Am J Physiol, 235: H516-H522. 011166

Suliman HB; Carraway MS; Tatro LG; Piantadosi CA (2007). A new activating role for CO in cardiac mitochondrial biogenesis. J Cell Sci, 120: 299-308. 193768

Sullivan J; Ishikawa N; Sheppard L; Siscovick D; Checkoway H; Kaufman J (2003). Exposure to ambient fine particulate matter and primary cardiac arrest among persons with and without clinically recognized heart disease. Am J Epidemiol, 157: 501-509. 043156

Sylvester KP; Patey RA; Rafferty GF; Rees D; Thein SL; Greenough A (2005). Exhaled carbon monoxide levels in children with sickle cell disease. Eur J Pediatr, 164: 162-165. 191954

Symons JM; Wang L; Guallar E; Howell E; Dominici F; Schwab M; Ange BA; Samet J; Ondov J; Harrison D; Geyh A (2006). A case-crossover study of fine particulate matter air pollution and onset of congestive heart failure symptom exacerbation leading to hospitalization. Am J Epidemiol, 164: 421-433. 091258

Szyszkowicz M (2007). Air pollution and emergency department visits for ischemic heart disease in Montreal, Canada. Int J Occup Med Environ Health, 20: 167-173. 193793

Tarkiainen TH; Timonen KL; Vanninen EJ; Alm S; Hartikainen JEK; Pekkanen J (2003). Effect of acute carbon monoxide exposure on heart rate variability in patients with coronary artery disease. Clin Physiol Funct Imaging, 23: 98-102. 053625

Teran FJ; Johnson RA; Stevenson BK; Peyton KJ; Jackson KE; Appleton SD; Durante W; Johnson FK (2005). Heme oxygenase-derived carbon monoxide promotes arteriolar endothelial dysfunction and contributes to salt-induced hypertension in Dahl salt-sensitive rats. Am J Physiol Regul Integr Comp Physiol, 288: 615-622. 193770

Thom SR (1993). Functional inhibition of leukocyte B2 integrins by hyperbaric oxygen in carbon monoxide-mediated brain injury in rats. Toxicol Appl Pharmacol, 123: 248-256. 013895

Thom SR; Bhopale VM; Han ST; Clark JM; Hardy KR (2006). Intravascular neutrophil activation due to carbon monoxide poisoning. Am J Respir Crit Care Med, 174: 1239-1248. 098418

Thom SR; Fisher D; Manevich Y (2001). Roles for platelet-activating factor and NO-derived oxidants causing neutrophil adherence after CO poisoning. Am J Physiol Heart Circ Physiol, 281: H923-H930. 193779

Thom SR; Fisher D; Xu YA; Garner S; Ischiropoulos H (1999). Role of nitric oxide-derived oxidants in vascular injury from carbon monoxide in the rat. Am J Physiol, 276: H984-H992. 016753

Thom SR; Fisher D; Xu YA; Notarfrancesco K; Ischiropoulos H (2000). Adaptive responses and apoptosis in endothelial cells exposed to carbon monoxide. PNAS, 97: 1305-1310. 011574

Thom SR; Garner S; Fisher D; Ischiropoulos H (1998). Vascular nitrosative stress from CO exposure. Undersea Hyperb Med, 25: 47. 016750

Thom SR; Ischiropoulos H (1997). Mechanism of oxidative stress from low levels of carbon monoxide. Health Effects Institute. Boston, MA. 085644

Thom SR; Ohnishi ST; Fisher D; Xu YA; Ischiropoulos H (1999). Pulmonary vascular stress from carbon monoxide. Toxicol Appl Pharmacol, 154: 12-19. 016757

Thom SR; Ohnishi ST; Ischiropoulos H (1994). Nitric oxide released by platelets inhibits neutrophil B2 integrin function following acute carbon monoxide poisoning. Toxicol Appl Pharmacol, 128: 105-110. 076459

Thom SR; Xu YA; Ischiropoulos H (1997). Vascular endothelial cells generate peroxynitrite in response to carbon monoxide exposure. Chem Res Toxicol, 10: 1023-1031. 084337

Thomsen HK (1974). Carbon monoxide-induced atherosclerosis in primates: an electron-microscopic study on the coronary arteries of Macaca trus monkeys. Atherosclerosis, 20: 233-240. 010704

Thorup C; Jones CL; Gross SS; Moore LC; Goligorsky MS (1999). Carbon monoxide induces vasodilation and nitric oxide release but suppresses endothelial NOS. Am J Physiol, 277: F882-F889. 193782

Timonen KL; Pekkanen J; Tiittanen P; Salonen RO (2002). Effects of air pollution on changes in lung function induced by exercise in children with chronic respiratory symptoms. Occup Environ Med, 59: 129-134. 025653

Timonen KL; Vanninen E; De Hartog J; Ibald-Mulli A; Brunekreef B; Gold DR; Henrich J; Hoek G; Lanki T; Peters A; Tarkiainen T; Tiittanen P; Kreyling W; Pekkanen J (2006). Effects of ultrafine and fine particulate and gaseous air pollution on cardiac autonomic control in subjects with coronary artery disease: The ULTRA study. J Expo Sci Environ Epidemiol, 16: 332-341. 088747

Tolbert PE; Klein M; Peel JL; Sarnat SE; Sarnat JA (2007). Multipollutant modeling issues in a study of ambient air quality and emergency department visits in Atlanta. J Expo Sci Environ Epidemiol, 17: S29-S35. 090316

Tolcos M; Mallard C; McGregor H; Walker D; Rees S (2000). Exposure to prenatal carbon monoxide and postnatal hyperthermia: short and long-term effects on neurochemicals and neuroglia in the developing brain. Exp Neurol, 162: 235-246. 010468

Tolcos M; McGregor H; Walker D; Rees S (2000). Chronic prenatal exposure to carbon monoxide results in a reduction in tyrosine hydroxylase-immunoreactivity and an increase in choline acetyltransferase-immunoreactivity in the fetal medulla: implications for sudden infant death syndrome. J Neuropathol Exp Neurol, 59: 218-228. 015997

Toyoda M; Saito H; Matsuki N (1996). Nitric oxide but not carbon monoxide is involved in spatial learning of mice. J Pharmacol Sci, 71: 205-211. 079945

Tsai S-S; Chen C-C; Hsieh H-J; Chang C-C; Yang C-Y (2006). Air pollution and postneonatal mortality in a tropical city: Kaohsiung, Taiwan. Inhal Toxicol, 18: 185-189. 090709

Tsai S-S; Goggins WB; Chiu H-F; Yang C-Y (2003). Evidence for an association between air pollution and daily stroke admissions in Kaohsiung, Taiwan. Stroke, 34: 2612-2616. 080133

Tschugguel W; Stonek F; Zhegu Z; Dietrich W; Schneeberger C; Stimpfl T; Waldhoer T; Vycudilik W; Huber JC (2001). Estrogen increases endothelial carbon monoxide, heme oxygenase 2, and carbon monoxide-derived cGMP by a receptor-mediated system. J Clin Endocrinol Metab, 86: 3833-3839. 193785

Turner DM; Lee PN; Roe FJ; Gough KJ (1979). Atherogenesis in the White Carneau pigeon: further studies of the role of carbon monoxide and dietary cholesterol. Atherosclerosis, 34: 407-417. 012328

U.S. Census Bureau (2000). Census Bureau projects doubling of nation's population by 2100. Retrieved 13-MAY-01, from http://www.census.gov/Press-Release/www/2000/cb00-05.html. 157064

U.S. Census Bureau (2008). American Housing Survey for the United States: 2007. U.S. Government Printing Office. Washington, DC. 194013

U.S. EPA (1978). Altitude as a factor in air pollution. U.S. Envrionmental Protection Agency. Research Triangle Park, NC. EPA-600/9-78-015. 086321

U.S. EPA (1991). Air quality criteria for carbon monoxide. U.S. Environmental Protection Agency. Research Triangle Park, NC. EPA/600/8-90/045F. http://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=3000554R.txt. 017643

U.S. EPA (2000). Air quality criteria for carbon monoxide. National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency. Research Triangle Park, NC. EPA 600/P-99/001F. 000907

U.S. EPA (2003). Framework for cumulative risk assessment. National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency. Washington, DC. EPA/630/P-02/001F. 192145

U.S. EPA (2006). Aging and Toxic Response: Issues Relevant to Risk Assessment (Final). U.S. Environmental Protection Agency. Washington, DC.http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=156648. 192082

U.S. EPA (2008). Plan for review of the National Ambient Air Quality Standards for carbon monoxide. U.S. Environmental Protection Agency. Research Triangle Park, NC. EPA-HQ-OAR-2008-0015; FRL-8792-1. 193995

U.S. EPA (2009). Susceptible subpopulations. Retrieved 15-MAY-09, from http://www.epa.gov/nerl/goals/health/populations.html. 192149

Ueda N; Kaushal GP; Hong X; Shah SV (1998). Role of enhanced ceramide generation in DNA damage and cell death in chemical hypoxic injury to LLC-PK1 cells. Kidney Int, 54: 399-406. 195136

Vedal S; Brauer M; White R; Petkau J (2003). Air pollution and daily mortality in a city with low levels of pollution. Environ Health Perspect, 111: 45-51. 039044

Vedal S; Rich K; Brauer M; White R; Petkau J (2004). Air pollution and cardiac arrhythmias in patients with implantable cardiovascular defibrillators. Inhal Toxicol, 16: 353-362. 055630

Verma A; Hirsch DJ; Glatt CE; Ronnett GV; Snyder SH (1993). Carbon monoxide: a putative neural messenger. Science, 259: 381-384. 193999

Vesely AE; Somogyi RB; Sasano H; Sasano N; Fisher JA; Duffin J (2004). The effects of carbon monoxide on respiratory chemoreflexes in humans. Environ Res, 94: 227-233. 194000

Villamor E; Perez-Vizcaino F; Cogolludo AL; Conde-Oviedo J; Zaragoza-Arnaez F; Lopez-Lopez JG; Tamargo J (2000). Relaxant effects of carbon monoxide compared with nitric oxide in pulmonary and systemic vessels of newborn piglets. Pediatr Res, 48: 546-553. 015838

Villeneuve PJ; Burnett RT; Shi Y; Krewski D; Goldberg MS; Hertzman C; Chen Y; Brook J (2003). A time-series study of air pollution, socioeconomic status, and mortality in Vancouver, Canada. J Expo Sci Environ Epidemiol, 13: 427-435. 055051

Villeneuve PJ; Chen L; Stieb D; Rowe BH (2006). Associations between outdoor air pollution and emergency department visits for stroke in Edmonton, Canada. Eur J Epidemiol, 21: 689-700. 090191

Villeneuve PJ; Doiron M-S; Stieb D; Dales R; Burnett RT; Dugandzic R (2006). Is outdoor air pollution associated with physician visits for allergic rhinitis among the elderly in Toronto, Canada? Allergy, 61: 750-758. 091179

Vogel JA; Gleser MA (1972). Effect of carbon monoxide on oxygen transport during exercise. J Appl Physiol, 32: 234-239. 010898

Von Klot S; Wolke G; Tuch T; Heinrich J; Dockery DW; Schwartz J; Kreyling WG; Wichmann HE; Peters A (2002). Increased asthma medication use in association with ambient fine and ultrafine particles. Eur Respir J, 20: 691-702. 034706

Von Klot S; Peters A; Aalto P; Bellander T; Berglind N; D'Ippoliti D; Elosua R; Hormann A; Kulmala M; Lanki T; Lowel H; Pekkanen J; Picciotto S; Sunyer J; Forastiere F; Health Effects of Particles on Susceptible Subpopulations (HEAPSS) Study Group (2005). Ambient air pollution is associated with increased risk of hospital cardiac readmissions of myocardial infarction survivors in five European cities. Circulation, 112: 3073-3079. 088070

Vreman HJ; Wong RJ; Kadotani T; Stevenson DK (2005). Determination of carbon monoxide (CO) in rodent tissue: effect of heme administration and environmental CO exposure. Anal Biochem, 341: 280-289. 193786

Wang R (1998). Resurgence of carbon monoxide: an endogenous gaseous vasorelaxing factor. Can J Physiol Pharmacol, 76: 1-15. 086074

Wang R; Wu L; Wang Z (1997). The direct effect of carbon monoxide on KCa channels in vascular smooth muscle cells. Pflugers Arch, 434: 285-291. 084341

Wang T-N; Ko Y-C; Chao Y-Y; Huang C-C; Lin R-S (1999). Association between indoor and outdoor air pollution and adolescent asthma from 1995 to 1996 in Taiwan. Environ Res, 81: 239-247. 008105

Weaver LK; Valentine KJ; Hopkins RO (2007). Carbon monoxide poisoning: risk factors for cognitive sequelae and the role of hyperbaric oxygen. Am J Respir Crit Care Med, 176: 491 - 497. 193939

Webber D; Lopez I; Korsak R; Hirota S; Acuna D; Edmond J (2005). Limiting iron availability confers neuroprotection from chronic mild carbon monoxide exposure in the developing auditory system of the rat. J Neurosci Res, 80: 620-633. 190514

Webber DS; Korsak RA; Sininger LK; Sampogna SL; Edmond J (2003). Mild carbon monoxide exposure impairs the developing auditory system of the rat. J Neurosci Res, 74: 655-665. 190515

Wellenius GA; Batalha JRF; Diaz EA; Lawrence J; Coull BA; Katz T; Verrier RL; Godleski JJ (2004). Cardiac effects of carbon monoxide and ambient particles in a rat model of myocardial infarction. Toxicol Sci, 80: 367-376. 087874

Wellenius GA; Bateson TF; Mittleman MA; Schwartz J (2005). Particulate air pollution and the rate of hospitalization for congestive heart failure among medicare beneficiaries in Pittsburgh, Pennsylvania. Am J Epidemiol, 161: 1030-1036. 087483

Wellenius GA; Coull BA; Batalha JRF; Diaz EA; Lawrence J; Godleski JJ (2006). Effects of ambient particles and carbon monoxide on supraventricular arrhythmias in a rat model of myocardial infarction. Inhal Toxicol, 18: 1077-1082. 156152

Wellenius GA; Saldiva PHN; Batalha JRF; Murthy GGK; Coull BA; Verrier RL; Godleski JJ (2002). Electrocardiographic changes during exposure to residual oil fly ash (ROFA) particles in a rat model of myocardial infarction. Toxicol Sci, 66: 327-335. 025405

Wellenius GA; Schwartz J; Mittleman MA (2005). Air pollution and hospital admissions for ischemic and hemorrhagic stroke among medicare beneficiaries. Stroke, 36: 2549-2553. 088685

Wellenius GA; Yeh GY; Coull BA; Suh HH; Phillips RS; Mittleman MA (2007). Effects of ambient air pollution on functional status in patients with chronic congestive heart failure: a repeated-measures study. Environ Health, 6: 1-7. 092830

Wheeler A; Zanobetti A; Gold DR; Schwartz J; Stone P; Suh HH (2006). The relationship between ambient air pollution and heart rate variability differs for individuals with heart and pulmonary disease. Environ Health Perspect, 114: 560-566. 088453

Wilhelm M; Meng YY; Rull RP; English P; Balmes J; Ritz B (2008). Environmental public health tracking of childhood asthma using California health interview survey, traffic, and outdoor air pollution data. Environ Health Perspect, 116: 1254-1260. 191912

Wilhelm M; Ritz B (2005). Local variations in CO and particulate air pollution and adverse birth outcomes in Los Angeles County, California, USA. Environ Health Perspect, 113: 1212-1221. 088668

Wittenberg BA; Wittenberg JB (1993). Effects of carbon monoxide on isolated heart muscle cells. Health Effects Institute. Cambridge, MA. 013909

Wollmann HA (1998). Intrauterine growth restriction: definition and etiology. Horm Res, 49: 1-6. 193812

Woodruff TJ; Darrow LA; Parker JD (2008). Air pollution and postneonatal infant mortality in the United States, 1999-2002. Environ Health Perspect, 116: 110-115. 098386

Yamaya M; Sekizawa K; Ishizuka S; Monma M; Mizuta K; Sasaki H (1998). Increased carbon monoxide in exhaled air of subjects with upper respiratory tract infections. Am J Respir Crit Care Med, 158: 311-314. 047525

Yang C-Y; Chen Y-S; Yang C-H; Ho S-C (2004). Relationship between ambient air pollution and hospital admissions for cardiovascular diseases in Kaohsiung, Taiwan. J Toxicol Environ Health A Curr Iss, 67: 483-493. 094376

Yang C-Y; Hsieh H-J; Tsai S-S; Wu T-N; Chiu H-F (2006). Correlation between air pollution and postneonatal mortality in a subtropical city: Taipei, Taiwan. J Toxicol Environ Health A Curr Iss, 69: 2033-2040. 090760

Yang CY (2008). Air pollution and hospital admissions for congestive heart failure in a subtropical city: Taipei, Taiwan. J Toxicol Environ Health A Curr Iss, 71: 1085-1090. 157160

Yang Q; Chen Y; Krewski D; Burnett RT; Shi Y; McGrail KM (2005). Effect of short-term exposure to low levels of gaseous pollutants on chronic obstructive pulmonary disease hospitalizations. Environ Res, 99: 99-105. 090184

Yang Q; Chen Y; Shi Y; Burnett RT; McGrail KM; Krewski D (2003). Association between ozone and respiratory admissions among children and the elderly in Vancouver, Canada. Inhal Toxicol, 15: 1297-1308. 055621

Yasuda H; Yamaya M; Nakayama K; Ebihara S; Sasaki T; Okinaga S; Inoue D; Asada M; Nemoto M; Sasaki H (2005). Increased arterial carboxyhemoglobin concentrations in chronic obstructive pulmonary disease. Am J Respir Crit Care Med, 171: 1246-1251. 191953

Yoshimura S; Banno Y; Nakashima S; Hayashi K; Yamakawa H; Sawada M; Sakai N; Nozawa Y (1999). Inhibition of neutral sphingomyelinase activation and ceramide formation by glutathione in hypoxic PC12 cell death. J Neurochem, 73: 675-683. 195135

Yu O; Sheppard L; Lumley T; Koenig JQ; S (2000). Effects of ambient air pollution on symptoms of asthma in Seattle-area children enrolled in the CAMP study. Environ Health Perspect, 108: 1209-1214. 013254

Zamudio S; Palmer SK; Dahms TE; Berman JC; Young DA; Moore LG (1995). Alterations in uteroplacental blood flow precede hypertension in preeclampsia at high altitude. J Appl Physiol, 79: 15-22. 193908

Zanobetti A; Canner MJ; Stone PH; Schwartz J; Sher D; Eagan-Bengston E; Gates KA; Hartley LH; Suh H; Gold DR (2004). Ambient pollution and blood pressure in cardiac rehabilitation patients. Circulation, 110: 2184-2189. 087489

Zanobetti A; Schwartz J (2001). Are diabetics more susceptible to the health effects of airborne particles? Am J Respir Crit Care Med, 164: 831-833. 016710

Zanobetti A; Schwartz J (2006). Air pollution and emergency admissions in Boston, MA. J Epidemiol Community Health, 60: 890-895. 090195

Zenclussen ML; Anegon I; Bertoja AZ; Chauveau C; Vogt K; Gerlof K; Sollwedel A; Volk HD; Ritter T; Zenclussen AC (2006). Over-expression of heme oxygenase-1 by adenoviral gene transfer improves pregnancy outcome in a murine model of abortion. Am J Reprod Immunol, 69: 35-52. 193873

Zevin S; Saunders S; Gourlay SG; Jacob P III; Benowitz NL (2001). Cardiovascular effects of carbon monoxide and cigarette smoking. J Am Coll Cardiol, 38: 1633-1638. 021120

Zhang X; Shan P; Alam J; Fu XY; Lee PJ (2005). Carbon monoxide differentially modulates STAT1 and STAT3 and inhibits apoptosis via a phosphatidylinositol 3-kinase/akt and p38 kinase-dependent STAT3 pathway during anoxia-reoxygenation injury. J Biol Chem, 280: 8714-8721. 184460

Zhao H; Wong RJ; Doyle TC; Nayak N; Vreman HJ; Contag CH; Stevenson DK (2008). Regulation of maternal and fetal hemodynamics by heme oxygenase in mice. Biol Reprod, 78: 744-751. 193883

Zhu Y; Hinds WC; Kim S; Shen S; Sioutas C (2002). Study of ultrafine particles near a major highway with heavy-duty diesel traffic. Atmos Environ, 36: 4323-4335. 041553

Zhuo M; Small SA; Kandel ER; Hawkins RD (1993). Nitric oxide and carbon monoxide produce activity-dependent long-term synaptic enhancement in hippocampus. Science, 260: 1946-1950. 013905

Zinkham WH; Houtchens RA; Caughey WS (1980). Carboxyhemoglobin levels in an unstable hemoglobin disorder (Hb Zürich): effect on phenotypic expression. Science, 209: 406-408. 011435

Zuckerbraun BS; Chin BY; Bilban M; d'Avila JC; Rao J; Billiar TR; Otterbein LE (2007). Carbon monoxide signals via inhibition of cytochrome c oxidase and generation of mitochondrial reactive oxygen species. FASEB J, 21: 1099-1106. 193884

Annex A. Atmospheric Science

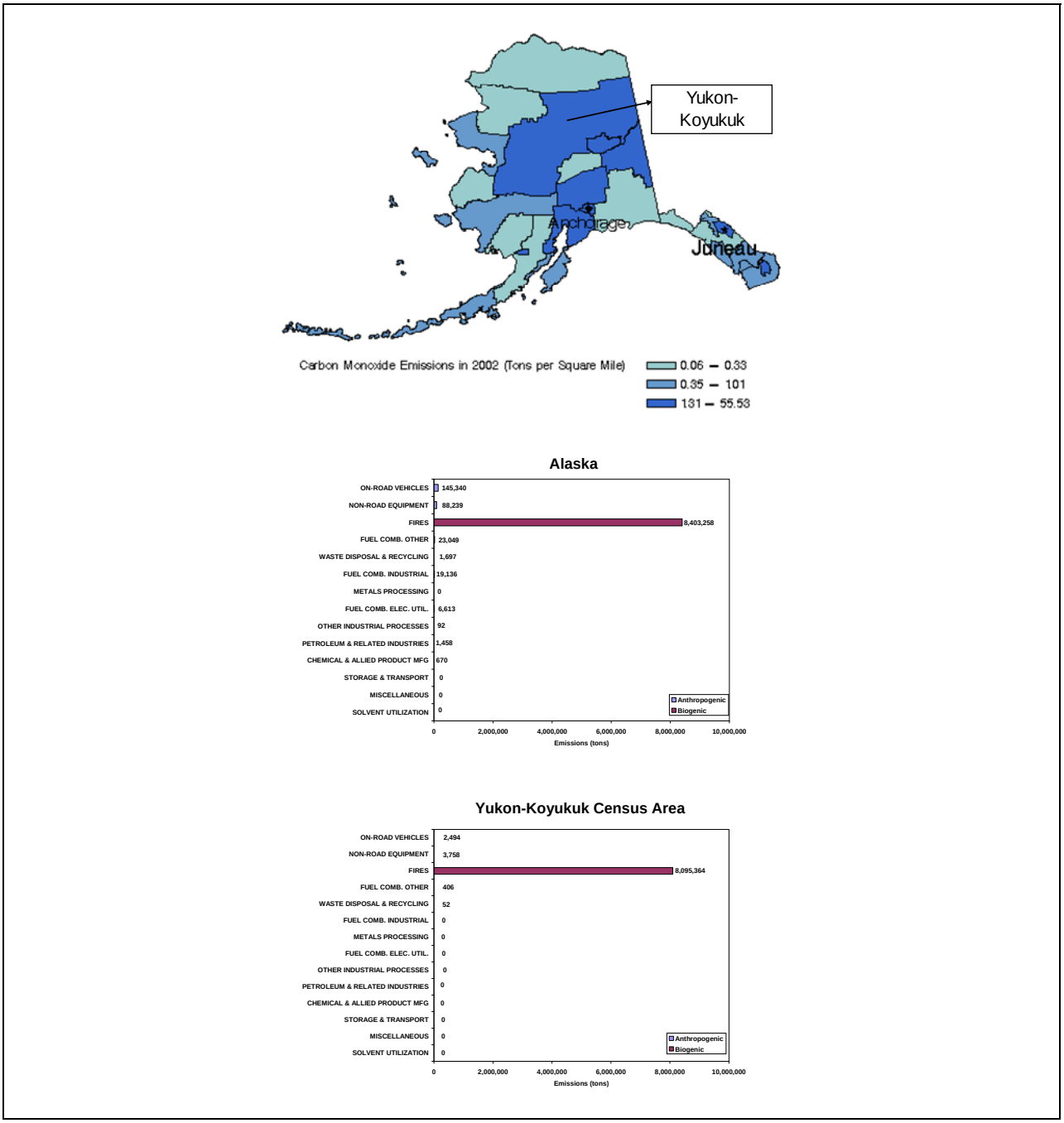


Figure A-1. CO emissions density map and distribution for the state of Alaska and for Yukon-Koyukuk County in Alaska.

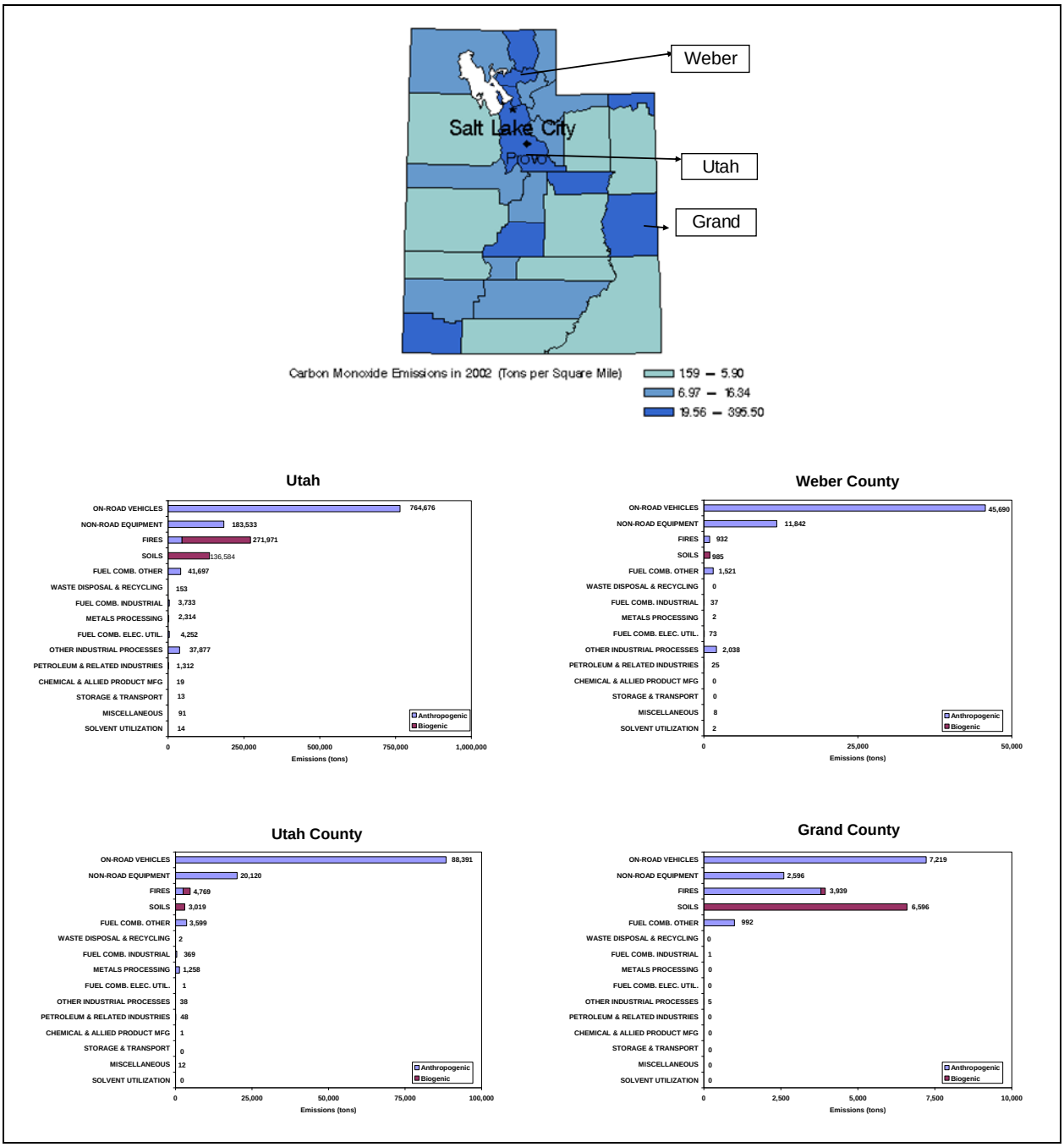


Figure A-2. CO emissions density map and distribution for the state of Utah and for selected counties in Utah.

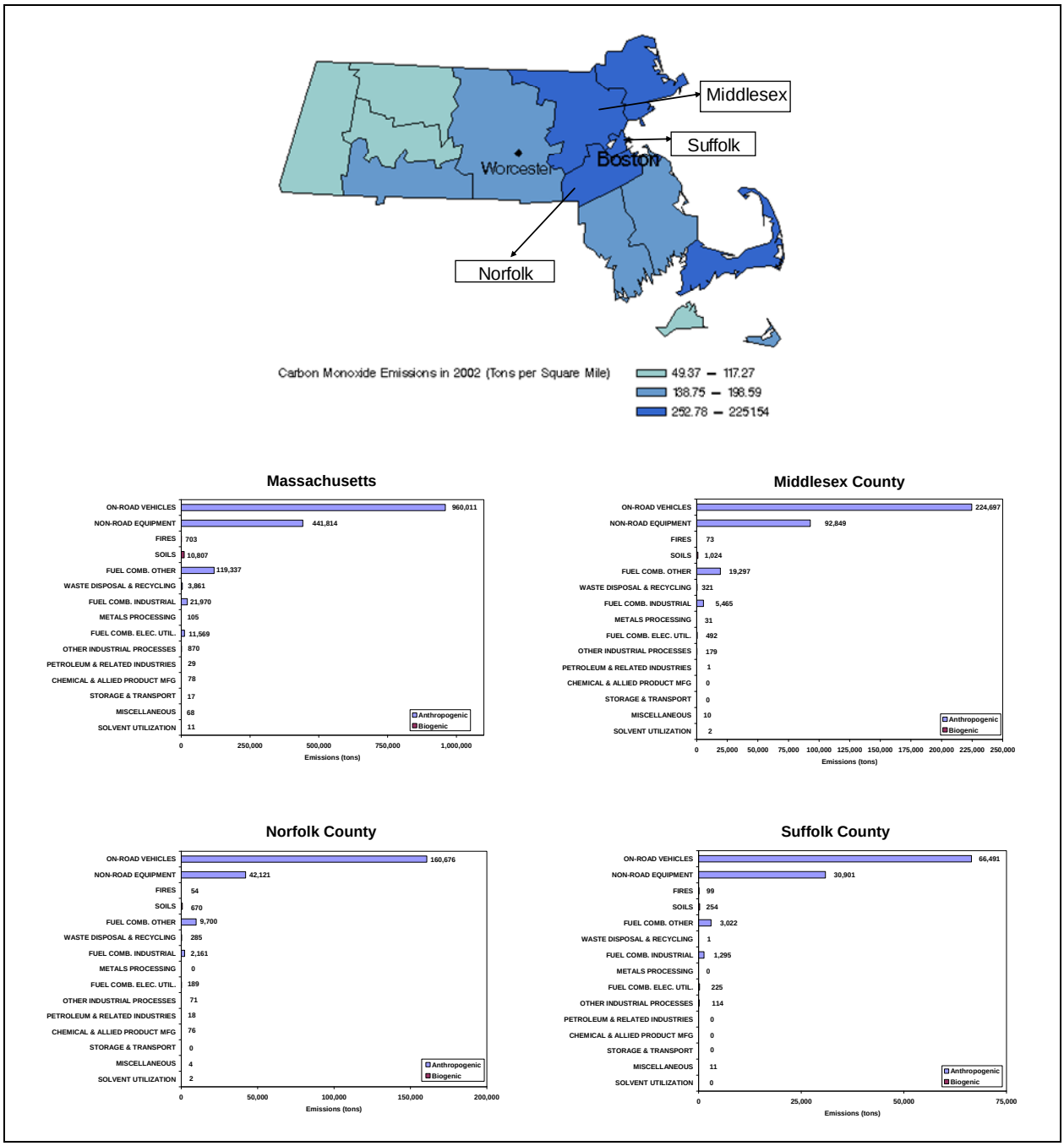


Figure A-3. CO emissions density map and distribution for the state of Massachusetts and for selected counties in Massachusetts.

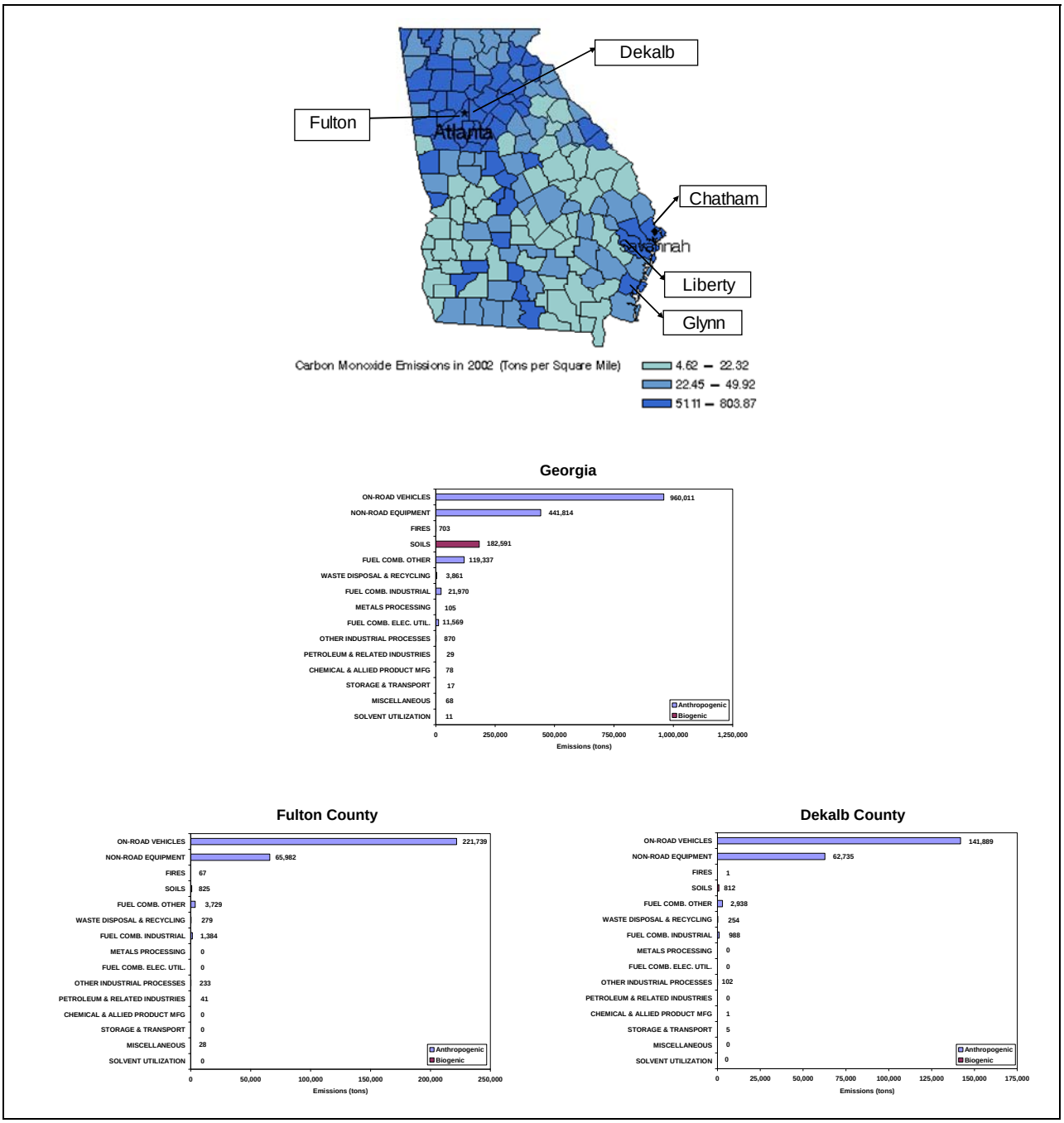


Figure A-4. CO emissions density map and distribution for the state of Georgia and for selected counties in Georgia (Figure 1 of 2).

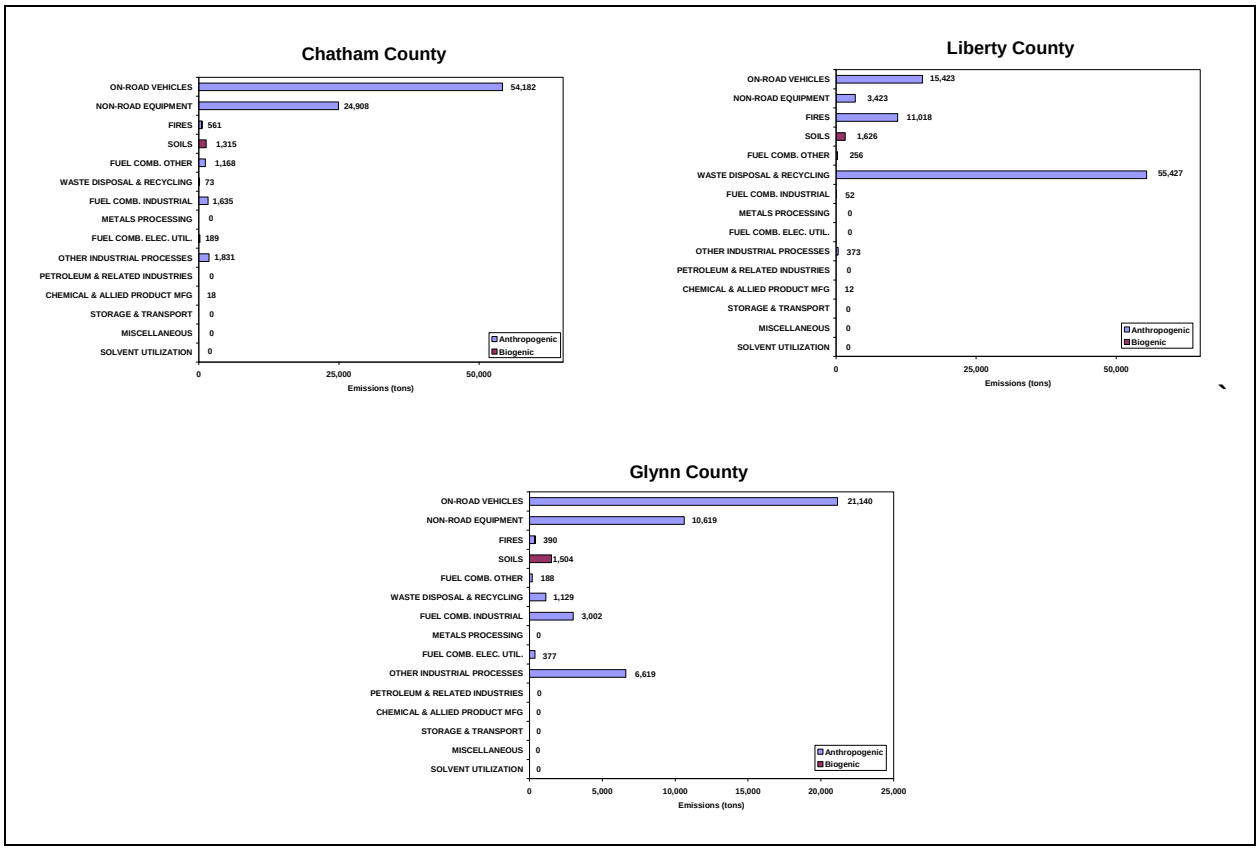


Figure A-5. CO emissions distribution for selected counties in Georgia (Figure 2 of 2).

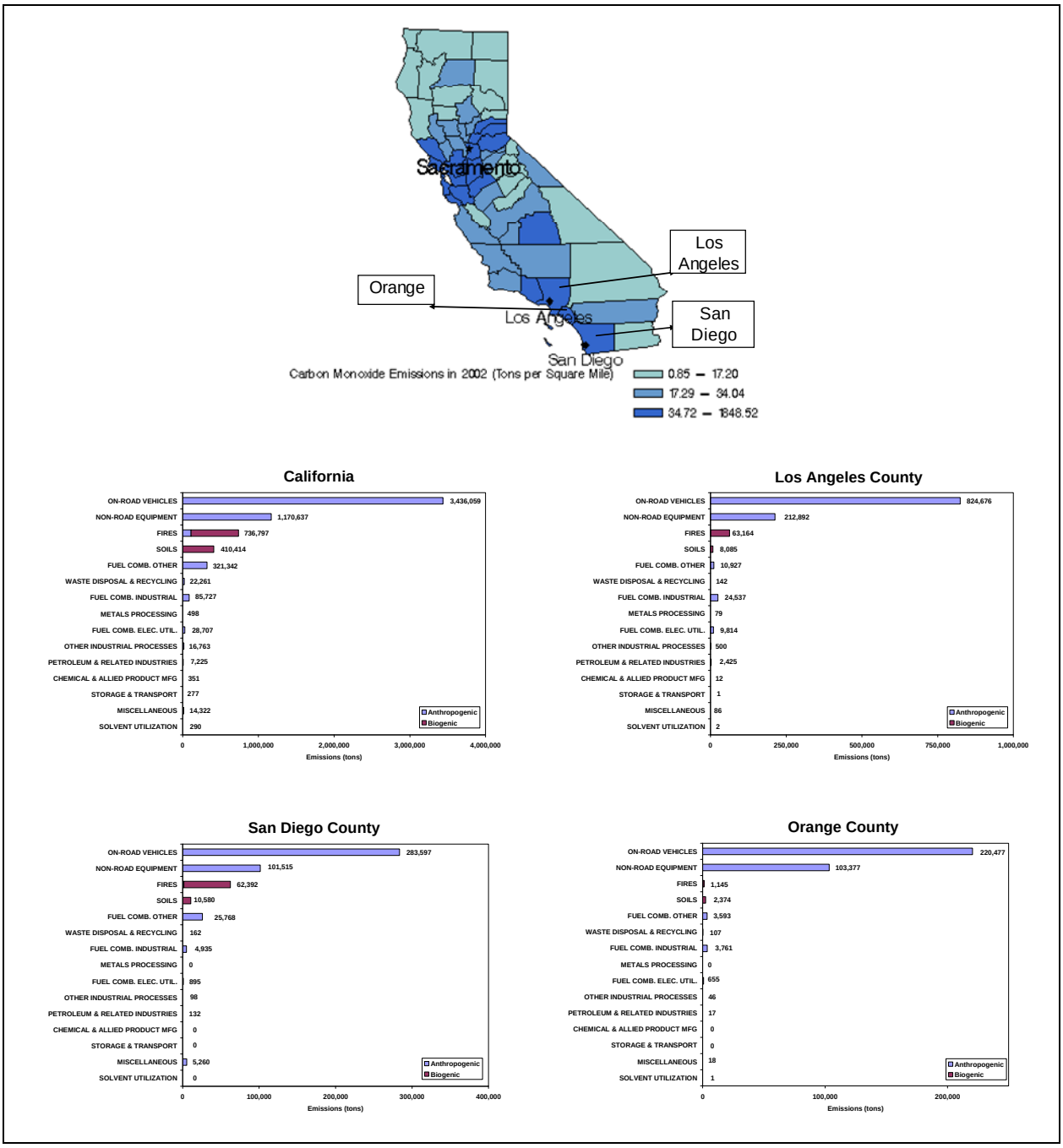
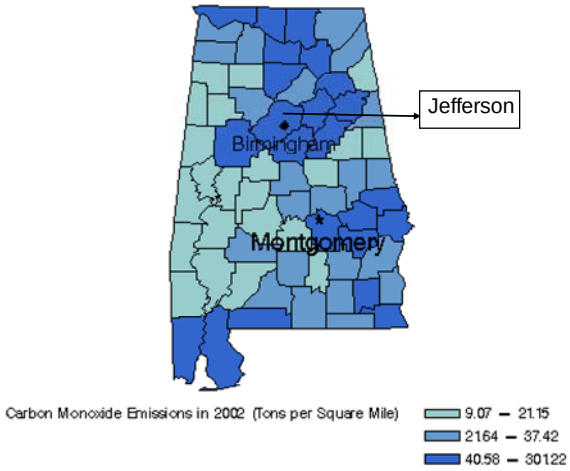
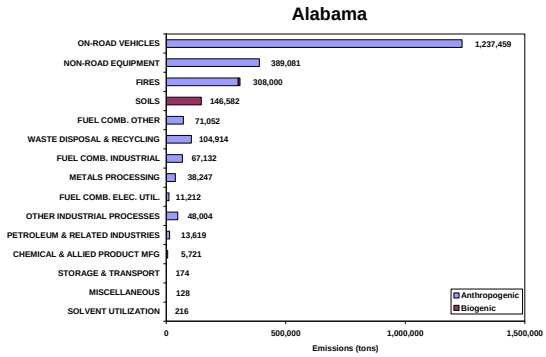


Figure A-6. CO emissions density map and distribution for the state of California and for selected counties in California.





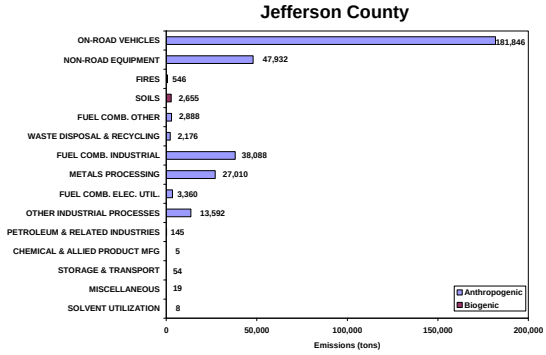


Figure A-7. CO emissions density map and distribution for the state of Alabama and for Jefferson County in Alabama.

Table A-1. Listing of all CO monitors currently in use, along with their limits of detection.

Method Code	Method Description	Reference Method Id	Fed MDL (ppm)
008	BENDIX 8501-5CA	RFCA-0276-008	0.50000
012	BECKMAN 866	RFCA-0876-012	0.50000
018	MSA 202S	RFCA-0177-018	0.50000
033	HORIBA AQM-10--11--12	RFCA-1278-033	0.50000
041	MONITOR LABS 8310	RFCA-0979-041	0.50000
048	HORIBA 300E/300SE	RFCA-1180-048	0.50000
050	MASS-CO 1 (MASSACHUSETTS)	RFCA-1280-050	0.50000
051	DASIBI 3003	RFCA-0381-051	0.50000
054	THERMO ELECTRON 48, 48C	RFCA-0981-054	0.50000
055	Gas Filter Correlation Thermo Electron 48C-TL	N/A	0.04000
066	MONITOR LABS 8830	RFCA-0388-066	0.50000
067	DASIBI 3008	RFCA-0488-067	0.50000
088	LEAR SIEGLER MODEL ML 9830	RFCA-0992-088	0.50000
093	API MODEL 300 GAS FILTER	RFCA-1093-093	0.50000
106	HORIBA INSTR. MODEL APMA-360	RFCA-0895-106	0.50000
108	ENVIRONMENT SA MODEL CO11M	RFCA-0995-108	0.50000
147	Environnement S.A. Model CO12M Co Analyzer	RFCA-0206-147	0.50000
158	HORIBA INSTR. MODEL APMA-370	RFCA-0506-158	0.50000
167	DKK-TOA Cork Mode GFC-311E	RFCA-0907-167	0.50000
172	SIR S.A. Model S5006	RFCA-0708-172	0.50000
554	Gas Filter Correlation Thermo Electron 48C-TLE	N/A	0.04000
588	Ecotech EC9830T	RFCA-0992-088	0.04000
593	API Model 300 EU	RFCA-1093-093	0.04000

Table A-2. Microscale monitors meeting 75% completeness criteria, 2005-2007.

Monitor Code	State Name	City Name	Traffic Count	Road Type
02-090-0002-42101-1	Alaska	Fairbanks	NR	NR
04-013-0016-42101-1	Arizona	Phoenix	50,000	ARTERIAL
04-019-1014-42101-1	Arizona	Tucson	41,200	MAJ ST OR HY
06-065-1003-42101-1	California	Riverside	40,000	FREEWAY
06-073-0007-42101-1	California	San Diego	6,000	THRU ST OR HY
08-013-0009-42101-1	Colorado	Longmont	20,000	MAJ ST OR HY
08-031-0002-42101-2	Colorado	Denver	17,200	MAJ ST OR HY
08-031-0019-42101-1	Colorado	Denver	500	MAJ ST OR HY
08-041-0015-42101-1	Colorado	Colorado Springs	44,200	MAJ ST OR HY
08-077-0018-42101-1	Colorado	Grand Junction	13,525	THRU ST OR HY
09-003-0017-42101-1	Connecticut	Hartford	10,000	THRU ST OR HY
11-001-023-42101-1	District Of Columbia	Washington	30,000	THRU ST OR HY
12-057-1070-42101-1	Florida	Tampa	133,855	ARTERIAL
12-086-4002-42101-1	Florida	Miami	5,000	LOCAL ST OR HY
12-095-1005-42101-1	Florida	Orlando	30,000	MAJ ST OR HY
12-103-0024-42101-1	Florida	Saint Petersburg	35,000	MAJ ST OR HY
12-103-2008-42101-1	Florida	Clearwater	67,751	MAJ ST OR HY
12-115-1004-42101-1	Florida	Sarasota	31,000	MAJ ST OR HY
13-121-0099-42101-1	Georgia	Atlanta	44,000	MAJ ST OR HY
17-031-0063-42101-1	Illinois	Chicago	5,000	LOCAL ST OR HY
17-031-6004-42101-1	Illinois	Maywood	NR	NR
17-143-0036-42101-1	Illinois	Peoria	18,500	ARTERIAL
17-167-0008-42101-1	Illinois	Springfield	16,400	MAJ ST OR HY
17-201-0011-42101-1	Illinois	Rockford	11,400	ARTERIAL
18-003-0011-42101-1	Indiana	Fort Wayne	30430	MAJ ST OR HY
18-089-0015-42101-1	Indiana	East Chicago	NR	NR
18-097-0072-42101-1	Indiana	Indianapolis	21,237	MAJ ST OR HY
18-163-0019-42101-1	Indiana	Evansville	24,498	LOCAL ST OR HY
21-111-1019-42101-1	Kentucky	Louisville	22,000	MAJ ST OR HY
27-053-0954-42101-1	Minnesota	Minneapolis	29,352	MAJ ST OR HY
27-123-0050-42101-1	Minnesota	St. Paul	NR	NR
27-137-0018-42101-1	Minnesota	Duluth	12,000	MAJ ST OR HY
27-145-3048-42101-1	Minnesota	St. Cloud	NR	NR
30-029-0010-42101-1	Montana	Kalispell	NR	THRU ST OR HY
30-031-0013-42101-1	Montana	Not in a city	2,000	THRU ST OR HY
33-011-1009-42101-1	New Hampshire	Nashua	40,000	MAJ ST OR HY
34-005-1001-42101-1	New Jersey	Burlington	8,000	THRU ST OR HY
34-017-1002-42101-1	New Jersey	Jersey City	25,000	THRU ST OR HY
37-067-0023-42101-1	North Carolina	Winston-Salem	22,000	MAJ ST OR HY
39-035-0048-42101-1	Ohio	Cleveland	24,300	THRU ST OR HY

Monitor Code	State Name	City Name	Traffic Count	Road Type
39-035-0051-42101-1	Ohio	Cleveland	16,150	MAJ ST OR HY
39-035-0053-42101-1	Ohio	Cleveland	19,550	MAJ ST OR HY
39-049-0036-42101-1	Ohio	Columbus	16,800	MAJ ST OR HY
39-061-0021-42101-1	Ohio	Cincinnati	17,250	LOCAL ST OR HY
39-085-0006-42101-1	Ohio	Mentor	25,240	MAJ ST OR HY
39-113-0034-42101-1	Ohio	Dayton	7,100	THRU ST OR HY
39-153-0022-42101-1	Ohio	Akron	13,150	MAJ ST OR HY
41-029-0018-42101-1	Oregon	Medford	NR	NR
41-039-0013-42101-1	Oregon	Eugene	17,500	MAJ ST OR HY
41-051-0087-42101-1	Oregon	Portland	4,150	LOCAL ST OR HY
45-079-0020-42101-1	South Carolina	Columbia	31,500	MAJ ST OR HY
47-037-0021-42101-1	Tennessee	Nashville	15,000	MAJ ST OR HY
47-157-0036-42101-1	Tennessee	Memphis	25,000	THRU ST OR HY
48-029-0046-42101-1	Texas	San Antonio	5,820	MAJ ST OR HY
48-201-0075-42101-1	Texas	Houston	6,576	LOCAL ST OR HY
53-033-0019-42101-1	Washington	Bellevue	100,000	MAJ ST OR HY
53-063-0049-42101-1	Washington	Spokane	10,000	MAJ ST OR HY

"NR" denotes that the value was not reported.

Table A-3. Middle scale monitors meeting 75% completeness criteria, 2005-2007.

Monitor Code	State Name	City Name	Traffic Count	Road Type
04-013-3010-42101-1	Arizona	Phoenix	18,500	ARTERIAL
06-029-0010-42101-1	California	Bakersfield	30,300	ARTERIAL
06-037-1301-42101-1	California	Lynwood	35,000	ARTERIAL
06-037-9033-42101-1	California	Lancaster	2,320	LOCAL ST OR HY
06-059-1003-42101-1	California	Costa Mesa	1,000	LOCAL ST OR HY
06-071-9004-42101-1	California	San Bernardino	21,900	THRU ST OR HY
06-085-0005-42101-1	California	San Jose	NR	LOCAL ST OR HY
12-0011-0010-42101-1	Florida	Fort Lauderdale	1,000	LOCAL ST OR HY
12-031-0080-42101-1	Florida	Jacksonville	1,000	LOCAL ST OR HY
12-031-0084-42101-1	Florida	Jacksonville	500	LOCAL ST OR HY
12-099-1004-42101-1	Florida	Palm Beach	30,000	MAJ ST OR HY
12-103-2006-42101-1	Florida	Clearwater	23,400	MAJ ST OR HY
17-031-3103-42101-1	Illinois	Schiller Park	47,900	ARTERIAL
20-209-0021-42101-1	Kansas	Kansas City	7,720	MAJ ST OR HY
24-510-0040-42101-1	Maryland	Baltimore	15,300	THRU ST OR HY
32-031-0022-42101-1	Nevada	Reno	NR	NR
34-003-0004-42101-1	New Jersey	Fort Lee	250,000	ARTERIAL
36-061-0056-42101-1	New York	New York	45,000	MAJ ST OR HY
39-049-0005-42101-1	Ohio	Columbus	36,600	FREEWAY
39-081-1001-42101-1	Ohio	Mingo Junction	2,500	LOCAL ST OR HY
39-151-0020-42101-1	Ohio	Canton	11,000	MAJ ST OR HY
40-143-0191-42101-1	Oklahoma	Tulsa	50,800	FREEWAY
42-003-0038-42101-1	Pennsylvania	Pittsburgh	15,000	MAJ ST OR HY
42-101-0047-42101-1	Pennsylvania	Philadelphia	NR	NR
45-019-0046-42101-1	South Carolina	Not in a city	NR	LOCAL ST OR HY
45-045-0008-42101-1	South Carolina	Greenville	NR	LOCAL ST OR HY
45-045-0009-42101-1	South Carolina	Taylors	9,500	LOCAL ST OR HY
47-163-0007-42101-1	Tennessee	Kingsport	NR	NR
48-439-1002-42101-1	Texas	Fort Worth	100	LOCAL ST OR HY
50-007-0014-42101-1	Vermont	Burlington	NR	MAJ ST OR HY
72-127-0003-42101-1	Puerto Rico	San Juan	64,000	MAJ ST OR HY

"NR" denotes that the value was not reported.

Table A-4. Neighborhood scale monitors meeting 75% completeness criteria, 2005-2007.

Monitor Code	State Name	City Name	Traffic Count	Road Type
01-073-1003-42101-1	Alabama	Fairfield	5,000	LOCAL ST OR HY
01-073-6004-42101-1	Alabama	Birmingham	NR	NR
02-020-0018-42101-1	Alaska	Anchorage	NR	NR
02-020-0048-42101-1	Alaska	Anchorage	5,000	LOCAL ST OR HY
02-090-0020-42101-1	Alaska	Fairbanks	NR	NR
04-013-0019-42101-1	Arizona	Phoenix	NR	LOCAL ST OR HY
04-013-3002-42101-1	Arizona	Phoenix	24,000	ARTERIAL
04-019-0002-42101-1	Arizona	Tucson	37,400	MAJ ST OR HY
04-019-1011-42101-1	Arizona	Tucson	47,000	MAJ ST OR HY
04-019-1028-42101-1	Arizona	Tucson	52,900	MAJ ST OR HY
06-001-1001-42101-1	California	Fremont (Centerville)	500	LOCAL ST OR HY
06-013-0002-42101-1	California	Concord	41,218	MAJ ST OR HY
06-037-5005-42101-1	California	Los Angeles	1,252	LOCAL ST OR HY
06-053-1003-42101-1	California	Salinas	33,193	THRU ST OR HY
06-065-9001-42101-1	California	Lake Elsinore	NR	NR
06-067-0007-42101-1	California	Sacramento	20,000	THRU ST OR HY
06-073-0001-42101-1	California	Chula Vista	5,000	LOCAL ST OR HY
06-073-1002-42101-1	California	Escondido	NR	NR
06-073-2007-42101-1	California	Otay Mesa	18,000	LOCAL ST OR HY
06-083-1025-42101-1	California	Capitan	NR	NR
06-083-2004-42101-1	California	Lompoc	NR	NR
06-083-2011-42101-1	California	Goleta	5,000	THRU ST OR HY
06-083-4003-42101-1	California	Vandenberg Air Force Base	NR	NR
08-01-3001-42101-1	Colorado	Welby	500	EXPRESSWAY
08-067-7001-42101-1	Colorado	Not in a city	2,436	LOCAL ST OR HY
08-069-1004-42101-1	Colorado	Fort Collins	5,000	THRU ST OR HY
08-123-0010-42101-1	Colorado	Greeley	6,650	THRU ST OR HY
11-001-0041-42101-1	District Of Columbia	Washington	540	LOCAL ST OR HY
12-011-2004-42101-1	Florida	Pompano Beach	1,000	LOCAL ST OR HY
12-011-3002-42101-1	Florida	Hollywood	1,000	LOCAL ST OR HY
12-031-0083-42101-1	Florida	Jacksonville	10,000	LOCAL ST OR HY
12-086-0031-42101-1	Florida	Miami	62,000	MAJ ST OR HY
12-086-1019-42101-1	Florida	Miami	8,000	MAJ ST OR HY
12-095-2002-42101-1	Florida	Winter Park	7,000	MAJ ST OR HY
12-103-0018-42101-1	Florida	Saint Petersburg	2,000	MAJ ST OR HY
17-031-4002-42101-1	Illinois	Cicero	NR	NR
17-163-0010-42101-1	Illinois	East Saint Louis	8,900	LOCAL ST OR HY
18-097-0073-42101-1	Indiana	Indianapolis (Remainder)	11,261	THRU ST OR HY
20-173-0010-42101-1	Kansas	Wichita	6,884	LOCAL ST OR HY
21-111-0046-42101-1	Kentucky	Louisville	6,500	THRU ST OR HY

Monitor Code	State Name	City Name	Traffic Count	Road Type
22-033-0009-42101-1	Louisiana	Baton Rouge	5,000	LOCAL ST OR HY
25-013-0016-42101-1	Massachusetts	Springfield	5,000	LOCAL ST OR HY
25-017-0007-42101-1	Massachusetts	Lowell	15,000	THRU ST OR HY
25-025-0042-42101-1	Massachusetts	Boston	12,785	LOCAL ST OR HY
27-03-0600-42101-1	Minnesota	Fridley	1,400	LOCAL ST OR HY
27-037-0020-42101-1	Minnesota	Rosemount	NR	NR
27-037-0423-42101-1	Minnesota	Inver Grove Heights (RR name Inver Grove)	NR	NR
29-510-0086-42101-1	Missouri	St. Louis	81,850	MAJ ST OR HY
30-111-0085-42101-1	Montana	Billings	5,700	THRU ST OR HY
31-055-0035-42101-1	Nebraska	Omaha	2,900	LOCAL ST OR HY
32-003-0538-42101-1	Nevada	Las Vegas	20,000	LOCAL ST OR HY
32-003-0539-42101-1	Nevada	Las Vegas	21,000	MAJ ST OR HY
32-003-0561-42101-1	Nevada	Las Vegas	28,400	MAJ ST OR HY
32-003-1021-42101-1	Nevada	Las Vegas	NR	NR
32-003-2002-42101-1	Nevada	Las Vegas	6,750	THRU ST OR HY
32-031-0016-42101-1	Nevada	Reno	22,700	LOCAL ST OR HY
32-031-0020-42101-1	Nevada	Reno	NR	NR
32-031-0025-42101-1	Nevada	Reno	NR	NR
32-031-1005-42101-1	Nevada	Sparks	2,600	LOCAL ST OR HY
32-031-2009-42101-1	Nevada	Lemmon Valley-Golden Valley	NR	NR
32-510-0004-42101-1	Nevada	Carson City	1	LOCAL ST OR HY
33-011-0020-42101-1	New Hampshire	Manchester	500	LOCAL ST OR HY
34-003-5001-42101-1	New Jersey	Hackensack	15,000	THRU ST OR HY
34-007-0003-42101-1	New Jersey	Camden	45,000	MAJ ST OR HY
35-001-019-42101-1	New Mexico	Albuquerque	1	ARTERIAL
35-001-0023-42101-1	New Mexico	Albuquerque	41,200	MAJ ST OR HY
35-001-0024-42101-1	New Mexico	Albuquerque	15,500	MAJ ST OR HY
35-001-0028-42101-1	New Mexico	Albuquerque	2,0600	THRU ST OR HY
35-001-1014-42101-1	New Mexico	Albuquerque	8,000	THRU ST OR HY
35-043-9004-42101-1	New Mexico	Not in a city	100	LOCAL ST OR HY
36-063-2008-42101-1	New York	Niagara Falls	5,000	LOCAL ST OR HY
37-119-0041-42101-1	North Carolina	Charlotte	16,400	MAJ ST OR HY
37-119-0041-42101-3	North Carolina	Charlotte	16,400	MAJ ST OR HY
39-035-0070-42101-1	Ohio	Cleveland	100	LOCAL ST OR HY
39-113-0028-42101-1	Ohio	Dayton	5,100	LOCAL ST OR HY
39-153-0020-42101-1	Ohio	Akron	200	LOCAL ST OR HY
40-021-9002-42101-1	Oklahoma	Park Hill	10,300	LOCAL ST OR HY
40-071-9010-42101-1	Oklahoma	Not in a city	300	LOCAL ST OR HY
40-109-0047-42101-1	Oklahoma	Oklahoma City	27,000	MAJ ST OR HY
41-051-0080-42101-1	Oregon	Portland	5,000	LOCAL ST OR HY
42-003-0031-42101-1	Pennsylvania	Pittsburgh	4,562	THRU ST OR HY
42-013-0801-42101-1	Pennsylvania	Altoona	100	LOCAL ST OR HY

Monitor Code	State Name	City Name	Traffic Count	Road Type
42-017-0012-42101-1	Pennsylvania	Bristol	500	LOCAL ST OR HY
42-021-0011-42101-1	Pennsylvania	Johnstown	6,000	LOCAL ST OR HY
42-049-0003-42101-1	Pennsylvania	Erie	1,000	LOCAL ST OR HY
42-071-0007-42101-1	Pennsylvania	Lancaster	2,000	THRU ST OR HY
42-073-0015-42101-1	Pennsylvania	New Castle	4,500	LOCAL ST OR HY
42-091-0013-42101-1	Pennsylvania	Norristown	8,500	MAJ ST OR HY
42-095-0025-42101-1	Pennsylvania	Freemansburg	100	LOCAL ST OR HY
42-101-0004-42101-1	Pennsylvania	Philadelphia	13800	MAJ ST OR HY
42-101-0027-42101-1	Pennsylvania	Philadelphia	46000	MAJ ST OR HY
42-107-0003-42101-1	Pennsylvania	Shenandoah	100	LOCAL ST OR HY
42-125-0005-42101-1	Pennsylvania	Charleroi	NR	NR
44-007-1010-42101-1	Rhode Island	East Providence	100,000	FREEWAY
48-061-0006-42101-1	Texas	Brownsville	30	LOCAL ST OR HY
48-113-0069-42101-2	Texas	Dallas	1,000	LOCAL ST OR HY
48-141-0002-42101-1	Texas	El Paso	7,270	THRU ST OR HY
48-141-0029-42101-1	Texas	El Paso	2,790	LOCAL ST OR HY
48-141-0037-42101-1	Texas	El Paso	5,000	LOCAL ST OR HY
48-141-0044-42101-1	Texas	El Paso	15,200	ARTERIAL
48-141-0053-42101-1	Texas	El Paso	1,992	FREEWAY
48-141-0057-42101-1	Texas	Socorro	500	LOCAL ST OR HY
48-141-0058-42101-1	Texas	El Paso	1,080	LOCAL ST OR HY
48-201-0024-42101-1	Texas	Not in a city	5,300	MAJ ST OR HY
48-201-0047-42101-1	Texas	Houston	5,860	MAJ ST OR HY
48-201-1035-42101-1	Texas	Houston	13,440	MAJ ST OR HY
48-201-1039-42101-1	Texas	Deer Park	16010	MAJ ST OR HY
48-439-3011-42101-1	Texas	Arlington	10,573	LOCAL ST OR HY
48-453-0014-42101-1	Texas	Austin	3,420	LOCAL ST OR HY
48-479-0017-42101-1	Texas	Laredo	30,380	ARTERIAL
49-035-0003-42101-1	Utah	Not in a city	16,500	THRU ST OR HY
50-021-0002-42101-1	Vermont	Rutland	NR	NR
51-059-0005-42101-1	Virginia	Not in a city	25	LOCAL ST OR HY
51-650-0004-42101-2	Virginia	Hampton	2,000	LOCAL ST OR HY
51-760-0024-42101-1	Virginia	Richmond	7,591	THRU ST OR HY
51-770-0015-42101-1	Virginia	Roanoke	NR	NR
54-009-0011-42101-1	West Virginia	Weirton	NR	NR
54-029-0009-42101-1	West Virginia	Weirton	NR	NR
54-029-1004-42101-1	West Virginia	Weirton	50	LOCAL ST OR HY

"NR" denotes that the value was not reported.

Table A-5. Urban scale monitors meeting 75% completeness criteria, 2005-2007.

Monitor Code	State Name	City Name	Traffic Count	Road Type
06-059-0007-42101-1	California	Anaheim	1,000	LOCAL ST OR HY
13-089-0002-42101-1	Georgia	Decatur	9,250	LOCAL ST OR HY
13-223-0003-42101-1	Georgia	Not in a city	6	LOCAL ST OR HY
25-027-0023-42101-1	Massachusetts	Worcester	NR	LOCAL ST OR HY
34-007-1001-42101-1	New Jersey	Not in a city	4,000	THRU ST OR HY
42-003-0010-42101-1	Pennsylvania	Pittsburgh	1,000	MAJ ST OR HY
42-007-0014-42101-1	Pennsylvania	Beaver Falls	NR	NR
42-129-0008-42101-1	Pennsylvania	Greensburg	100	THRU ST OR HY
42-133-0008-42101-1	Pennsylvania	York	8,400	THRU ST OR HY
48-141-0055-42101-1	Texas	El Paso	2450	LOCAL ST OR HY
51-059-0030-42101-1	Virginia	Franconia	200	LOCAL ST OR HY

"NR" denotes that the value was not reported.

Table A-6. Regional scale monitors meeting 75% completeness criteria, 2005-2007.

Monitor Code	State Name	City Name	Traffic Count	Road Type
23-009-0103-42101-1	Maine	Not in a city	3,500	LOCAL ST OR HY
35-001-0029-42101-1	New Mexico	South Valley	8,800	LOCAL ST OR HY

"NR" denotes that the value was not reported.

Table A-7. Monitors meeting 75% completeness criteria, 2005-2007 with no scale delared.

Monitor Code	State Name	City Name	Traffic Count	Road Type
04-013-9997-42101-1	Arizona	Phoenix	250	LOCAL ST OR HY
06-001-0007-42101-1	California	Livermore	2,400	LOCAL ST OR HY
06-007-0002-42101-1	California	Chico	44,000	LOCAL ST OR HY
06-013-1002-42101-1	California	Bethel Island	NR	NR
06-013-1004-42101-1	California	San Pablo	NR	THRU ST OR HY
06-013-3001-42101-1	California	Pittsburg	9,600	THRU ST OR HY
06-019-0007-42101-1	California	Fresno	500	LOCAL ST OR HY
06-019-0008-42101-1	California	Fresno	20,000	MAJ ST OR HY
06-019-0242-42101-1	California	Fresno	500	LOCAL ST OR HY
06-019-5001-42101-1	California	Clovis	16,461	THRU ST OR HY
06-025-0005-42101-1	California	Calexico	7,000	LOCAL ST OR HY
06-025-0006-42101-1	California	Calexico	10	THRU ST OR HY
06-025-1003-42101-1	California	El Centro	NR	NR
06-037-0002-42101-1	California	Azusa	600	THRU ST OR HY
06-037-0113-42101-1	California	West Los Angeles	NR	NR
06-037-1002-42101-1	California	Burbank	2,400	LOCAL ST OR HY
06-037-1103-42101-1	California	Los Angeles	9,000	THRU ST OR HY
06-037-1201-42101-1	California	Reseda	NR	NR
06-037-1701-42101-1	California	Pomona	NR	NR
06-037-2005-42101-1	California	Pasadena	18,000	THRU ST OR HY
06-037-4002-42101-1	California	Long Beach	24,000	LOCAL ST OR HY
06-037-6012-42101-1	California	Santa Clarita	4,395	LOCAL ST OR HY
06-041-0001-42101-1	California	San Rafael	15,000	MAJ ST OR HY
06-045-0008-42101-1	California	Ukiah	12,000	LOCAL ST OR HY
06-045-0009-42101-1	California	Willits	18,000	MAJ ST OR HY
06-055-0003-42101-1	California	Napa	NR	NR
06-059-2022-42101-1	California	Mission Viejo	42,400	MAJ ST OR HY
06-059-5001-42101-1	California	La Habra	NR	NR
06-065-5001-42101-1	California	Palm Springs	NR	NR
06-065-8001-42101-1	California	Rubidoux (West Riverside)	18,000	THRU ST OR HY
06-067-0002-42101-1	California	North Highlands	NR	NR
06-067-0006-42101-1	California	Sacramento	10,000	LOCAL ST OR HY
06-067-0013-42101-1	California	Sacramento	100	LOCAL ST OR HY
06-071-0001-42101-1	California	Barstow	NR	NR
06-071-0306-42101-1	California	Victorville	454	LOCAL ST OR HY
06-071-1004-42101-1	California	Upland	15,000	THRU ST OR HY
06-075-0005-42101-1	California	San Francisco	240,700	FREEWAY
06-077-1002-42101-1	California	Stockton	6,000	LOCAL ST OR HY
06-081-1001-42101-1	California	Redwood City	1,000	LOCAL ST OR HY
06-087-0003-42101-1	California	Davenport	NR	NR

Monitor Code	State Name	City Name	Traffic Count	Road Type
06-095-0004-42101-1	California	Vallejo	9,350	THRU ST OR HY
06-097-0003-42101-1	California	Santa Rosa	2,608	THRU ST OR HY
06-099-0005-42101-1	California	Modesto	NR	NR
06-099-0006-42101-1	California	Turlock	500	LOCAL ST OR HY
09-003-1003-42101-1	Connecticut	East Hartford	800	LOCAL ST OR HY
10-003-1008-42101-1	Delaware	Not in a city	NR	NR
10-003-2004-42101-1	Delaware	Wilmington	28,046	MAJ ST OR HY
15-003-0010-42101-1	Hawaii	Ewa Beach	NR	NR
18-063-0002-42101-1	Indiana	Pittsboro	500	LOCAL ST OR HY
25-025-0002-42101-1	Massachusetts	Boston	35,000	MAJ ST OR HY
29-077-0032-42101-1	Missouri	Springfield	1,000	LOCAL ST OR HY
29-189-0004-42101-1	Missouri	Sunset Hills	33,300	MAJ ST OR HY
30-013-0001-42101-1	Montana	Great Falls	26,155	MAJ ST OR HY
31-109-0018-42101-1	Nebraska	Lincoln	NR	NR
34-023-2003-42101-1	New Jersey	Perth Amboy	14,000	LOCAL ST OR HY
34-025-2001-42101-1	New Jersey	Freehold	NR	NR
34-027-0003-42101-1	New Jersey	Morristown	NR	NR
36-001-0012-42101-1	New York	Albany	12,000	MAJ ST OR HY
36-029-0005-42101-1	New York	Buffalo	26,000	ARTERIAL
36-055-1007-42101-1	New York	Rochester	NR	NR
36-067-0017-42101-1	New York	Syracuse	NR	NR
36-081-0124-42101-1	New York	New York	10,000	EXPRESSWAY
36-093-0003-42101-1	New York	Schenectady	37,000	EXPRESSWAY
36-103-0009-42101-2	New York	Holtsville	10,000	THRU ST OR HY
48-479-0016-42101-1	Texas	Laredo	16,180	MAJ ST OR HY
49-057-0006-42101-1	Utah	Ogden	38,000	ARTERIAL
51-013-0020-42101-1	Virginia	Not in a city	6,000	MAJ ST OR HY
51-059-1005-42101-1	Virginia	Annandale	24,000	MAJ ST OR HY
51-059-5001-42101-1	Virginia	McLean	36,845	MAJ ST OR HY
51-510-0009-42101-1	Virginia	Alexandria	3,974	LOCAL ST OR HY
56-039-1012-42101-1	Wyoming	Not in a city	NR	NR

"NR" denotes that the value was not reported.

Table A-8. Numbers of high LOD and trace-level monitors in each state that met completeness criteria for 2005-2007.

State	Number of high LOD monitors	Number of trace-level monitors
Alabama	2	0
Alaska	4	0
Arizona	9	0
Arkansas	0	0
California	65	0
Colorado	9	0
Connecticut	2	0
Delaware	2	0
District of Columbia	2	0
Florida	18	0
Georgia	3	0
Hawaii	1	0
Idaho	0	0
Illinois	8	0
Indiana	6	0
Iowa	0	0
Kansas	2	0
Kentucky	2	0
Louisiana	0	1
Maine	0	1
Maryland	1	0
Massachusetts	4	1
Michigan	0	0
Minnesota	7	0
Mississippi	0	0
Missouri	3	0
Montana	4	0
Nebraska	2	0
Nevada	12	0
New Hampshire	2	0
New Jersey	9	0
New Mexico	7	0
New York	9	0
North Carolina	2	1
North Dakota	0	0
Ohio	14	0
Oklahoma	4	0
Oregon	3	1
Pennsylvania	19	0
Puerto Rico	1	0

State	Number of high LOD monitors	Number of trace-level monitors
Rhode Island	1	0
South Carolina	3	1
South Dakota	0	0
Tennessee	3	0
Texas	19	2
Utah	2	0
Vermont	2	0
Virginia	9	0
Washington	2	0
West Virginia	3	0
Wisconsin	0	0
Wyoming	1	0

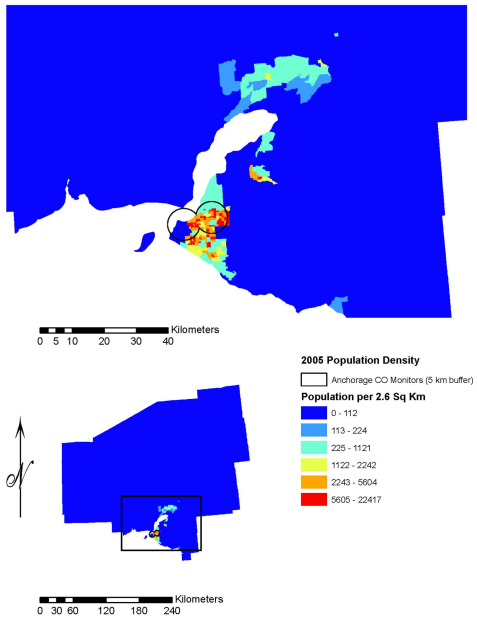


Figure A-8. Map of CO monitor locations with respect to population density in the Anchorage CBSA, total population.

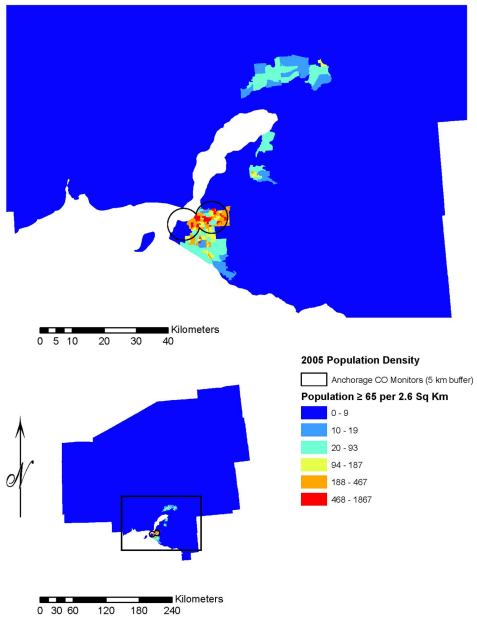


Figure A-9. Map of CO monitor locations with respect to population density in the Anchorage CBSA, ages 65 yr and older.

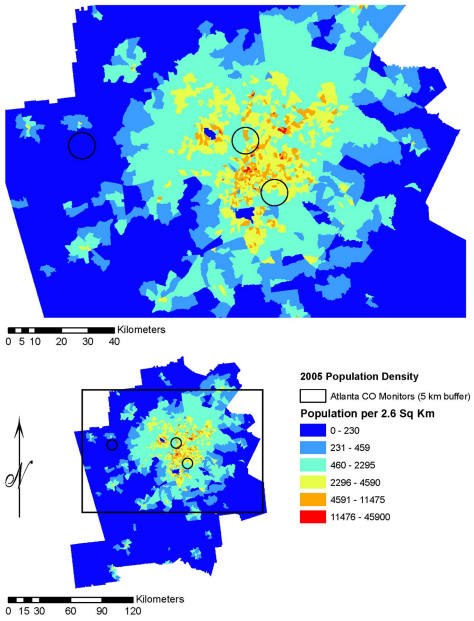


Figure A-10. Map of CO monitor locations with respect to population density in the Atlanta CSA, total population.

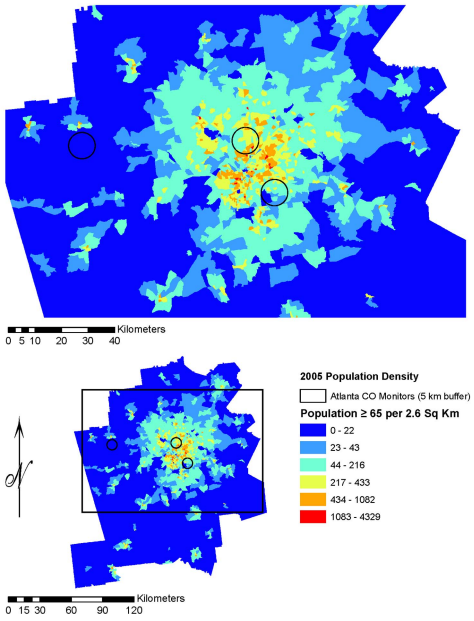


Figure A-11. Map of CO monitor locations with respect to population density in the Atlanta CSA, ages 65 yr and older.

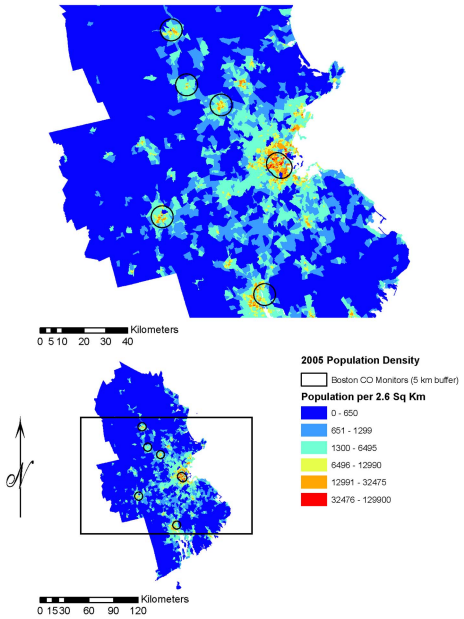


Figure A-12. Map of CO monitor locations with respect to population density in the Boston CSA, total population.

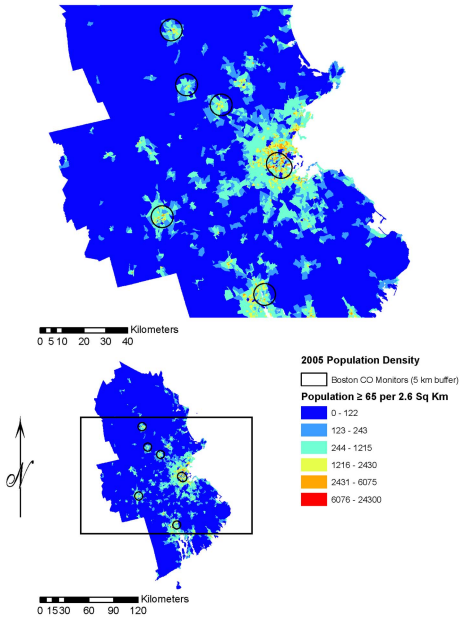


Figure A-13. Map of CO monitor locations with respect to population density in the Boston CSA, ages 65 yr and older.

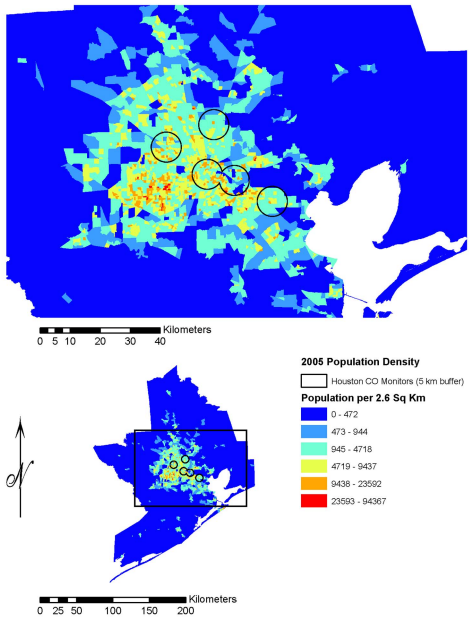


Figure A-14. Map of CO monitor locations with respect to population density in the Houston CSA, total population.

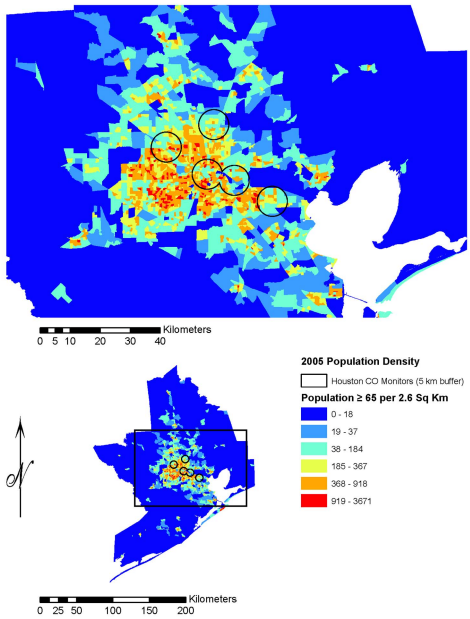


Figure A-15. Map of CO monitor locations with respect to population density in the Houston CSA, ages 65 yr and older.

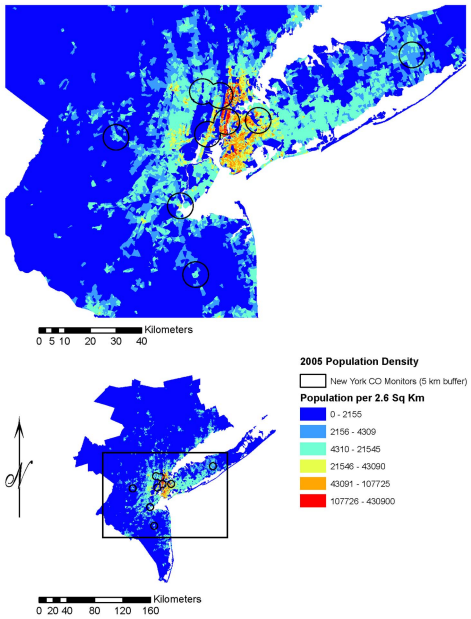


Figure A-16. Map of CO monitor locations with respect to population density in the New York City CSA, total population.

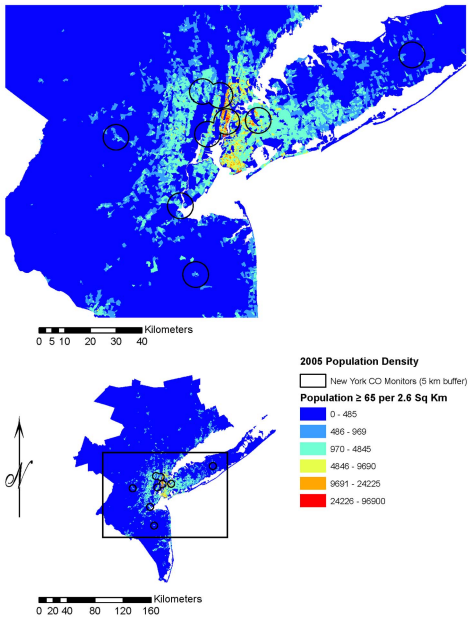


Figure A-17. Map of CO monitor locations with respect to population density in the New York City CSA, ages 65 yr and older.

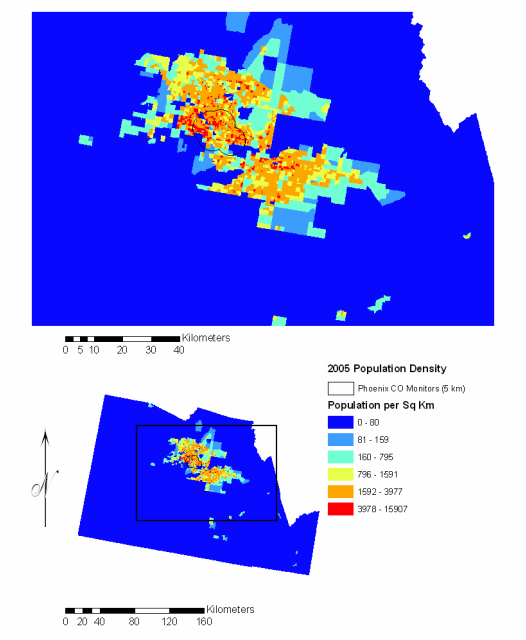


Figure A-18. Map of CO monitor locations with respect to population density in the Phoenix CSA, total population.

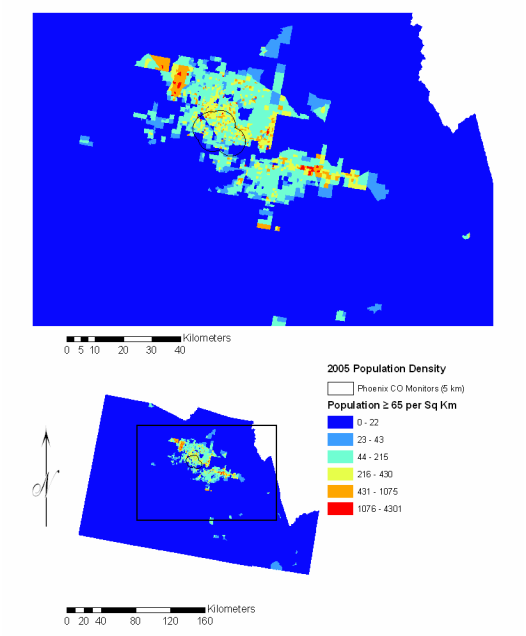


Figure A-19. Map of CO monitor locations with respect to population density in the Phoenix CSA, ages 65 yr and older.

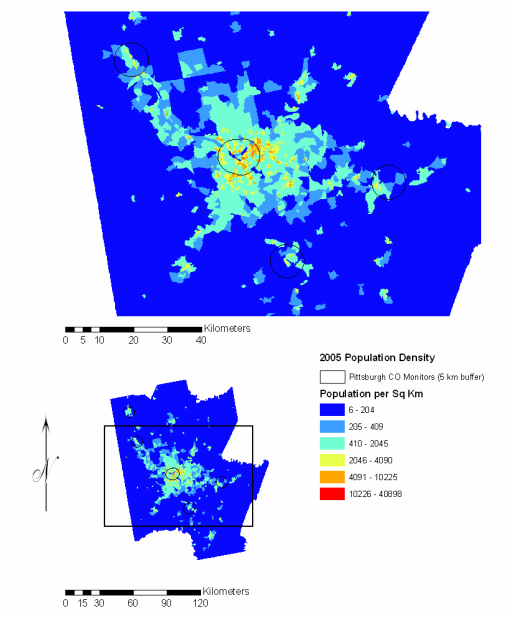


Figure A-20. Map of CO monitor locations with respect to population density in the Pittsburgh CSA, total population.

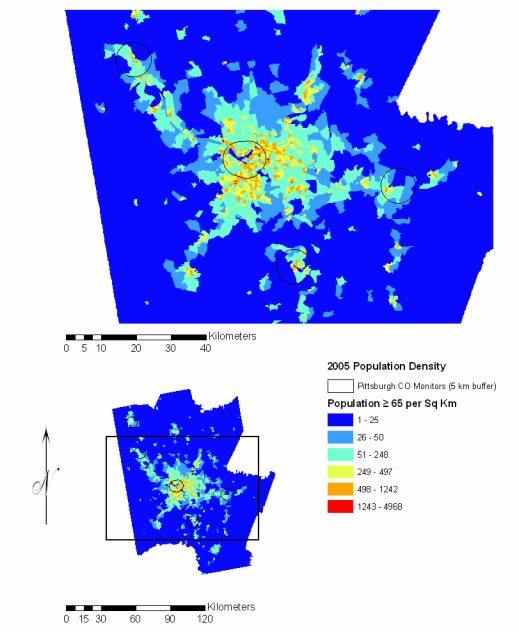


Figure A-21. Map of CO monitor locations with respect to population density in the Pittsburgh CSA, ages 65 yr and older.

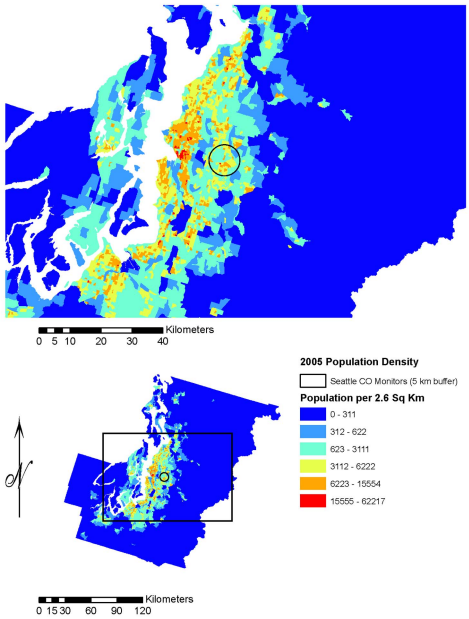


Figure A-22. Map of CO monitor locations with respect to population density in the Seattle CSA, total population.

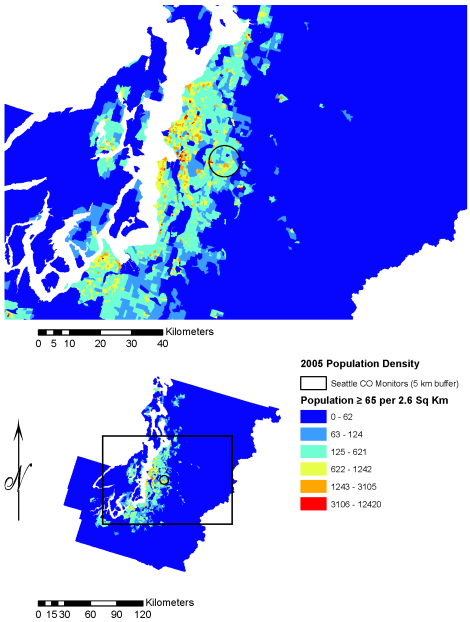


Figure A-23. Map of CO monitor locations with respect to population density in the Seattle CSA, ages 65 yr and older.

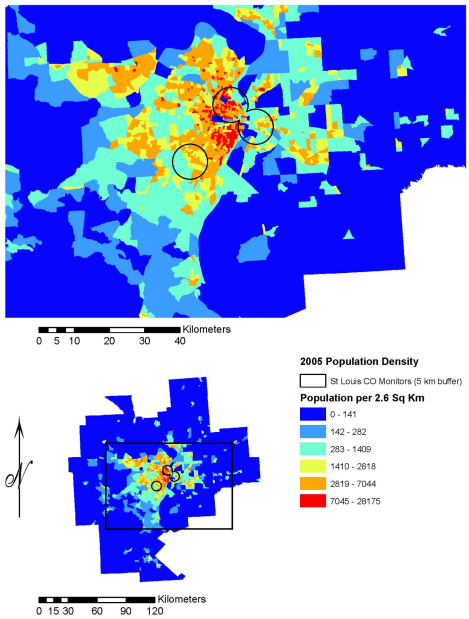


Figure A-24. Map of CO monitor locations with respect to population density in the St. Louis CSA, total population.

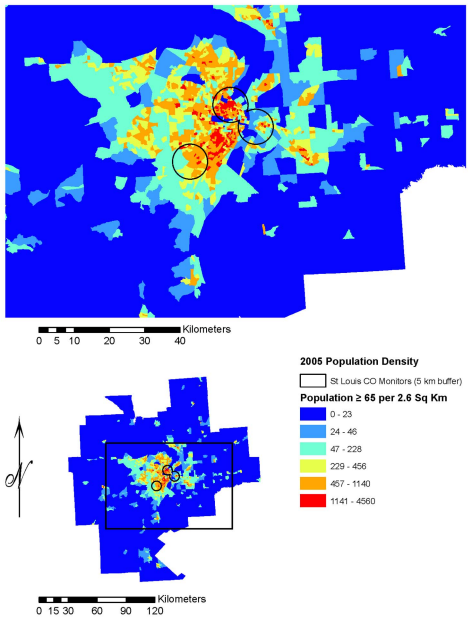


Figure A-25. Map of CO monitor locations with respect to population density in the St. Louis CSA, ages 65 yr and older.

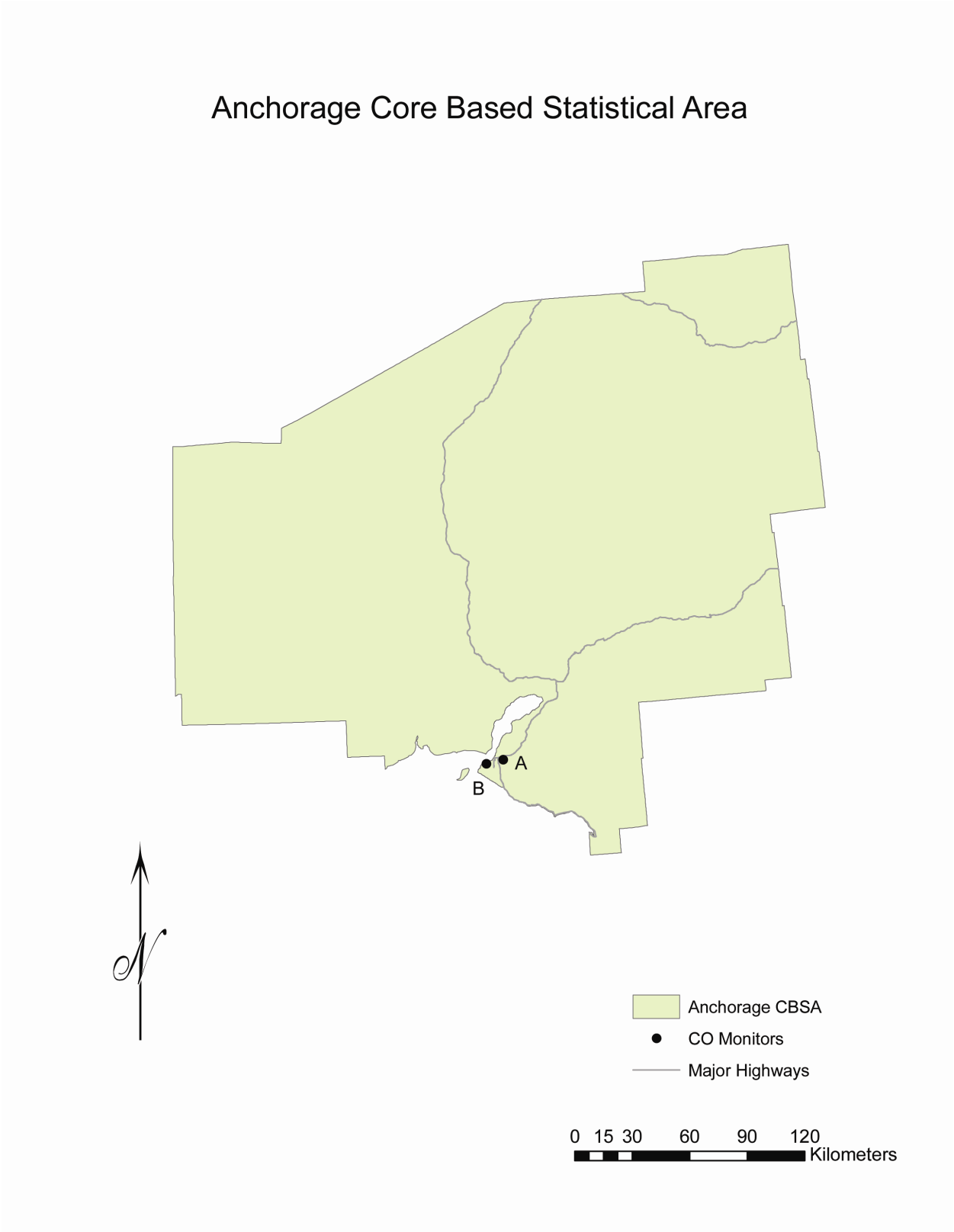


Figure A-26. Map of CO monitor locations with AQS Site IDs for Anchorage, AK.

Table A-9. Table of inter-sampler comparison statistics, including Pearson r, P90 (ppm), COD, and d (km), as defined in the text, for each pair of hourly CO monitors reporting to AQS in Anchorage, AK.

		Neighborhood	
		A	**B**
Neighborhood	**A**	1.00	0.73
		0.0	1.1
		0.00	0.32
		0	9.0
	B	**Legend**	1.00
		r	0.0
		P90	0.00
		COD	0
		d	

	A	B
Site ID	02-020-0018	02-020-0048
Mean	1.04	1.10
SD	0.94	1.04
Obs	12969	12703

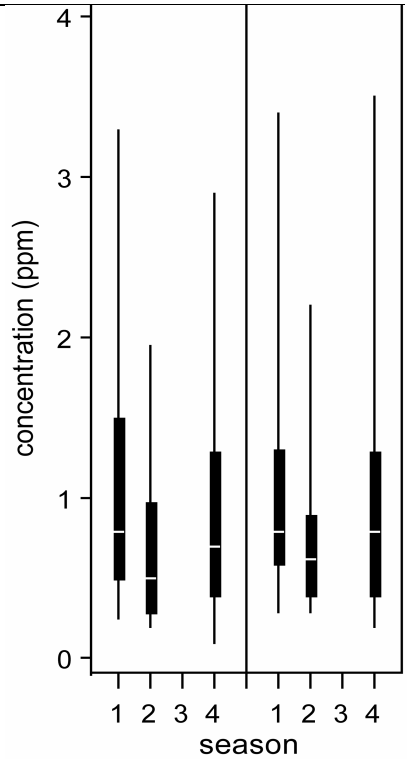


Figure A-27. Box plots illustrating the seasonal distribution of hourly CO concentrations in Anchorage, AK. Note: 1 = winter, 2 = spring, 3 = summer, and 4 = fall on the x-axis.

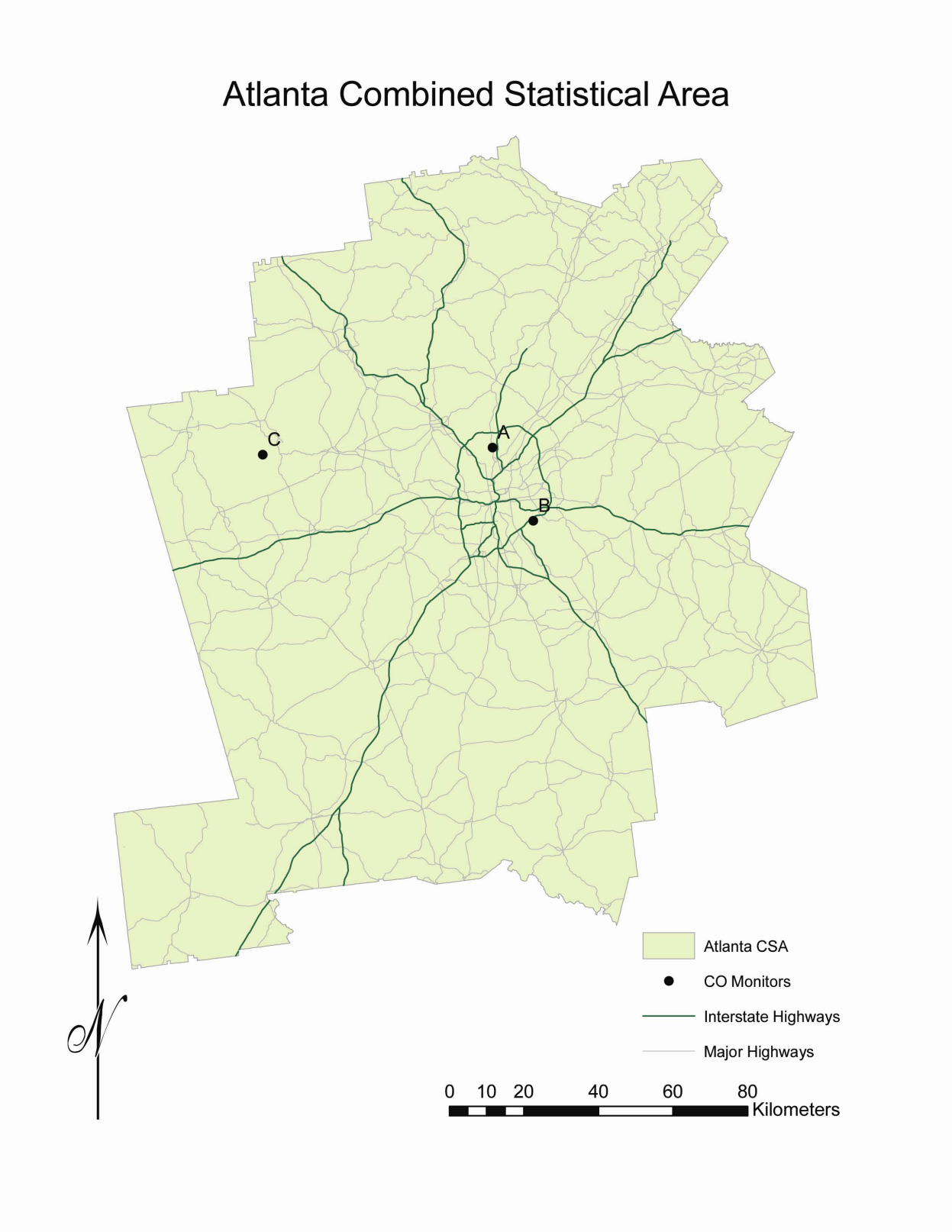


Figure A-28. Map of CO monitor locations with AQS Site IDs for Atlanta, GA.

Table A-10. Table of inter-sampler comparison statistics, including Pearson r, P90 (ppm), COD, and d (km), as defined in the text, for each pair of hourly CO monitors reporting to AQS in Atlanta, GA.

		Micro	Urban	
		A	B	C
Micro	A	1.00	0.60	0.10
		0.0	0.5	0.7
		0.00	0.27	0.38
		0	22.5	61.7
Urban	B		1.00	0.12
			0.0	0.7
			0.00	0.37
			0	74.7
	C	Legend		1.00
		r		0.0
		P90		0.00
		COD		0
		d		

1

	A	B	C
Site ID	13-121-0099	13-089-0002	13-223-0003
Mean	0.58	0.53	0.30
SD	0.30	0.35	0.13
Obs	25440	25531	25712

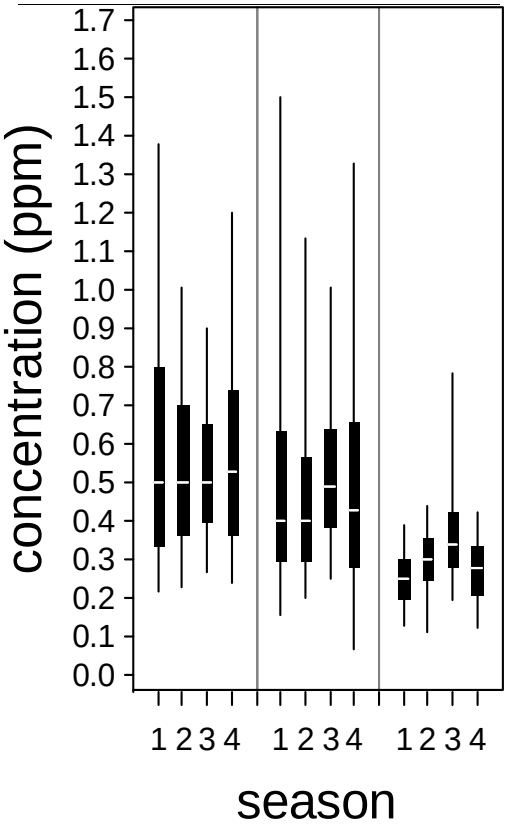


Figure A-29. Box plots illustrating the seasonal distribution of hourly CO concentrations in Atlanta, GA. Note: 1 = winter, 2 = spring, 3 = summer, and 4 = fall on the x-axis.

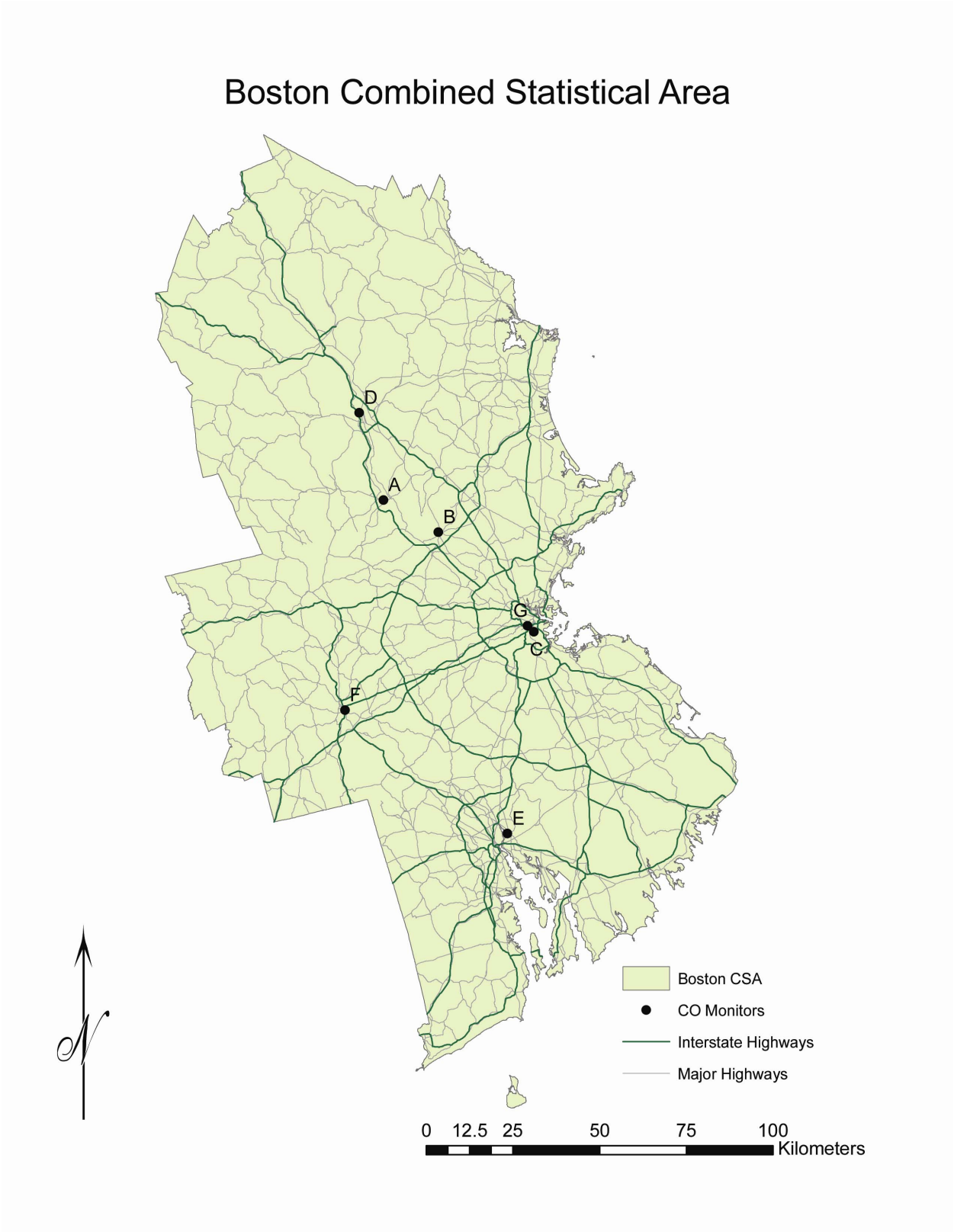


Figure A-30. Map of CO monitor locations with AQS Site IDs for Boston, MA.

Table A-11. Table of inter-sampler comparison statistics, including Pearson r, P90 (ppm), COD, and d (km), as defined in the text, for each pair of hourly CO monitors reporting to AQS in Boston, MA.

		Micro	Neighborhood				Urban	Null
		A	B	C	D	E	F	G
Micro	A	1.00	0.50	0.38	0.49	0.43	0.46	0.35
		0.0	0.6	0.6	0.5	0.6	0.5	0.7
		0.00	0.44	0.46	0.30	0.39	0.25	0.60
		0	18.3	57.5	26.1	102.6	61.5	55.1
Neighborhood	B		1.00	0.50	0.41	0.40	0.49	0.35
			0.0	0.4	0.4	0.4	0.5	0.4
			0.00	0.48	0.41	0.40	0.42	0.58
			0	39.7	41.3	89.1	57.9	37.2
	C			1.00	0.26	0.36	0.37	0.52
				0.0	0.5	0.4	0.5	0.4
				0.00	0.45	0.47	0.45	0.56
				0	80.7	58.7	58.9	2.5
	D				1.00	0.29	0.40	0.27
					0.0	0.4	0.4	0.5
					0.00	0.37	0.28	0.58
			Legend		0	128.6	85.8	78.2
	E		r			1.00	0.34	0.34
			P90			0.0	0.5	0.4
			COD			0.00	0.39	0.55
			d			0	58.9	60.2
Urban	F						1.00	0.34
							0.0	0.6
							0.00	0.59
							0	58.0
Null	G							1.00
								0.0
								0.00
								0

	A	B	C	D	E	F	G
Site ID	33-011-1009	25-017-0007	25-025-0042	33-011-0020	44-007-1010	25-027-0023	25-025-0002
Mean	0.60	0.33	0.36	0.45	0.34	0.53	0.26
SD	0.37	0.22	0.26	0.27	0.22	0.23	0.24
Obs	25869	24362	24260	25197	23707	24446	24134

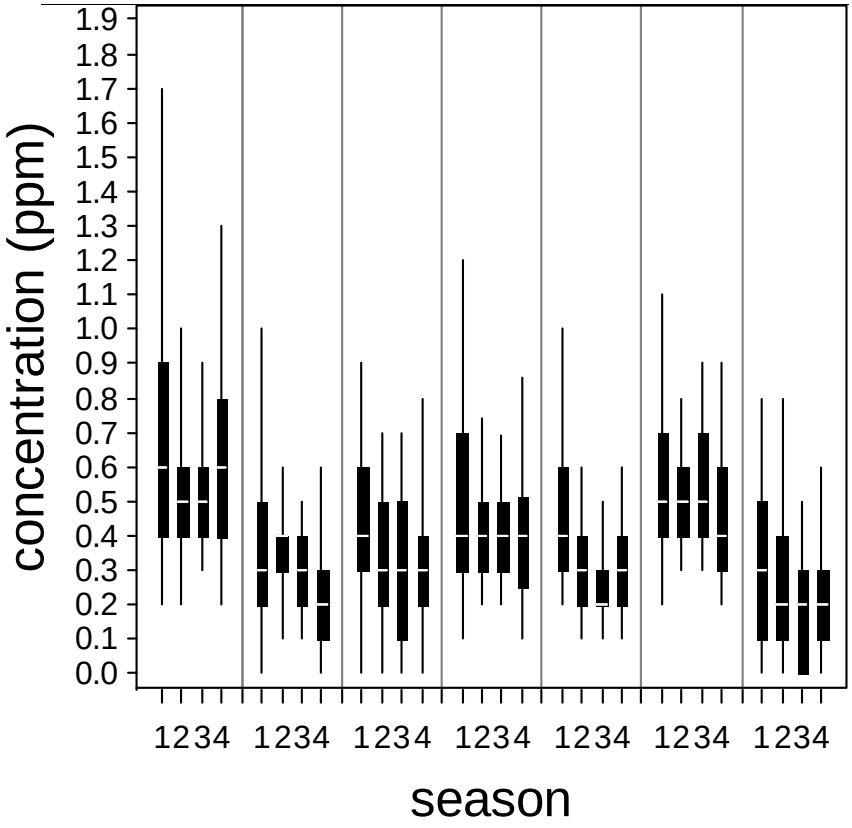


Figure A-31. Box plots illustrating the seasonal distribution of hourly CO concentrations in Boston, MA. Note: 1 = winter, 2 = spring, 3 = summer, and 4 = fall on the x-axis.

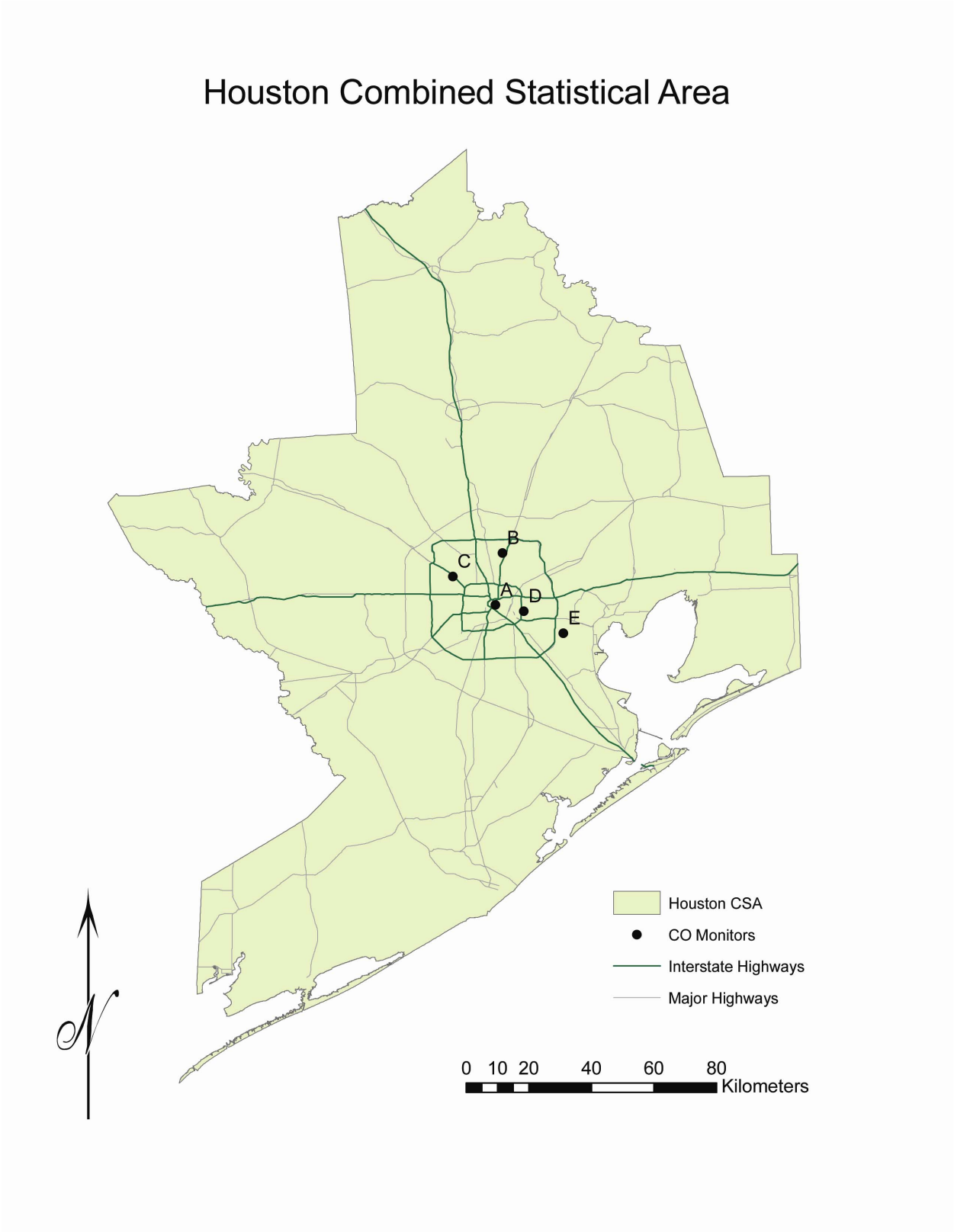


Figure A-32. Map of CO monitor locations with AQS Site IDs for Houston, TX.

Table A-12. Table of inter-sampler comparison statistics, including Pearson r, P90 (ppm), COD, and d (km), as defined in the text, for each pair of hourly CO monitors reporting to AQS in Houston, TX.

		Micro	Neighborhood			
		A	**B**	**C**	**D**	**E**
		1.00	0.45	0.56	0.53	0.43
Micro	**A**	0.0	0.4	0.4	0.5	0.4
		0.00	0.47	0.47	0.74	0.47
		0.0	16.7	16.3	9.3	23.5
			1.00	0.72	0.56	0.68
Neighborhood	**B**		0.0	0.3	0.5	0.3
			0.00	0.29	0.73	0.24
			0.0	17.5	19.8	32.2
				1.00	0.65	0.63
	C			0.0	0.5	0.4
				0.00	0.73	0.29
				0.0	25.2	39.7
					1.00	0.57
	D				0.0	0.4
					0.00	0.72
		Legend			0.0	14.5
		r				1.00
	E	**P90**				0.0
		COD				0.00
		d				0.0

1

	A	B	C	D	E
Site ID	48-201-0075	48-201-0024	48-201-0047	48-201-1035	48-201-1039
Mean	0.35	0.42	0.39	0.14	0.33
SD	0.26	0.27	0.33	0.22	0.16
Obs	24922	23997	25241	25285	24480

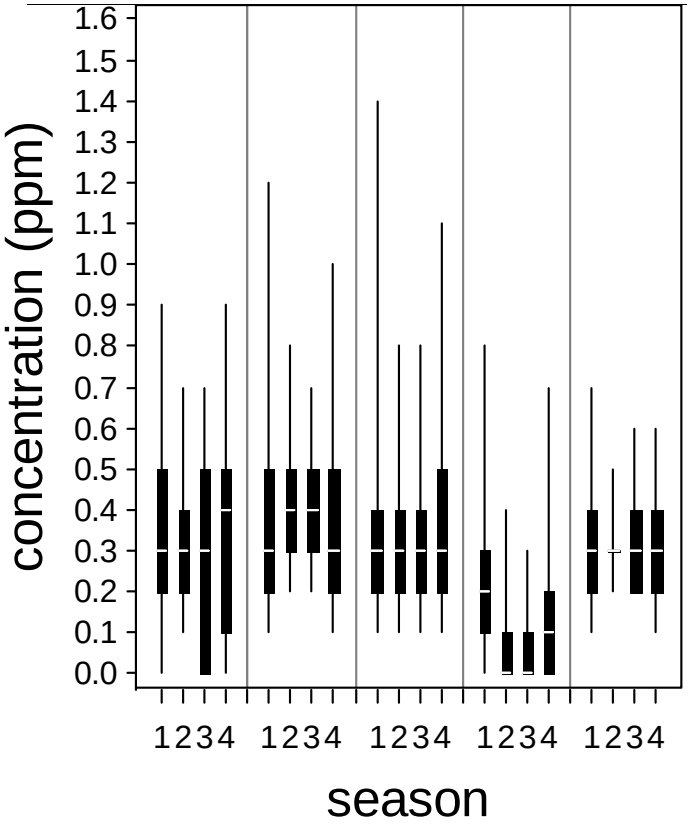


Figure A-33. Box plots illustrating the seasonal distribution of hourly CO concentrations in Houston, TX. Note: 1 = winter, 2 = spring, 3 = summer, and 4 = fall on the x-axis.

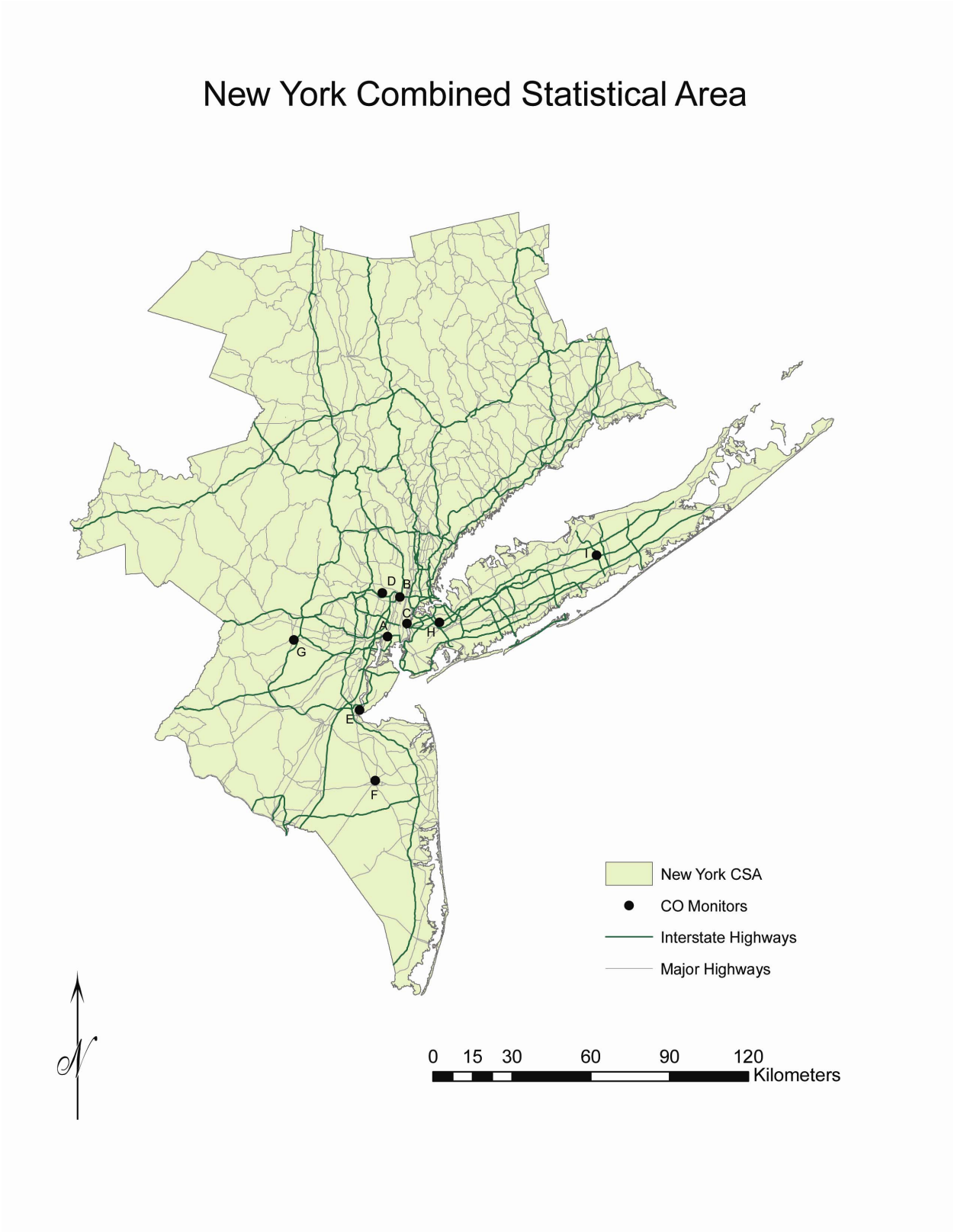


Figure A-34. Map of CO monitor locations with AQS Site IDs for New York City, NY.

Table A-13. Table of inter-sampler comparison statistics, including Pearson r, P90 (ppm), COD, and d (km), as defined in the text, for each pair of hourly CO monitors reporting to AQS in New York City, NY.

		Micro	Middle		Neighborhood	Null				
		A	B	C	D	E	F	G	H	I
Micro	A	1.00	0.65	0.52	0.64	0.54	0.32	0.48	0.43	0.31
		0.0	0.7	0.7	0.8	0.9	0.9	0.9	0.9	1.3
		0.00	0.28	0.24	0.29	0.35	0.34	0.34	0.35	0.81
		0	15.9	8.9	16.8	29.9	55.0	35.7	20.5	85.5
Middle	B		1.00	0.56	0.58	0.55	0.40	0.56	0.41	0.30
			0.0	0.4	0.4	0.4	0.4	0.4	0.5	0.8
			0.00	0.23	0.22	0.25	0.25	0.24	0.28	0.75
			0	10.5	7.0	45.8	70.6	43.7	17.8	76.5
	C			1.00	0.54	0.41	0.33	0.41	0.46	0.29
				0.0	0.4	0.4	0.4	0.4	0.4	0.7
				0.00	0.23	0.28	0.25	0.26	0.26	0.77
				0	15.0	37.5	61.0	43.6	12.3	76.8
Neighborhood	D				1.00	0.55	0.35	0.54	0.59	0.49
					0.0	0.4	0.5	0.4	0.4	0.7
					0.00	0.23	0.26	0.23	0.23	0.74
					0	45.4	71.5	38.1	24.5	82.9
Null	E					1.00	0.50	0.57	0.46	0.33
						0.0	0.4	0.4	0.4	0.7
						0.00	0.24	0.23	0.27	0.72
						0	27.5	36.7	45.1	107.8
	F						1.00	0.47	0.33	0.32
							0.0	0.4	0.4	0.6
							0.00	0.23	0.27	0.73
							0	61.9	65.0	120.3
	G		Legend					1.00	0.34	0.31
			r					0.0	0.4	0.7
			P90					0.00	0.27	0.72
			COD					0	55.8	119.7
	H		d						1.00	0.43
									0.0	0.6
									0.00	0.73
									0	65.1
	I									1.00
										0.0
										0.00
										0

	A	B	C	D	E	F	G	H	I
Site ID	34-017-1002	34-003-0004	36-061-0056	34-003-5001	34-023-2003	34-025-2001	34-027-0003	36-081-0124	36-103-0009
Mean	0.85	0.55	0.62	0.52	0.48	0.50	0.49	0.47	0.12
SD	0.43	0.27	0.21	0.30	0.27	0.24	0.25	0.23	0.17
Obs	25646	23113	25547	25150	25028	25727	25691	25022	25749

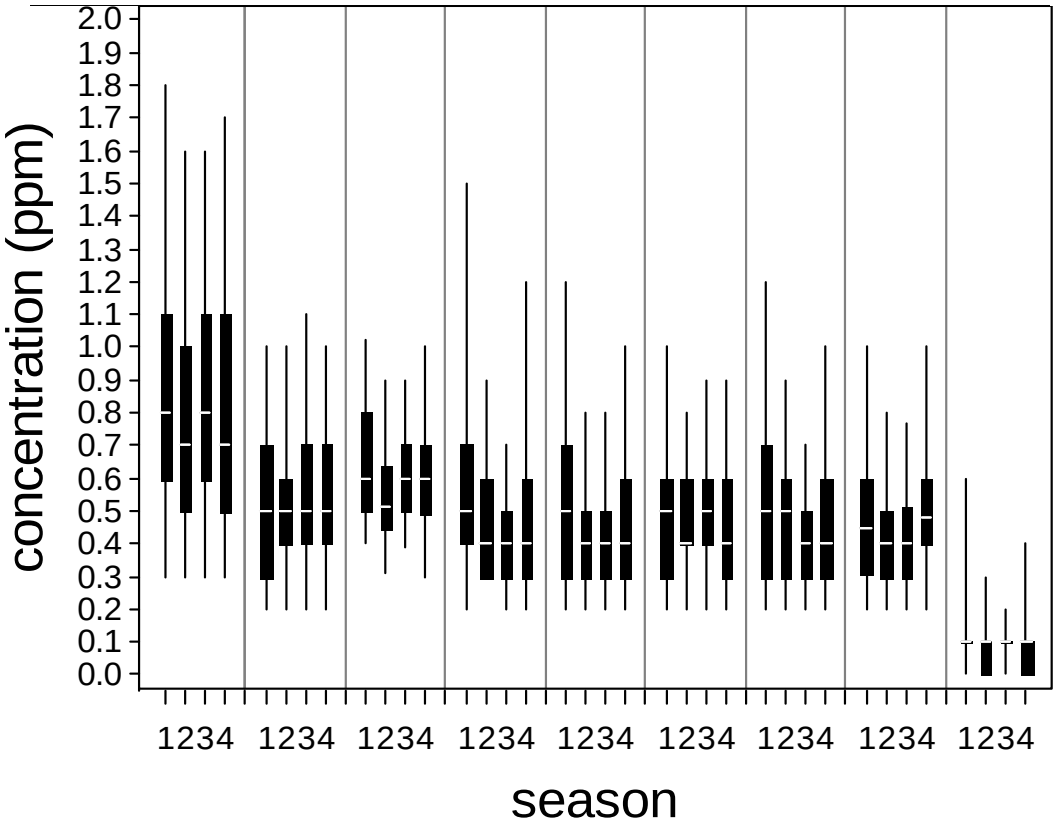


Figure A-35. Box plots illustrating the seasonal distribution of hourly CO concentrations in New York City, NY. Note: 1 = winter, 2 = spring, 3 = summer, and 4 = fall on the x-axis.

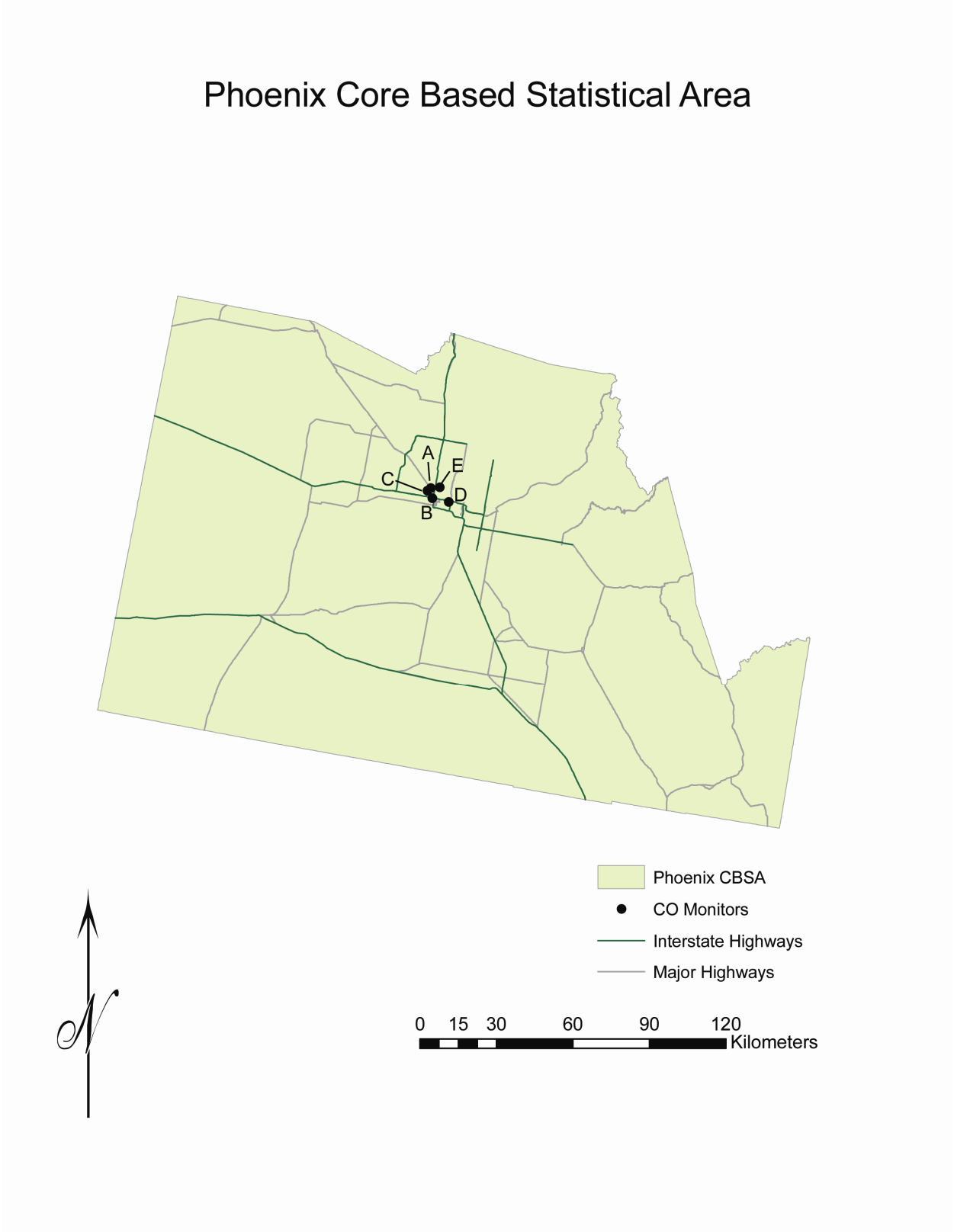


Figure A-36. Map of CO monitor locations with AQS Site IDs for Phoenix, AZ.

Table A-14. Table of inter-sampler comparison statistics, including Pearson r, P90 (ppm), COD, and d (km), as defined in the text, for each pair of hourly CO monitors reporting to AQS in Phoenix, AZ.

		Micro	Middle	Neighborhood		Null
		A	B	C	D	E
Micro	A	1.00	0.86	0.89	0.80	0.84
		0.0	0.8	0.7	1.1	0.9
		0.00	0.39	0.37	0.43	0.37
		0.0	3.9	1.6	8.9	3.5
Middle	B		1.00	0.88	0.81	0.83
			0.0	0.6	0.7	0.6
			0.00	0.34	0.41	0.33
			0.0	3.4	6.6	5.2
Neighborhood	C			1.00	0.81	0.89
				0.0	0.9	0.7
				0.00	0.38	0.24
		Legend		0.0	9.4	4.9
	D	r			1.00	0.85
		P90			0.0	0.6
		COD			0.00	0.36
		d			0.0	6.8
Null	E					1.00
						0.0
						0.00
						0.0

	A	B	C	D	E
Site ID	04-013-0016	04-013-3010	04-013-0019	04-013-3002	04-013-9997
Mean	0.93	0.76	0.84	0.58	0.79
SD	0.95	0.72	0.88	0.64	0.64
Obs	25382	25414	25589	25657	25435

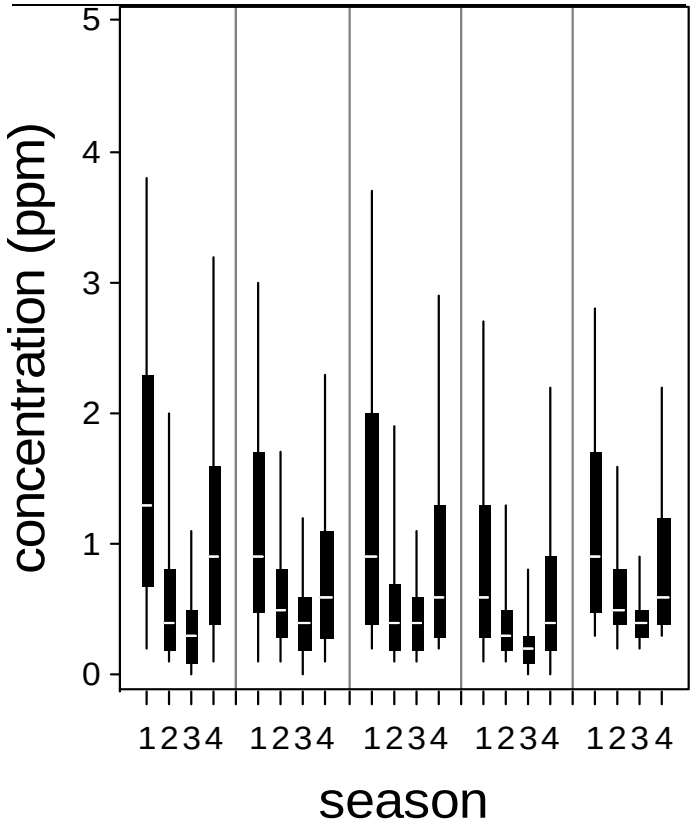


Figure A-37. Box plots illustrating the seasonal distribution of hourly CO concentrations in Phoenix, AZ. Note: 1 = winter, 2 = spring, 3 = summer, and 4 = fall on the x-axis.

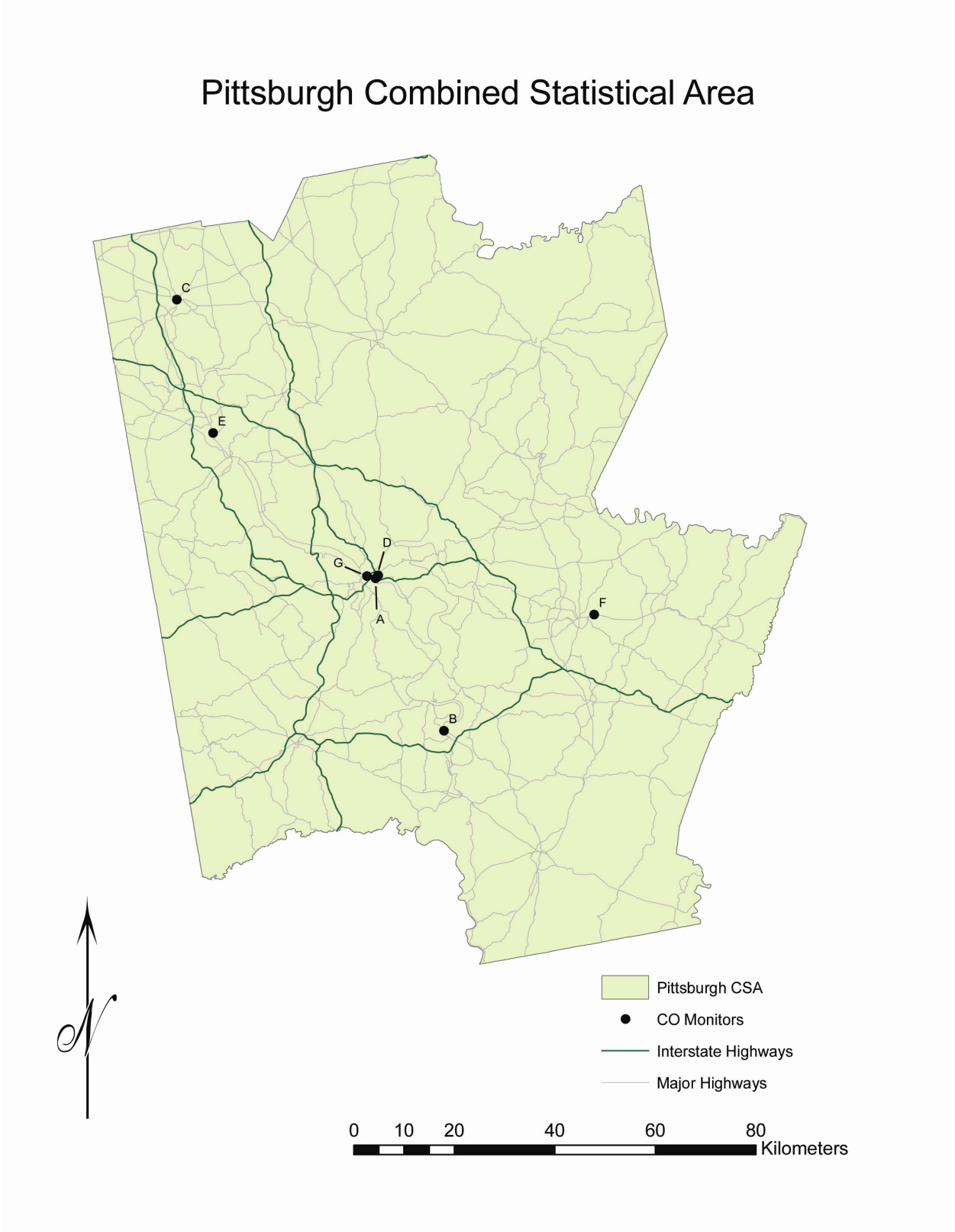


Figure A-38. Map of CO monitor locations with AQS Site IDs for Pittsburgh, PA.

Table A-15. Table of inter-sampler comparison statistics, including Pearson r, P90 (ppm), COD, and d (km), as defined in the text, for each pair of hourly CO monitors reporting to AQS in Pittsburgh, PA.

		Middle	Neighborhood			Urban		
		A	B	C	D	E	F	G
Middle	A	1.00	0.25	0.39	0.73	0.20	0.30	0.43
		0.0	0.7	0.6	0.4	0.7	0.8	0.6
		0.00	0.65	0.51	0.39	0.56	0.88	0.68
		0	33.3	68.2	0.7	43.4	44.1	1.8
Neighborhood	B		1.00	0.26	0.29	0.09	0.09	0.42
			0.0	0.5	0.5	0.6	0.5	0.5
			0.00	0.68	0.62	0.69	0.90	0.73
			0	101.0	33.6	75.0	37.8	34.4
	C			1.00	0.42	0.16	0.21	0.11
				0.0	0.4	0.6	0.6	0.6
				0.00	0.51	0.57	0.87	0.72
				0	68.0	27.5	104.1	66.8
	D				1.00	0.30	0.35	0.52
					0.0	0.5	0.5	0.5
					0.00	0.54	0.86	0.69
					0	43.4	43.7	2.2
Urban	E					1.00	0.02	0.05
						0.0	0.7	0.7
						0.00	0.87	0.74
						0	84.1	41.9
	F						1.00	0.18
							0.0	0.7
							0.00	0.88
			Legend				0	45.8
	G		r					1.00
			P90					0.0
			COD					0.00
			d					0

	A	B	C	D	E	F	G
SiteID	42-003-0038	42-125-0005	42-073-0015	42-003-0031	42-007-0014	42-129-0008	42-003-0010
Mean	0.47	0.21	0.32	0.32	0.28	0.07	0.28
SD	0.33	0.23	0.26	0.26	0.27	0.15	0.32
Obs	25818	25319	25745	25936	25500	25785	25655

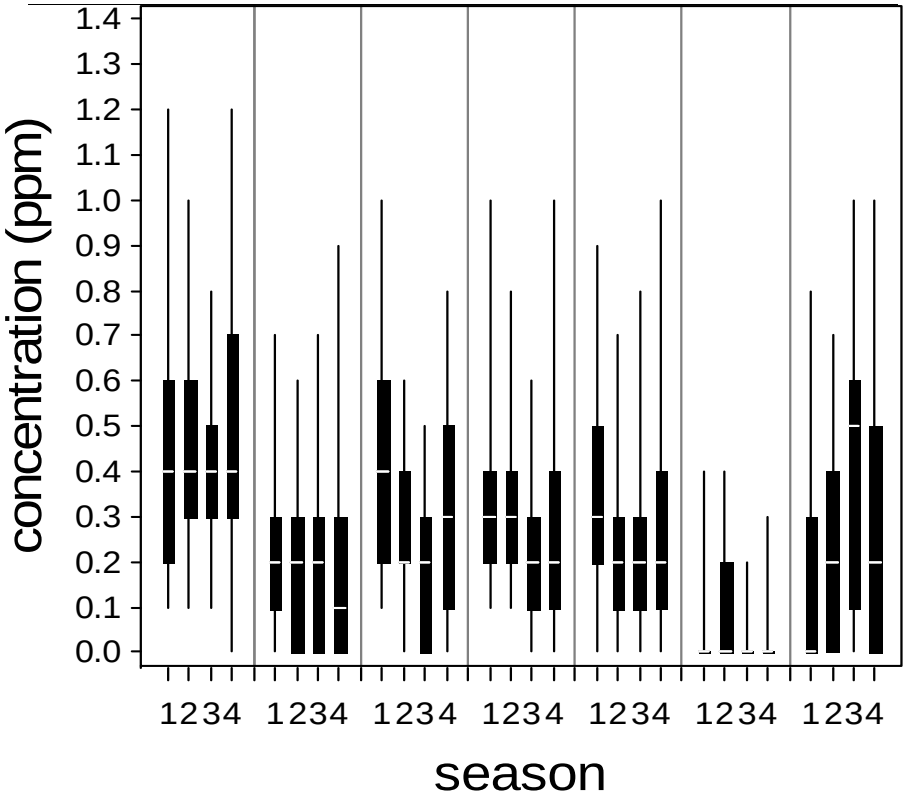


Figure A-39. Box plots illustrating the seasonal distribution of hourly CO concentrations in Pittsburgh, PA. Note: 1 = winter, 2 = spring, 3 = summer, and 4 = fall on the x-axis.

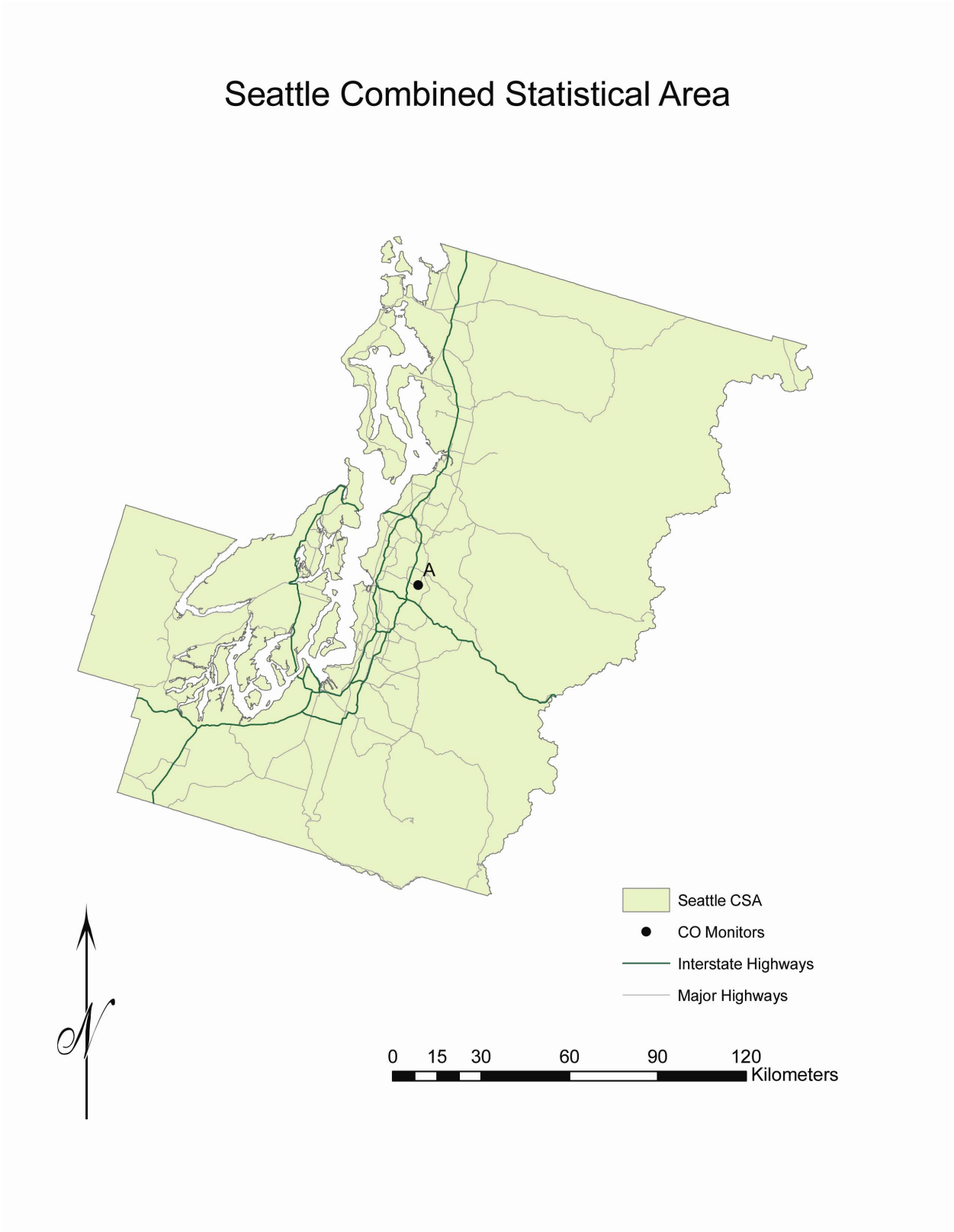


Figure A-40. Map of CO monitor locations with AQS Site IDs for Seattle, WA.

	A
Site ID	53−033−0019
Mean	0.75
SD	0.49
Obs	25818

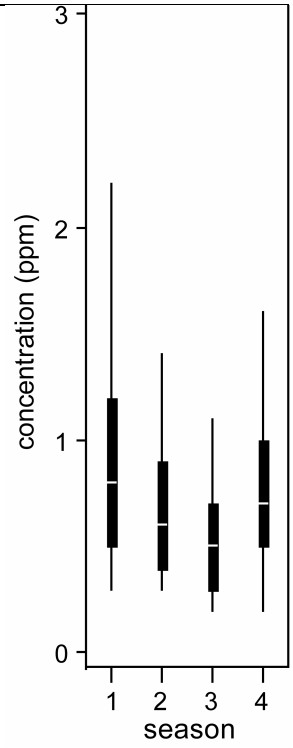


Figure A-41. Box plots illustrating the seasonal distribution of hourly CO concentrations in Seattle, WA. Note: 1 = winter, 2 = spring, 3 = summer, and 4 = fall on the x-axis.

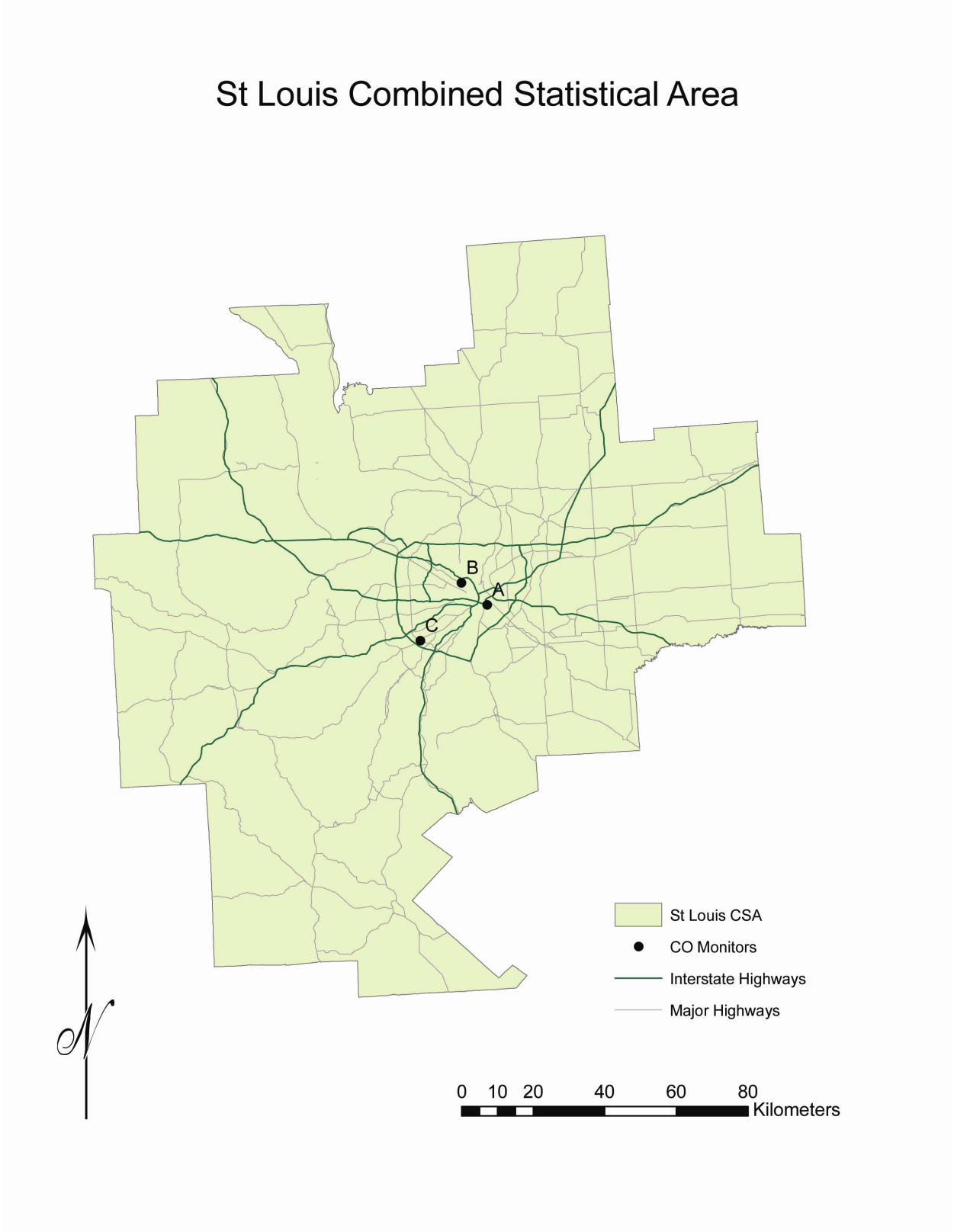


Figure A-42. Map of CO monitor locations with AQS Site IDs for St. Louis, MO.

Table A-16. Table of inter-sampler comparison statistics, including Pearson r, P90 (ppm), COD, and d (km), as defined in the text, for each pair of hourly CO monitors reporting to AQS in St. Louis, MO.

		Neighborhood		Null
		A	B	C
Neighborhood	A	1.00	0.60	0.19
		0.0	0.3	0.5
		0.00	0.24	0.40
		0	9.5	21.2
	B		1.00	0.19
			0.0	0.5
			0.00	0.42
			0	19.8
Null	C	Legend		1.00
		r		0.0
		P90		0.00
		COD		0
		d		

	A	B	C
Site ID	17-163-0010	29-510-0086	29-189-0004
Mean	0.44	0.42	0.43
SD	0.25	0.29	0.25
Obs	25325	25938	25879

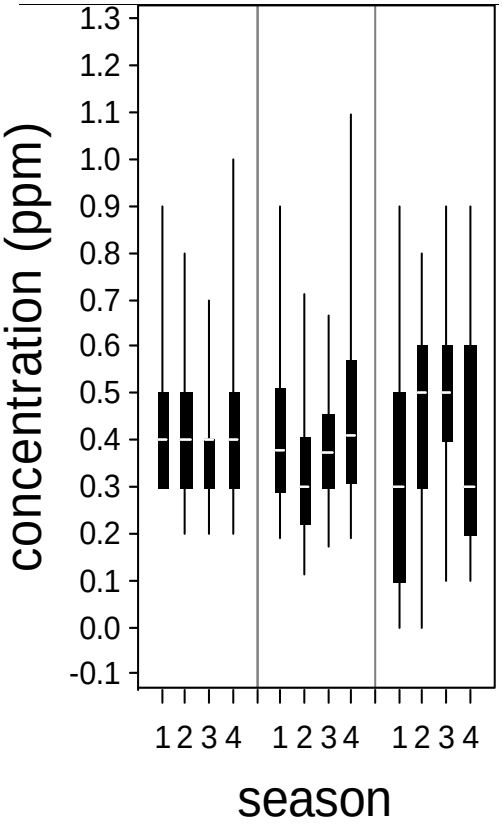


Figure A-43. Box plots illustrating the seasonal distribution of hourly CO concentrations in St. Louis, MO. Note: 1 = winter, 2 = spring, 3 = summer, and 4 = fall on the x-axis.

Table A-17. Comparison of distributional data at different monitoring scales for hourly, 1-h daily max, 24-h avg, and 8-h daily max data for Atlanta, GA.

				PERCENTILES									
Time Scale	**N**	**Mean**	**Min**	**1**	**5**	**10**	**25**	**50**	**75**	**90**	**95**	**99**	**max**
ALL HOURLY													
Microscale	25,440	0.6	0.0	0.2	0.2	0.3	0.4	0.4	0.5	0.7	0.7	1.0	1.2
Urban Scale	51,243	0.4	0.0	0.0	0.1	0.2	0.3	0.3	0.3	0.4	0.5	0.7	1.0
1-H DAILY MAX													
Microscale	1,075	1.0	0.2	0.3	0.4	0.6	0.7	0.8	1.0	1.2	1.2	1.6	1.9
Urban Scale	2,154	0.7	0.0	0.2	0.2	0.3	0.3	0.4	0.5	0.8	0.9	1.3	1.5
1-H DAILY AVG													
Microscale	1,075	0.6	0.2	0.2	0.3	0.3	0.4	0.5	0.5	0.6	0.7	0.8	1.0
Urban Scale	2,154	0.4	0.0	0.1	0.2	0.2	0.3	0.3	0.4	0.5	0.5	0.7	0.9
8-H DAILY MAX													
Microscale	1,075	0.8	0.3	0.3	0.3	0.4	0.5	0.6	0.7	0.9	0.9	1.2	1.3
Urban Scale	2,154	0.5	0.0	0.1	0.2	0.3	0.3	0.3	0.4	0.6	0.7	1.0	1.3

Table A-18. Comparison of distributional data at different monitoring scales for hourly, 1-h daily max, 24-h avg, and 8-h daily max data for Boston, MA.

				PERCENTILES									
Time Scale	**N**	**Mean**	**Min**	**1**	**5**	**10**	**25**	**50**	**75**	**90**	**95**	**99**	**max**
ALL HOURLY													
Microscale	25,869	0.6	0.0	0.1	0.2	0.3	0.4	0.4	0.5	0.7	0.7	1.0	1.2
Neighborhood Scale	97,526	0.4	0.0	0.0	0.0	0.1	0.2	0.3	0.3	0.4	0.5	0.6	0.8
Urban Scale	24,446	0.5	0.0	0.1	0.3	0.3	0.4	0.4	0.5	0.6	0.6	0.8	0.9
1-H DAILY MAX													
Microscale	1,080	1.2	0.2	0.4	0.5	0.6	0.7	0.8	0.9	1.2	1.4	2.0	2.5
Neighborhood Scale	4,212	0.6	0.0	0.1	0.2	0.3	0.4	0.4	0.5	0.7	0.7	1.1	1.4
Urban Scale	1,086	0.8	0.0	0.3	0.4	0.5	0.6	0.6	0.8	0.9	1.0	1.2	1.4
1-H DAILY AVG													
Microscale	1,080	0.6	0.1	0.2	0.3	0.3	0.4	0.5	0.6	0.7	0.7	0.9	1.1
Neighborhood Scale	4,212	0.4	0.0	0.0	0.1	0.1	0.2	0.3	0.4	0.4	0.5	0.6	0.7
Urban Scale	1,086	0.5	0.0	0.1	0.3	0.4	0.4	0.5	0.5	0.6	0.6	0.7	0.8
8-H DAILY MAX													
Microscale	1,080	0.8	0.3	0.3	0.3	0.4	0.6	0.6	0.7	0.9	1.0	1.4	1.7
Neighborhood Scale	4,212	0.5	0.3	0.3	0.3	0.3	0.3	0.3	0.4	0.6	0.6	0.8	1.0
Urban Scale	1,086	0.7	0.3	0.3	0.3	0.3	0.5	0.5	0.6	0.8	0.8	1.0	1.1

Table A-19. Comparison of distributional data at different monitoring scales for hourly, 1-h daily max, 24-h avg, and 8-h daily max data for Denver, CO.

				PERCENTILES									
Time Scale	**N**	**Mean**	**Min**	**1**	**5**	**10**	**25**	**50**	**75**	**90**	**95**	**99**	**max**
ALL HOURLY													
Microscale	77,070	0.5	0.0	0.0	0.1	0.1	0.3	0.3	0.4	0.6	0.7	1.0	1.3
Neighborhood Scale	51,968	0.5	0.0	0.0	0.1	0.2	0.3	0.3	0.4	0.6	0.6	1.0	1.3
1-H DAILY MAX													
Microscale	3,190	1.2	0.1	0.3	0.4	0.5	0.7	0.8	1.0	1.4	1.5	2.2	2.7
Neighborhood Scale	2,173	1.1	0.1	0.2	0.3	0.4	0.6	0.6	0.9	1.3	1.5	2.1	2.6
1-H DAILY AVG													
Microscale	3,190	0.5	0.0	0.1	0.2	0.2	0.3	0.4	0.5	0.6	0.6	0.9	1.0
Neighborhood Scale	2,173	0.5	0.0	0.1	0.2	0.3	0.3	0.4	0.5	0.6	0.6	0.9	1.1
8-H DAILY MAX													
Microscale	3,190	0.8	0.3	0.3	0.3	0.4	0.5	0.5	0.7	0.9	1.0	1.4	1.8
Neighborhood Scale	2,173	0.8	0.3	0.3	0.3	0.3	0.4	0.5	0.7	0.9	1.0	1.5	1.8

Table A-20. Comparison of distributional data at different monitoring scales for hourly, 1-h daily max, 24-h avg, and 8-h daily max data for Houston, TX.

				PERCENTILES									
Time Scale	**N**	**Mean**	**Min**	**1**	**5**	**10**	**25**	**50**	**75**	**90**	**95**	**99**	**max**
ALL HOURLY													
Microscale	24,922	0.3	0.0	0.0	0.0	0.0	0.2	0.2	0.3	0.4	0.5	0.6	0.8
Neighborhood Scale	99,003	0.3	0.0	0.0	0.0	0.0	0.2	0.2	0.3	0.4	0.4	0.6	0.8
1-H DAILY MAX													
Microscale	1,043	0.7	0.0	0.0	0.2	0.3	0.4	0.5	0.6	0.8	0.9	1.2	1.4
Neighborhood Scale	4,145	0.7	0.0	0.0	0.1	0.2	0.4	0.4	0.5	0.8	0.8	1.3	1.7
1-H DAILY AVG													
Microscale	1,043	0.3	0.0	0.0	0.0	0.1	0.2	0.3	0.4	0.5	0.5	0.6	0.6
Neighborhood Scale	4,145	0.3	0.0	0.0	0.0	0.1	0.2	0.2	0.3	0.4	0.4	0.5	0.6
8-H DAILY MAX													
Microscale	1,043	0.5	0.3	0.3	0.3	0.3	0.3	0.3	0.4	0.6	0.6	0.8	1.0
Neighborhood Scale	4,145	0.5	0.3	0.3	0.3	0.3	0.3	0.3	0.4	0.5	0.6	0.9	1.1

Table A-21. Comparison of distributional data at different monitoring scales for hourly, 1-h daily max, 24-h avg, and 8-h daily max data for Los Angeles, CA.

				PERCENTILES								
Time Scale	**N**	**Mean**	**Min**	**1**	**5**	**10**	**25**	**50**	**75**	**90**	**95**	**99**	**max**
ALL HOURLY													
Microscale	24,885	0.7	0.0	0.2	0.3	0.3	0.4	0.4	0.5	0.7	0.8	1.2	1.6
Middle Scale	98,564	0.5	0.0	0.0	0.0	0.0	0.1	0.2	0.4	0.6	0.7	1.1	1.6
Neighborhood Scale	49,757	0.3	0.0	0.0	0.0	0.0	0.1	0.1	0.2	0.3	0.3	0.6	0.8
Urban Scale	24,264	0.4	0.0	0.0	0.1	0.1	0.1	0.2	0.3	0.4	0.5	1.0	1.4
1-H DAILY MAX													
Microscale	1,080	1.3	0.2	0.4	0.5	0.6	0.8	0.8	1.1	1.6	1.7	2.3	2.7
Middle Scale	4,299	1.2	0.0	0.1	0.1	0.2	0.5	0.6	0.9	1.3	1.5	2.5	3.7
Neighborhood Scale	2,164	0.7	0.0	0.0	0.0	0.1	0.3	0.3	0.5	0.8	0.9	1.3	1.7
Urban Scale	1,053	1.0	0.0	0.1	0.2	0.3	0.4	0.4	0.7	1.3	1.5	2.2	2.6
1-H DAILY AVG													
Microscale	1,080	0.7	0.2	0.3	0.3	0.4	0.5	0.5	0.6	0.7	0.8	1.1	1.2
Middle Scale	4,299	0.5	0.0	0.0	0.0	0.1	0.2	0.2	0.4	0.6	0.7	1.1	1.5
Neighborhood Scale	2,164	0.3	0.0	0.0	0.0	0.0	0.1	0.2	0.2	0.3	0.4	0.5	0.6
Urban Scale	1,053	0.4	0.0	0.0	0.1	0.1	0.2	0.2	0.3	0.5	0.6	0.9	1.1
8-H DAILY MAX													
Microscale	1,080	0.9	0.3	0.3	0.4	0.4	0.6	0.6	0.8	1.1	1.2	1.6	1.8
Middle Scale	4,299	0.8	0.3	0.3	0.3	0.3	0.3	0.3	0.6	0.9	1.0	1.8	2.4
Neighborhood Scale	2,164	0.5	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.5	0.6	0.9	1.2
Urban Scale	1,053	0.7	0.3	0.3	0.3	0.3	0.3	0.3	0.5	0.8	0.9	1.5	1.8

Table A-22. Comparison of distributional data at different monitoring scales for hourly, 1-h daily max, 24-h avg, and 8-h daily max data for New York City, NY.

				PERCENTILES									
Time Scale	**N**	**Mean**	**Min**	**1**	**5**	**10**	**25**	**50**	**75**	**90**	**95**	**99**	**max**
ALL HOURLY													
Microscale	25,646	0.8	0.0	0.2	0.3	0.4	0.5	0.6	0.8	1.0	1.1	1.4	1.6
Middle Scale	48,660	0.6	0.0	0.1	0.3	0.3	0.4	0.5	0.6	0.7	0.7	0.9	1.0
Neighborhood Scale	25,150	0.5	0.0	0.2	0.2	0.3	0.3	0.4	0.4	0.6	0.6	0.9	1.1
1-H DAILY MAX													
Microscale	1,077	1.4	0.3	0.4	0.6	0.8	1.0	1.1	1.4	1.7	1.8	2.1	2.4
Middle Scale	2,053	0.9	0.2	0.4	0.5	0.6	0.7	0.7	0.8	1.0	1.1	1.3	1.5
Neighborhood Scale	1,053	0.9	0.2	0.3	0.4	0.4	0.6	0.6	0.8	1.0	1.1	1.5	1.9
1-H DAILY AVG													
Microscale	1,077	0.8	0.2	0.3	0.4	0.5	0.6	0.7	0.8	1.0	1.0	1.3	1.4
Middle Scale	2,053	0.6	0.0	0.2	0.3	0.4	0.5	0.5	0.6	0.7	0.7	0.8	0.9
Neighborhood Scale	1,053	0.5	0.1	0.2	0.3	0.3	0.4	0.4	0.5	0.6	0.6	0.8	1.0
8-H DAILY MAX													
Microscale	1,077	1.2	0.3	0.4	0.6	0.7	0.9	0.9	1.1	1.4	1.4	1.7	1.9
Middle Scale	2,053	0.7	0.3	0.3	0.4	0.4	0.6	0.6	0.7	0.8	0.9	1.0	1.2
Neighborhood Scale	1,053	0.7	0.3	0.3	0.3	0.3	0.4	0.5	0.6	0.8	0.8	1.2	1.5

Table A-23. Comparison of distributional data at different monitoring scales for hourly, 1-h daily max, 24-h avg, and 8-h daily max data for Phoenix, AZ.

				PERCENTILES									
Time Scale	**N**	**Mean**	**Min**	**1**	**5**	**10**	**25**	**50**	**75**	**90**	**95**	**99**	**max**
ALL HOURLY													
Microscale	25,382	0.9	0.0	0.0	0.1	0.1	0.3	0.3	0.6	1.1	1.3	2.3	3.0
Middle Scale	25,414	0.8	0.0	0.0	0.1	0.1	0.3	0.3	0.5	0.9	1.0	1.8	2.3
Neighborhood Scale	51,246	0.7	0.0	0.0	0.1	0.1	0.2	0.3	0.4	0.7	0.8	1.8	2.4
1-H DAILY MAX													
Microscale	1,063	2.2	0.0	0.2	0.5	0.7	1.1	1.2	1.9	2.8	3.1	4.2	4.7
Middle Scale	1,066	1.8	0.1	0.3	0.5	0.7	1.0	1.1	1.6	2.2	2.4	3.2	3.8
Neighborhood Scale	2,156	1.8	0.1	0.2	0.4	0.5	0.8	0.9	1.5	2.3	2.6	3.6	4.2
1-H DAILY AVG													
Microscale	1,063	0.9	0.0	0.0	0.2	0.2	0.4	0.4	0.7	1.2	1.3	2.0	2.3
Middle Scale	1,066	0.8	0.0	0.1	0.2	0.3	0.4	0.5	0.7	0.9	1.0	1.5	1.7
Neighborhood Scale	2,156	0.7	0.0	0.1	0.2	0.2	0.3	0.4	0.5	0.9	0.9	1.5	1.8
8-H DAILY MAX													
Microscale	1,063	1.5	0.3	0.3	0.3	0.4	0.6	0.7	1.2	2.0	2.2	3.1	3.5
Middle Scale	1,066	1.2	0.3	0.3	0.3	0.4	0.7	0.7	1.0	1.5	1.7	2.3	2.7
Neighborhood Scale	2,156	1.2	0.3	0.3	0.3	0.3	0.5	0.6	0.9	1.5	1.7	2.5	3.0

Table A-24. Comparison of distributional data at different monitoring scales for hourly, 1-h daily max, 24-h avg, and 8-h daily max data for Pittsburgh, PA.

				PERCENTILES									
Time Scale	**N**	**Mean**	**Min**	**1**	**5**	**10**	**25**	**50**	**75**	**90**	**95**	**99**	**max**
ALL HOURLY													
Middle Scale	25,818	0.5	0.0	0.0	0.1	0.1	0.3	0.3	0.4	0.5	0.6	0.8	1.1
Neighborhood Scale	77,000	0.3	0.0	0.0	0.0	0.0	0.1	0.1	0.2	0.3	0.4	0.6	0.8
Urban Scale	76,940	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.3	0.3	0.6	0.8
1-H DAILY MAX													
Middle Scale	1,079	0.9	0.0	0.2	0.4	0.4	0.6	0.6	0.8	1.1	1.1	1.6	1.9
Neighborhood Scale	3,210	0.6	0.0	0.0	0.1	0.2	0.3	0.3	0.5	0.7	0.7	1.1	1.3
Urban Scale	3,208	0.4	0.0	0.0	0.0	0.0	0.1	0.2	0.4	0.6	0.7	1.0	1.2
1-H DAILY AVG													
Middle Scale	1,079	0.5	0.0	0.1	0.2	0.2	0.3	0.3	0.4	0.5	0.6	0.8	0.9
Neighborhood Scale	3,210	0.3	0.0	0.0	0.0	0.0	0.1	0.2	0.3	0.3	0.4	0.6	0.7
Urban Scale	3,208	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.3	0.3	0.6	0.7
8-H DAILY MAX													
Middle Scale	1,079	0.7	0.3	0.3	0.3	0.3	0.4	0.4	0.6	0.7	0.8	1.1	1.3
Neighborhood Scale	3,210	0.5	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.5	0.5	0.8	1.0
Urban Scale	3,208	0.4	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.4	0.5	0.8	1.0

Table A-25. Comparison of distributional data for hourly, 1-h daily max, 24-h avg, and 8-h daily max data for Seattle, WA. Microscale was the only scale at which monitoring was performed in Seattle, WA.

				PERCENTILES									
Time Scale	**N**	**Mean**	**Min**	**1**	**5**	**10**	**25**	**50**	**75**	**90**	**95**	**99**	**max**
ALL HOURLY													
Microscale	25,818	0.8	0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.9	0.9	1.3	1.6
1-H DAILY MAX													
Microscale	1,079	1.5	0.2	0.4	0.5	0.7	0.9	1.0	1.3	1.7	1.8	2.4	2.9
1-H DAILY AVG													
Microscale	1,079	0.8	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.9	0.9	1.2	1.4
8-H DAILY MAX													
Microscale	1,079	1.1	0.3	0.3	0.4	0.5	0.7	0.8	1.0	1.3	1.4	1.8	2.2

Table A-26. Comparison of distributional data for hourly, 1-h daily max, 24-h avg, and 8-h daily max data for St. Louis, MO. Neighborhood scale was the only scale at which monitoring was performed in St. Louis, MO.

				PERCENTILES									
Time Scale	**N**	**Mean**	**Min**	**1**	**5**	**10**	**25**	**50**	**75**	**90**	**95**	**99**	**max**
ALL HOURLY													
Neighborhood Scale	51,263	0.4	0.0	0.1	0.2	0.2	0.3	0.3	0.4	0.5	0.5	0.6	0.8
1-H DAILY MAX													
Neighborhood Scale	2,138	0.8	0.1	0.2	0.3	0.4	0.5	0.5	0.6	0.9	1.0	1.5	2.0
1-H DAILY AVG													
Neighborhood Scale	2,138	0.4	0.0	0.1	0.2	0.3	0.3	0.3	0.4	0.5	0.5	0.6	0.7
8-H DAILY MAX													
Neighborhood Scale	2,138	0.6	0.3	0.3	0.3	0.3	0.3	0.3	0.5	0.6	0.7	1.0	1.3

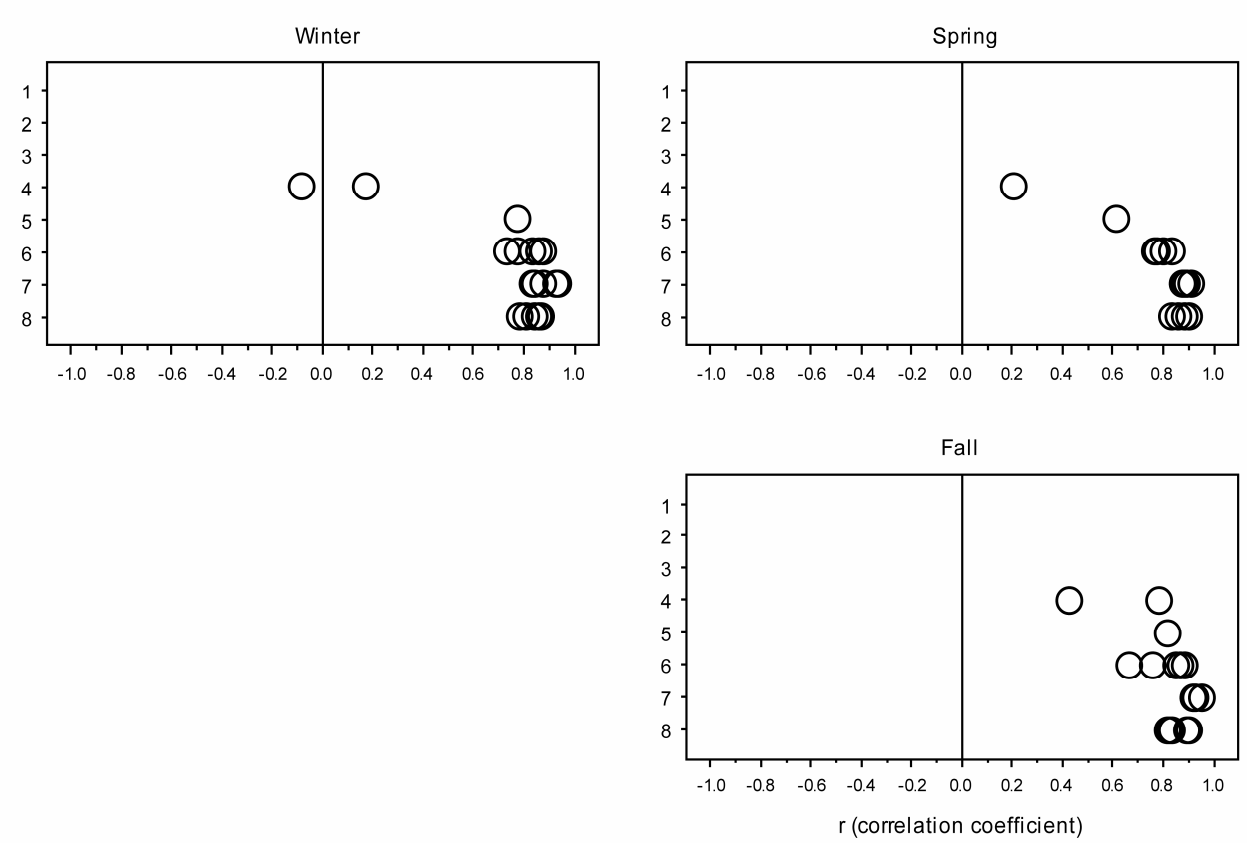


Figure A-44. Seasonal plots of correlations between hourly CO concentration with hourly (1) SO_2, (2) NO_2, (3) O_3, (4) PM_{10}, and (5) $PM_{2.5}$ concentrations for Anchorage, AK. Also shown are correlations between 24-h avg CO concentration with (6) daily max 1-h and (7) daily max 8-h CO concentrations and (8) between daily max 1-h and daily max 8-h CO concentrations. Refer the numbers in this caption to those on the y-axis of each seasonal plot. Note that the data are not obtained for Anchorage during the summer, and so are not presented here.

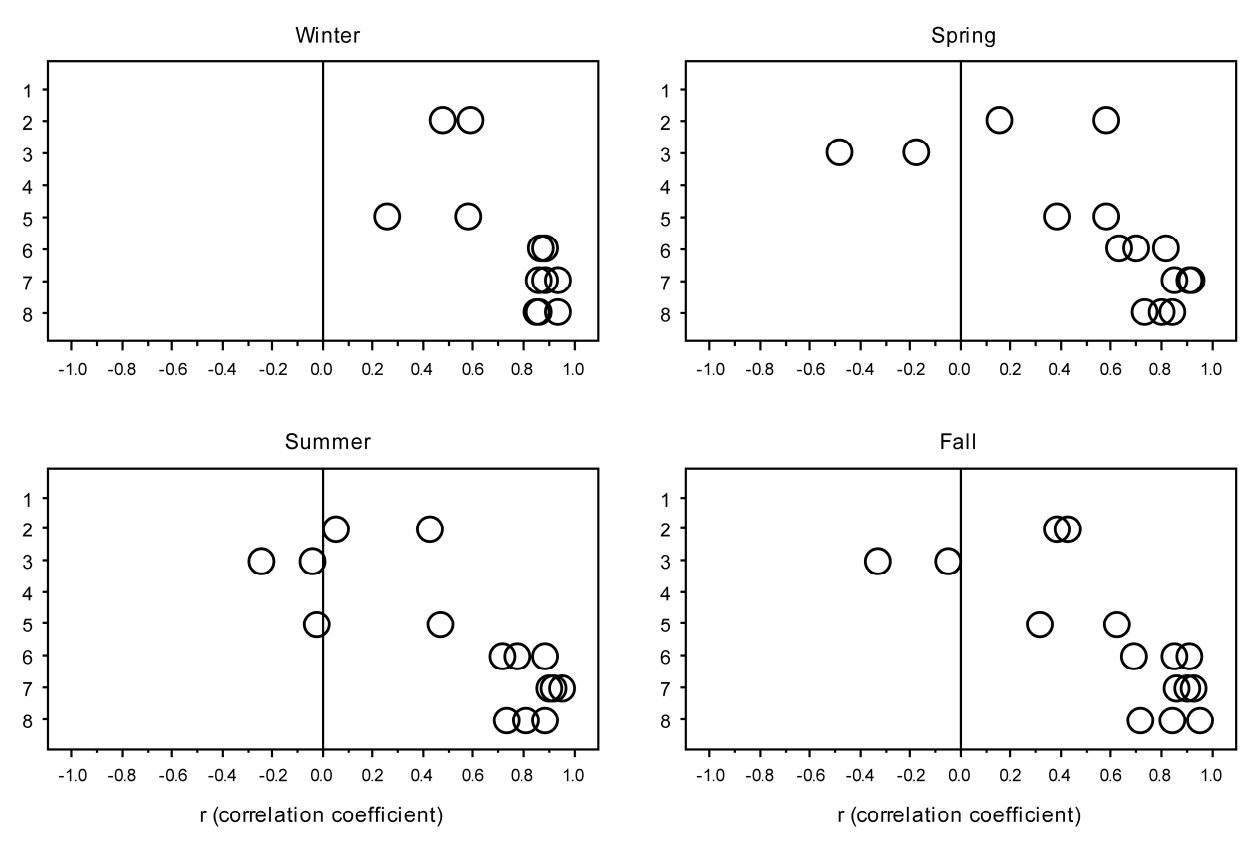


Figure A-45. Seasonal plots of correlations between hourly CO concentration with hourly (1) SO_2, (2) NO_2, (3) O_3, (4) PM_{10}, and (5) $PM_{2.5}$ concentrations for Atlanta, GA. Also shown are correlations between 24-h avg CO concentration with (6) daily max 1-h and (7) daily max 8-h CO concentrations and (8) between daily max 1-h and daily max 8-h CO concentrations. Refer the numbers in this caption to those on the y-axis of each seasonal plot.

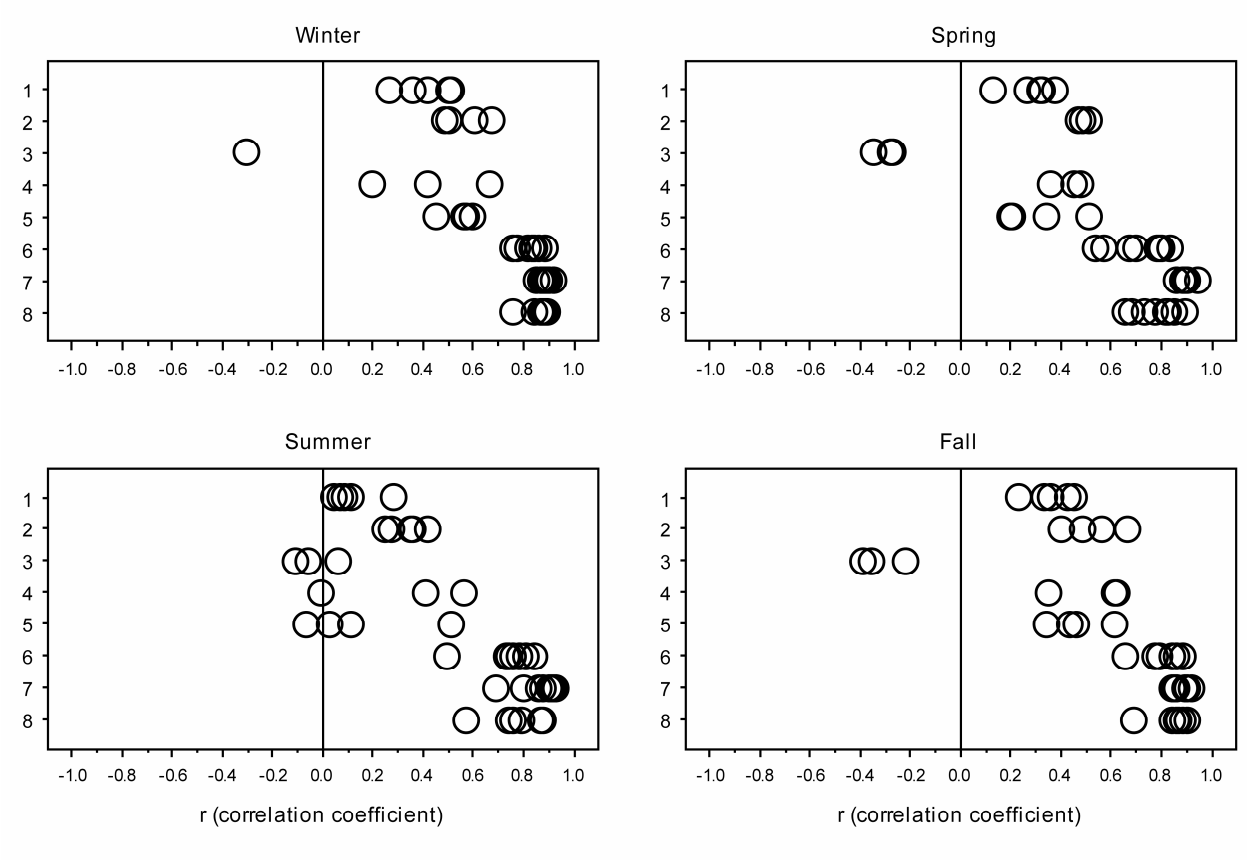


Figure A-46. Seasonal plots of correlations between hourly CO concentration with hourly (1) SO_2, (2) NO_2, (3) O_3, (4) PM_{10}, and (5) $PM_{2.5}$ concentrations for Boston, MA. Also shown are correlations between 24-h avg CO concentration with (6) daily max 1-h and (7) daily max 8-h CO concentrations and (8) between daily max 1-h and daily max 8-h CO concentrations. Refer the numbers in this caption to those on the y-axis of each seasonal plot.

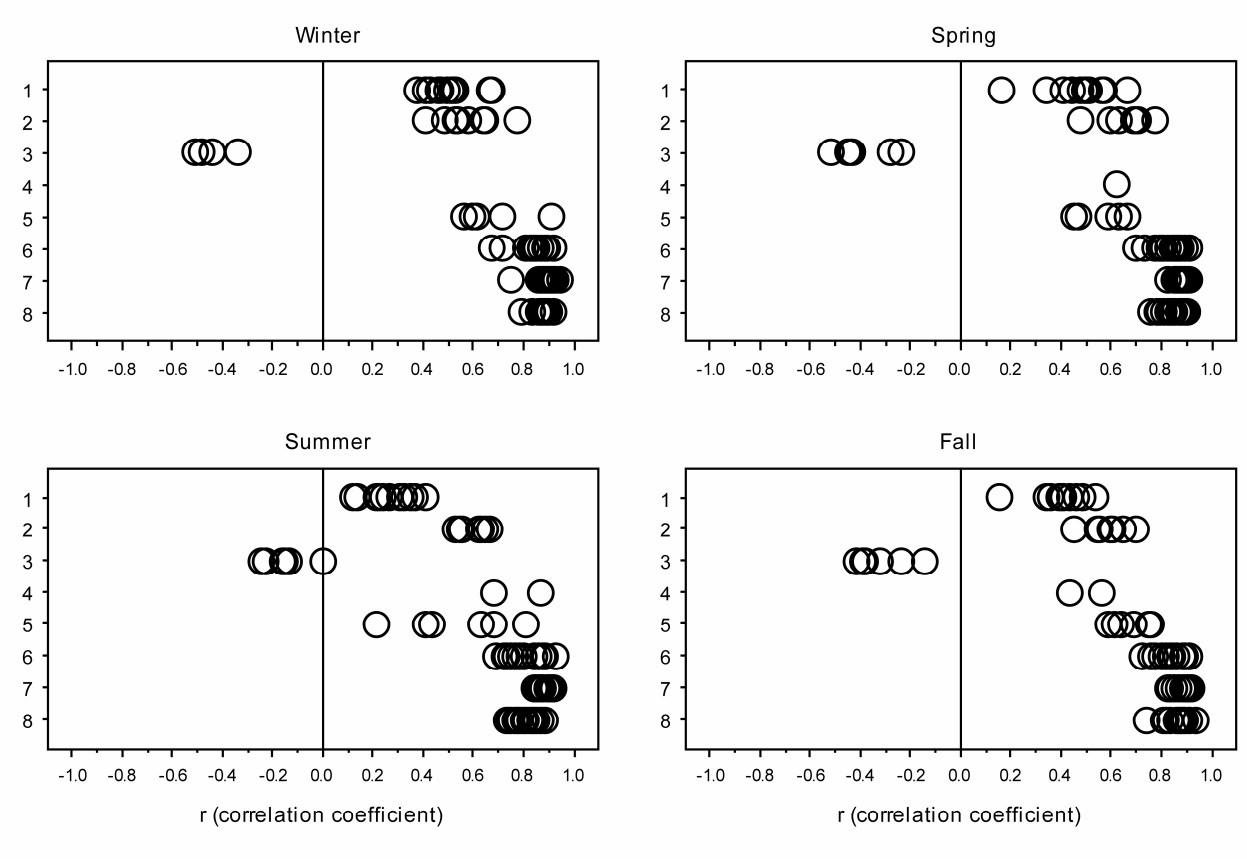


Figure A-47. Seasonal plots of correlations between hourly CO concentration with hourly (1) SO_2, (2) NO_2, (3) O_3, (4) PM_{10}, and (5) $PM_{2.5}$ concentrations for New York City, NY. Also shown are correlations between 24-h avg CO concentration with (6) daily max 1-h and (7) daily max 8-h CO concentrations and (8) between daily max 1-h and daily max 8-h CO concentrations. Refer the numbers in this caption to those on the y-axis of each seasonal plot.

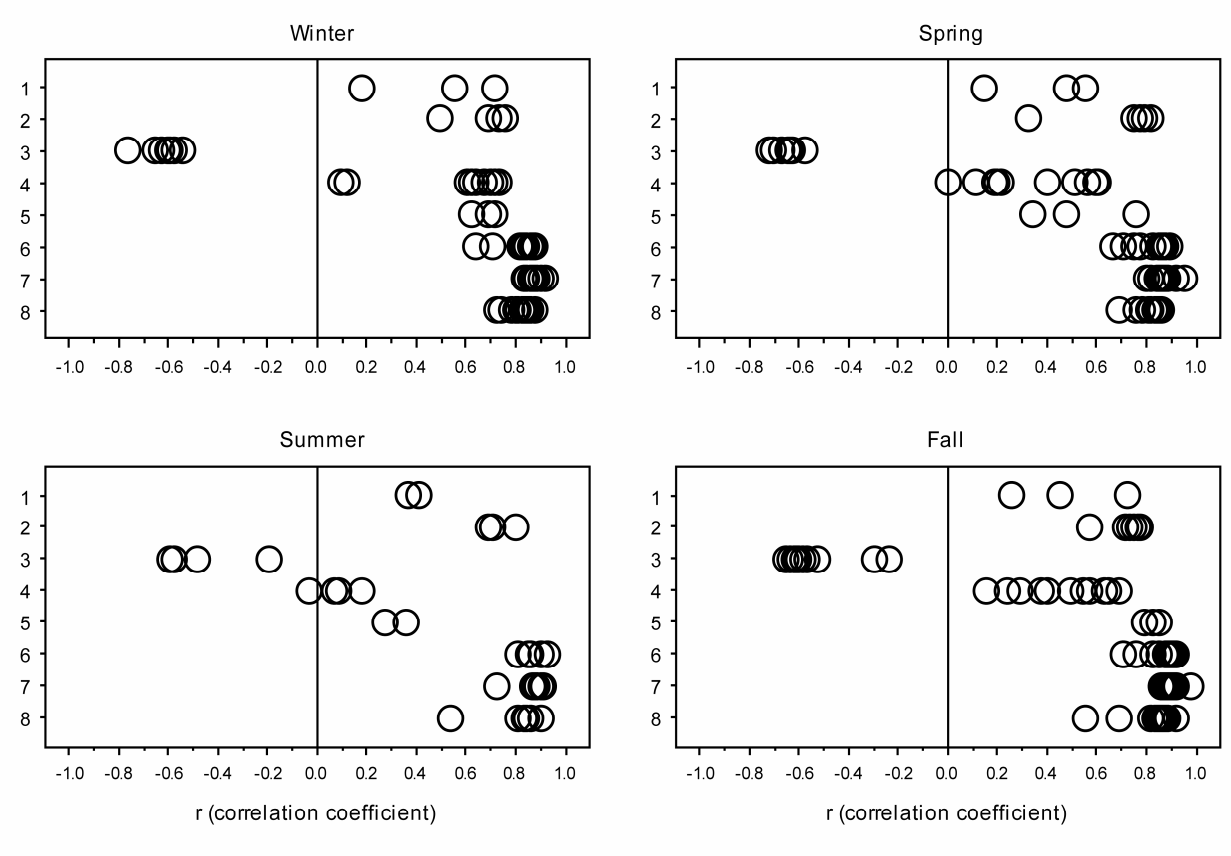


Figure A-48. Seasonal plots of correlations between hourly CO concentration with hourly (1) SO_2, (2) NO_2, (3) O_3, (4) PM_{10}, and (5) $PM_{2.5}$ concentrations for Phoenix, AZ. Also shown are correlations between 24-h avg CO concentration with (6) daily max 1-h and (7) daily max 8-h CO concentrations and (8) between daily max 1-h and daily max 8-h CO concentrations. Refer the numbers in this caption to those on the y-axis of each seasonal plot.

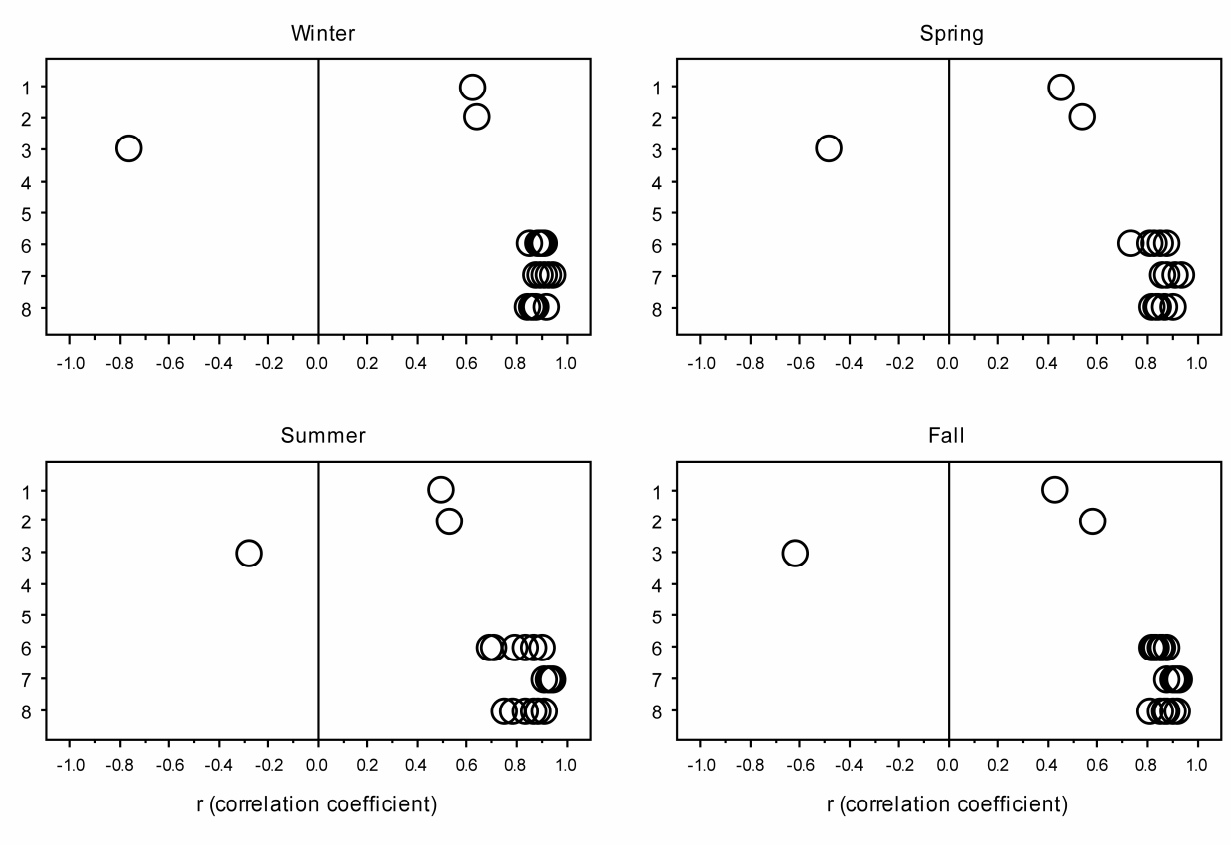


Figure A-49. Seasonal plots of correlations between hourly CO concentration with hourly (1) SO_2, (2) NO_2, (3) O_3, (4) PM_{10}, and (5) $PM_{2.5}$ concentrations for Seattle, WA. Also shown are correlations between 24-h avg CO concentration with (6) daily max 1-h and (7) daily max 8-h CO concentrations and (8) between daily max 1-h and daily max 8-h CO concentrations. Refer the numbers in this caption to those on the y-axis of each seasonal plot.

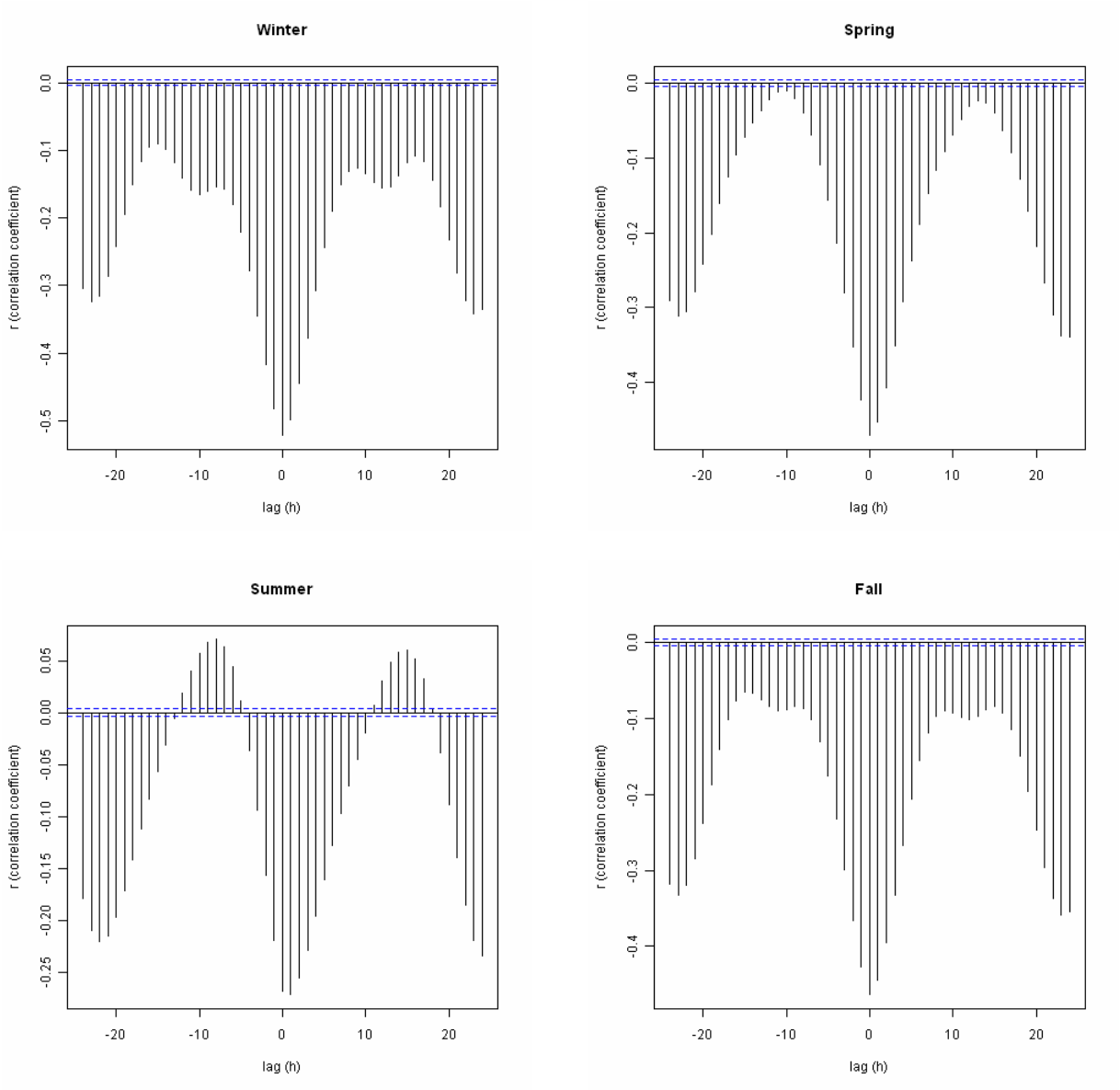


Figure A-50. Cross-correlation functions for each season combined across sites where CO and O_3 monitors were co-located in Atlanta, Boston, Denver, Los Angeles, New York City, and Phoenix.

Annex B. Dosimetry Studies

Table B-1. Recent studies related to CO dosimetry and pharmacokinetics.

Reference	Purpose	Findings
Aberg et al. (2009, 194082)	To investigate CO concentrations in blood donors in Sweden.	The mean CO concentration in blood donors was 84.5 µmol/L. Concentrations over 130 µmol/L were found in 6% of blood, and the highest concentration was 561 µmol/L . By using a calculation, 23% of banked blood bags could exceed 1.5% COHb, with a highest fraction of 7.2% COHb.
Abram et al. (2007, 193859)	To present the Quantitative Circulatory Physiology (QCP) model as a teaching module in the practice of medicine.	QCP is a dynamic mathematical model based on published models and parameters of biological interactions.
Alcantara et al. (2007, 193867)	To use a quantum mechanics/molecular mechanics approach to understand the cooperativity of Hb ligand binding and differences in energy between T and R Hb functional states.	The ligand binding energies between R and T states differ due to strain induced in the heme and its ligands and in protein contacts in the α and β chains.
Adir et al. (1999, 001026)	To determine if low concentrations of CO would affect exercise performance and myocardial perfusion in young healthy men.	Men with COHb levels between 4 and 6% had decreased exercise performance measured by decreased mean duration of exercise (1.52 min) and maximal effort described by metabolic equivalent units (2.04). No changes were seen in lactate/pyruvate ratio, arrhythmias, or myocardial perfusion.
Anderson et al. (2000, 011836)	To investigate if CO could be endogenously produced in the nose and paranasal sinuses.	Both nose and paranasal sinuses contained HO-like immunoreactivity, mostly in the respiratory epithelium, indicating local CO production in the upper respiratory airways.
Arora et al. (2001, 186713)	To evaluate the effect of multiple transfusion recipient thalassemics on pulmonary function.	D_LCO was decreased in all the patients with restrictive lung disease and fall in D_LCO showed a good correlation with the severity of restrictive disease. Thalassemics had a decrease in lung volume and a proportional decrease in flow rate.
Benignus et al. (2006, 151344)	To adapt and use a human model for toluene uptake and elimination including a brain compartment.	The QCP 2004 model was used to construct simulations of scenarios of toxicant exposure and human activities. QCP accurately predicted toluene blood concentrations from inhaled exposure.
Bos et al. (2006, 194084)	To use a PBPK model to set AEGL for methylene chloride.	This model adequately predicted COHb levels formed by various methylene chloride concentrations, specifically in nonconjugators lacking the GSTT-1 enzyme, and proposed AEGL values.
Bruce and Bruce (2003, 193975)	To create a mathematical model to predict uptake and distribution of CO in both vascular and tissue compartments during constant or variable inhalation levels of CO.	This model contains 5 compartments: lung, arterial blood, venous blood, muscle tissue, and nonmuscle tissue. It was constructed to include tissue compartment flux and difference between venous and arterial COHb for short exposures which is not possible with the CFK model.
Bruce and Bruce (2006, 193980)	To use their mathematical multicompartment model along with experimental data to predict the factors that influence the washout rates of CO, along with predicting the rates of CO uptake, distribution in vascular and extravascular (muscle and nonmuscle tissue) compartments, and washout over a range of exposure and conditions.	Rates of CO washout follow a biphasic elimination where washout was faster immediately post exposure. The difference in rates is likely due to slow equilibration between vascular and extravascular compartments. Important factors contributing to washout kinetics include: peak COHb level, exposure duration and concentration, time after exposure samples were obtained, and individual variability.
Bruce and Bruce (2008, 193977)	To develop a mathematical model able to integrate a large body of indirect experimental findings on the uptake and distribution of CO by accounting for arteriole to venule shunting via intratissue pathways and diffusion of blood gases into tissues from pre-capillary vessels like arterioles.	The former model of Bruce and Bruce (2006, 193980) was altered by adding a mass balance equation for O_2 so pO_2 is directly calculated in the compartments, and the muscle compartment is divided into two sub-compartments of muscle and nonmuscle tissue. CO uptake from blood by muscle is much slower than O_2, thus COHb% will fall rapidly while COMb% could remain high.

Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at http://epa.gov/hero. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISAs) and the Integrated Risk Information System (IRIS).

Reference	Purpose	Findings
Carraway et al. (2000, 021096)	To test the hypothesis that HO-1 gene expression and protein are upregulated in the lungs of rats during chronic hypoxia.	Rats were exposed to HH (17,000 ft) for 1-21 days. COHb increased after 1 day and progressively after 14 days. HO-1 protein and activity were upregulated during early chronic hypoxia. This HO-1 was localized to inflammatory cells and then to newly muscularized arterioles.
Castillo et al. (2006, 193234)	To describe a new method for measurement of CO D_LCO and V_A in sleeping infants (6-22 mo old), using a single 4-s breath-hold technique.	V_{A30} and D_LCO increased with increasing body length, and the method could be used as a measurement of lung development and growth.
Chakraborty et al. (2004, 193759)	To present an analytical expression for diffusing capacity of CO, NO, CO_2, and O_2 to the red blood cell in terms of optimum size and shape of the RBC, thickness of the unstirred plasma layer surrounding the RBC, diffusivities and solubilities of the gas in RBC and boundary layer, hematocrit, and the slope of the dissociation curve.	Results indicate the discoidal shape of the RBC is optimal for O_2 uptake and reaction velocity is limited by mass transfer resistance in surrounding stagnant plasma layer. The paper overviews rate constants and reaction kinetics for CO binding to Hb. CO diffusing capacity is shown to be reaction-rate limited at low pCO under normoxic and hyperoxic conditions, but diffusion-rate limited under hypoxic and high pCO conditions.
Cronenberger et al. (2008, 194085)	To develop a population-based model to describe and predict the pharmacokinetics of COHb in adult smokers.	This two-compartment model included zero-order input and first-order elimination and required a compartment for extravascular binding of CO to accurately predict COHb formation during multiple short and rapid inhalations, followed by a period of no exposure, as occurs in smoking. Smokers' COHb ranged from 0.8 to 11.1%.
Cronje et al. (2004, 180440)	To analyze CO uptake and elimination in the brain, muscle, heart, and blood of rats, with the intent of testing the Warburg hypothesis that CO partitioning is directly proportional to the CO/O_2 ratio.	Results indicate that tissue and blood CO concentration dissociate during CO inhalation, but CO concentration does not follow blood CO concentration or $1/pO_2$ as in the Warburg theory during intake or elimination. Tissue CO concentration increases later during the resolution period and varies significantly among animals and tissues. The deviation from the predicted values in the brain is likely due to the release of heme and increase in NADPH stimulating endogenous CO production by HO.
De las Heras et al. (2003, 194087)	To assess production of CO (venous COHb measured by CO-oximeter and exhaled CO) in patients with cirrhosis with and without spontaneous bacterial peritonitis.	Patients with SBP had higher CO production than noninfected cirrhotic patients and both groups of patients had higher CO production compared to healthy controls. CO production decreased slowly after resolution of the disease.
Dutton et al. (2001, 021307)	To monitor CO, NO_2, and PAH emissions during the operation of unvented natural gas fireplaces in two residences in Boulder, CO, at various times between 1997 and 2000.	Results showed significant accumulation of CO, NO_2, and PAH indoors when the fireplaces were used. CO concentrations could exceed 100 ppm. NO_2 concentrations averaged 0.36 ppm over 4 h. PAH 4-h time avg reached 35 ng/m^3.
Ehlers et al. (2009, 194089)	To determine the level of COHb found in banked blood in the Albany, NY region.	The avg COHb level was 0.78%. The highest recorded COHb level was 12%, and 10.3% of packed red blood cell units had levels of 1.5% COHb or higher.
Gosselin et al. (2009, 190946)	To develop a variant of the CFK model that links COHb levels in humans to ambient CO levels under various environmental or occupational exposure conditions.	The model adds alveoli-blood and blood-tissue CO exchanges and mass conservation of CO at all times to the CFK equation. The model better predicted COHb formation over a wide range of CO levels and scenarios with linear regression analysis of predicted vs observed values generating a slope of 0.996 (95% CI: 0.986-1.001) compared to 0.917 (95% CI: 0.906-0.927) using the CFK model
Hampson and Weaver (2007, 190272)	To present a case study of a man with drug-induced hemolytic anemia and hepatic failure.	The man had elevated endogenous CO production resulting in levels of COHb as high as 9.7%.
Hart et al. (2006, 194092)	To investigate the relationship between COHb and smoking habit and mortality.	COHb was related to self-reported smoking in a dose-dependent manner. COHb was positively associated with all causes of mortality analyzed including CHD, COPD, stroke, and lung cancer. Mean COHb levels ranged from 1.59% in never-smokers to 6.02% in the most often smoking group.
Hsia (2002, 193857)	To review the current concepts and practical relevance of the diffusing capacity/cardiac output interaction, in hopes of aiding in the interpretation of diffusing capacity, membrane diffusing capacity, and capillary blood volume.	This review helped to understand the determinants of changes in diffusing capacity, including hematocrit, erythrocyte distribution, blood volume, lung volume, and cardiac output.
Johnson et al. (2006, 193874)	To test that heme-derived CO formation is increased and contributes to hypertension and arteriolar endothelial dysfunction in obese Zucker rats.	Obese Zucker rats showed increased respiratory CO excretion that was lowered by HO inhibition. Skeletal muscle arterioles of obese rats had attenuated ACh and flow responses that were abolished by HO inhibition (HO inhibition enhanced dilation).
Lamberto et al. (2004, 193845)	To evaluate which component, alveolar membrane diffusing capacity (Dm) and pulmonary capillary blood volume (Vc), is responsible for decreased resting D_LCO in sarcoidosis patients and which component is the best predictor of gas exchange abnormalities.	Patients with pulmonary sarcoidosis had decreased lung volumes, a loss in D_LCO, and gas exchange abnormalities during exercise, including decreased P_aO_2 and increased alveolar-arterial oxygen pressure difference. Dm accounted for the majority of the decrease in D_LCO and was predictive for gas exchange abnormalities.

Reference	Purpose	Findings
Levesque et al. (2000, 011886)	To describe the results of air quality monitoring in an indoor ice skating rink during Monster Truck and car demolition exhibitions.	Maximum time-weighted avg levels of CO were 100 ppm, with several peaks exceeding 200 ppm (max: 1,600 ppm).
Lim et al. (2000, 126969)	To investigate the expression of HO-1 and HO-2 in bronchial biopsies obtained from patients with mild asthma compared with that of subjects without asthma.	HO-1 and HO-2 expression is widely distributed equally in healthy subjects and subjects with asthma and is not modulated by inhaled corticosteroid therapy.
Mahoney et al. (1993, 013859)	To compare CO-oximeter measurements of COHb against a gas chromatography reference method.	In general, the 5 CO-oximeters that were tested underestimated COHb concentrations for COHb >2.5% and overestimated COHb concentration for COHb ≤ 2.5%, when compared to reference gas chromatography method.
Marks et al. (2002, 030616)	To review the analytical methods for measurement of endogenous formation of CO in a variety of tissues.	A variety of methods have been used to measure endogenous CO. The rate of formation varies over a narrow range, from 0.029 nmol/mg protein/h to 0.28 nmol/mg protein/h depending on tissue. Brain and liver regions tend to have the highest rates of CO formation, likely due to high levels of HO activity in these tissues.
Marvisi et al. (2007, 186702)	To evaluate D_LCO impairment and microalbuminuria in patients with active ulcerative colitis (UC) and to assess whether these tests correlate with intestinal inflammation.	Reduced D_LCO was present in 67% of patients. Microalbuminuria was present in 63% of patients with ulcerative colitis.
Merx et al. (2001, 002006)	To investigate the effect of CO inactivation of Mb in wild-type and myo-/- mice on hemodynamics and oxygen dynamics.	Fully oxygenated Mb treated with 20% CO had no change in left ventricular developed pressure or coronary venous pO_2. Partially O_2-saturated Mb (87% O_2Mb) exposed to 20% CO had significantly decreased LVDP (12%) and PvO_2 (30%) in wild-type but not myo-/- hearts.
Monma et al. (1999, 180426).	To study whether exhaled CO levels were increased in seasonal allergic rhinitis.	Exhaled CO concentrations were higher in allergic rhinitis patients during cedar pollen season (3.6 ppm; SD 0.3 ppm) that out (1.2 ppm; SD 0.1 ppm).
Morimatsu et al. (2006, 194097)	To examine exhaled CO, arterial COHb, and bilirubin IXα levels in critically ill patients.	Exhaled CO concentrations were significantly higher in critically ill patients compared to controls. There was a significant correlation between exhaled CO and COHb or bilirubin. There was no correlation between exhaled CO and disease severity or degree of inflammation. There was higher exhaled CO in survivors compared to nonsurvivors.
Muchova et al. (2007, 194098)	To determine if long-term use of statins affects HO activity and blood and organ CO and bilirubin in FvB mice (6-8 wk).	Rosuvastatin and atorvastatin treatment increased COHb, plasma bilirubin, and heart tissue CO content. Both statins caused an increase in HO activity in heart tissue, whereas no changes were seen in brain or lung. Liver HO activity was inconsistent over time and between statins. Both statins decreased the heart antioxidant capacity, and changes in HO activity and antioxidant capacity can be reversed by HO inhibitor treatment.
Neto et al. (2008, 194672)	To develop a model of the respiratory system to analyze CO transport in the human body submitted to several physical activity levels.	The model contains 6 compartments including: alveolar, pulmonary capillaries, arterial, venous, tissue capillary, and tissues (muscular and nonmuscular). The highest and lowest COHb levels were simulated in the walking individual, suggesting that greater variability in COHb occurs in higher physical activity levels.
Pelham et al. (2002, 025716)	To review the literature on exposure and effects of mainly CO and NO_2 in enclosed ice rinks.	CO levels as high as 300 ppm were recorded after episodes of malfunctioning ice resurfacing equipment or inadequate ventilation.
Paredi et al. (1999, 194102)	To investigate the level of exhaled CO produced by diabetic patients.	Diabetic patients (types 1 and 2) had higher levels of exhaled CO than healthy subjects. Exhaled CO levels correlated with the incidence of glycemia and the duration of diabetes.
Paredi et al. (1999, 118798)	To investigate whether cystic fibrosis patients have higher exhaled levels of CO and if this is reduced by corticosteroid therapy.	Cystic fibrosis patients had higher exhaled CO concentrations compared to healthy controls. Patients receiving corticosteroid therapy had lower exhaled CO concentrations.
Pesola et al. (2004, 193842)	To determine if healthy African Americans may be misdiagnosed as having respiratory deficient due to comparison using Caucasian-derived prediction equation estimates of D_LCO.	The lung volume of African-American individuals is 10-15% lower than Caucasians. The measured D_LCO was consistently significantly lower in African-Americans than what would be predicted. Thus, the authors suggest a race correction reduction of the Miller PEE for diffusion of 12%.
Pesola et al. (2006, 193855)	To determine if healthy Asians may be misdiagnosed as having respiratory deficient due to comparison using Caucasian-derived prediction equation estimates of D_LCO.	The lung volume of Asian individuals is 10-15% lower than Caucasians. Thus a Chinese-derived prediction for D_LCO should be used.

Reference	Purpose	Findings
Prommer and Schmidt (2007, 180421)	To determine the error in total Hb mass measurements using the optimized CO-rebreathing method due to loss of CO to Mb	Optimal blood mixing (when venous and arterial blood COHb% are equivalent) was determined to be after 6 min. A small volume of administered CO leaves the vascular space (0.32% per min). A 2.3% increase in total Hb mass would be found if CO diffusion was not included.
Proudman et al. (2007, 186705)	To review the signs of pulmonary arterial hypertension, including a drop in D_LCO in patients with systemic sclerosis.	
Richardson et al. (2002, 037513)	To combine invasive vascular measures of arterial and venous blood and muscle blood flow with noninvasive magnetic spectroscopy of deoxy-myoglobin and high energy phosphates to determine the effects of mild CO poisoning (20% COHb) in humans during muscular work.	Five humans were analyzed under normoxia, hypoxia, normoxia + CO (20% COHb), and 100% O_2 + CO. Maximum works rates and maximal oxygen uptake were reduced in H, COnorm, and COhyper. CO and H caused elevated blood flow. Net muscle CO uptake from blood was less during 20% COHb trials than during normoxia and hypoxia (1-2%) trials.
Sakamaki et al. (2002, 186706)	To evaluate the association of patients with aortic aneurysm to the prevalence obstructive airway disease.	Patients with AA had lower FEV_1 and D_LCO than controls. Presence of AA and male gender were associated with a higher risk of airway obstruction.
Scharte et al. (2000, 194112)	To investigate whether exhaled CO concentrations are increased in critically ill patients.	Critically ill patients had higher exhaled CO concentrations and higher total CO production rates compared to healthy controls. No correlation was found between exhaled CO concentration and venous or arterial COHb.
Scharte et al. (2006, 194115)	To investigate the relationship between the severity of illness and endogenous CO production in critically ill patients.	CO production rates weakly correlated with the multiple organ dysfunction score (R=0.27). Cardiac disease patients and patients undergoing dialysis produced higher amounts of CO compared to critically ill control patients.
Schachter et al. (2003, 186707)	To evaluate the association between severe gastroesophageal reflux and lung function.	Patients with severe gastroesophageal reflux had reduced D_LCO, remaining significant after adjusting for age, gender, BMI, and smoking.
Shimazu et al. (2000, 016420)	To study the effects of short-term (min) or long-term (several h) CO exposure on COHb elimination and developing a mathematical model to simulate this event.	COHb exhibited an initial rapid decrease followed by a slower phase which is compatible with a 2-compartment model and biphasic elimination. Both exposures fit the 2-compartment, single-central-outlet mathematical model.
Shimazu (2001, 016331)	To discuss the findings of Weaver et al. (2000, 016421) on COHb t1/2.	The authors discuss that CO elimination is biphasic and is heavily affected by duration of exposure which was not taken into account in the Weaver et al. (2000, 016421) paper.
Sylvester et al. (2005, 191954)	To assess the usage of end tidal CO levels in children with sickle cell disease for measurement of hemolysis.	Children with sickle cell disease had higher exhaled CO levels (4.9 ppm; SD 1.7 ppm) compared to healthy controls (1.3 ppm; SD 0.4 ppm). A positive correlation existed between end-tidal CO levels and COHb and bilirubin.
Takeuchi et al. (2000, 005675)	To examine the relationship between min ventilation and rate of COHb reduction during breathing 100% O_2 and during normocapnic hyperoxic hyperpnea.	Patients were exposed to 400-1,000 ppm CO, resulting in 10-12% COHb. The half-time of COHb reduction was 78 ± 24 min during 100% O_2 treatment and 31 ± 6 min during normocapnic hyperpnea with O_2 treatment.
Tarquini et al. (2009, 194117)	To measure plasma CO levels in patients with liver cirrhosis and portal hypertension.	Plasma CO was higher in ascetic patients than nonascitic patients and both were higher than healthy controls. HO activity was higher in cirrhotic patients than healthy subjects and highest in patients with ascites.
Terzano et al. (2009, 108046)	To investigate the effect of postural changes on gas exchange in patients with COPD and healthy subjects.	D_LCO increased in healthy individuals from upright to supine position and upright to prone position. D_LCO did not significantly change in COPD patients from upright to prone position. This is explained by homogeneous perfusion in healthy individuals and increased rigidity of lung capillaries due to COPD.
Tran et al. (2007, 194120)	To assess the correlation of COHb to severity of liver disease.	No correlation was found with the Model for End Stage Liver Disease score, Child Turcotte Pugh score, or other biochemical or clinical measures of disease severity, such as spleen size, bilirubin, disease duration, or AST/ALT. The mean COHb was 2.1%.
Vreman et al. (2005, 193786)	To develop a sensitive and reproducible method of CO quantification in rodent (mouse and rat) tissue pre- and postexposure in hopes of understanding endogenous CO production.	Tissues were sonicated mixed with sulfosalicylic acid for 30 min at 0°C and then liberated CO was analyzed by gas chromatograph. Blood contained the highest CO concentration. Lowest concentrations were found in brain, testes, intestine, and lung (endogenously).
Vreman et al. (2006, 098272)	To test a method of CO quantification in frozen postmortem human tissues from 3 determined categories of fatalities: trauma with no suspected CO exposure (controls), fire-related, and CO asphyxiation.	CO levels were analyzed in adipose, brain, muscle, heart, kidney, lung, spleen, and blood (ordered from approximate low to high tissue concentration). It was suggested that blood, muscle, brain, lung, and kidney are suitable for diagnosing death due to lethal CO exposure due to regression analysis against COHb values.

Reference	Purpose	Findings
Weaver et al. (2000, 016421)	To determine in COHb half-life is influenced by CO poisoning vs experimental CO exposure, loss of consciousness, concurrent tobacco smoking, or P_aO_2.	COHb t1/2 determined was 74 ± 25 min with a range from 26 to 148 min by a single exponential decrease function. This is shorter than most clinical studies and was inversely proportionate to P_aO_2, however, not influenced by age, gender, smoke inhalation, loss of consciousness, tobacco smoking, or method of O_2 treatment.
Whincup et al. (2006, 195129)	To report COHb levels from a population-based study in men aged 60-79 yr during the 20-yr follow-up of the British Regional Heart Study cohort.	Mean COHb: 0.46%; Median COHb: 0.5% 9.2% of men had COHb levels of 2.5% or greater (93% were smokers) 0.1% of men had COHb levels of 7.5% or greater Smoking is the highest influence on COHb levels; however, other factors independently related were season, region, gas cooking and central heating, and active smoking
Widdop (2002, 030493)	To review carbon monoxide analysis methods, including CO-oximeters and gas chromatography.	
Wu and Wang (2005, 180411)	To review the endogenous production of CO through HO, as well as discuss physiological roles for CO both toxic and therapeutic.	CO is produced endogenously by HO-1 and -2 and acts as a gasotransmitter, inducing cell signaling cascades. The review discusses possible roles for CO in the various organ systems and the potential pharmacological and therapeutic applications for CO.
Yamaya et al. (1998, 047525)	To determine whether upper respiratory tract infections increase exhaled CO concentrations.	Exhaled CO increased in patients at the time of upper respiratory tract infection symptoms but decreased to nonsmoking healthy control levels during recovery.
Yamaya et al. (2001, 180130)	To determine whether the level of CO is related to the severity of asthma.	Severe asthmatics exhaled more CO than nonsmoking controls. Exhaled CO concentrations in unstable severe asthmatics were higher than in stable severe asthmatics. Mild and moderate asthmatics did not differ from controls. Exhaled CO was correlated with FEV_1 in all asthmatics.
Yasuda et al. (2002, 035206)	To determine whether arterial COHb is increased in patients with inflammatory pulmonary diseases.	Arterial COHb concentrations are increased in patients with inflammatory pulmonary diseases, including exacerbated bronchial asthma (1.05%), pneumonia (1.08%), and idiopathic pulmonary fibrosis (1.03%) over controls (0.6%).
Yasuda et al. (2004, 191955)	To determine if COHb levels in the venous blood and arteriovenous COHb (a-vCOHb) differences are increased in patients with inflammatory pulmonary diseases compared to patients with extrapulmonary inflammation and control subjects.	Patients with inflammatory pulmonary diseases, including bronchial asthma and pneumonia, had a large a-vCOHb difference. Both arterial and venous blood COHb increased in patients with inflammatory pulmonary disease, such as bronchial asthma, pneumonia, pyelonephritis and active rheumatoid arthritis.
Yasuda et al. (2005, 102183)	To study the relationship between COHb and disease severity in patients with COPD.	COHb concentrations increased in patients with COPD at a stable condition over controls and patients with COPD with exacerbations were further increased.
Yerushalmi et al. (2009, 186711)	To evaluate the association of dose-dense chemotherapy in breast cancer patients with pulmonary dysfunction.	Patients receiving dose-dense chemotherapy for breast cancer had a significant reduction in D_LCO.
Zegdi et al. (2002, 037461)	To compare endogenous CO production in mechanically ventilated critically ill adult patients with and without severe sepsis.	CO production was higher in septic patients during the first 3 days of treatment compared to controls. Survivors of sepsis had a significantly higher CO production compared to nonsurvivors.

References

Aberg AM; Sojka BN; Winsö O; Abrahamsson P; Johansson G; Larsson JE (2009). Carbon monoxide concentration in donated blood: Relation to cigarette smoking and other sources. Transfusion, 49: 347-353. 194082

Abram SR; Hodnett BL; Summers RL; Coleman TG; Hester RL (2007). Quantitative circulatory physiology: An integrative mathematical model of human physiology for medical education. Adv Physiol Educ, 31: 202-210. 193859

Adir Y; Merdler A; Haim SB; Front A; Harduf R; Bitterman H (1999). Effects of exposure to low concentrations of carbon monoxide on exercise performance and myocardial perfusion in young healthy men. Occup Environ Med, 56: 535-538. 001026

Alcantara RE; Xu C; Spiro TG; Guallar V (2007). A quantum-chemical picture of hemoglobin affinity. PNAS, 104: 18451-18455. 193867

Andersson JA; Uddman R; Cardell L-O (2000). Carbon monoxide is endogenously produced in the human nose and paranasal sinuses. J Allergy Clin Immunol, 105: 269-273. 011836

Arora M; Chandra J; Suri JC; Narayan S; Dutta AK (2001). Pulmonary function tests in beta thalassemia. Indian J Pediatr, 68: 239-242. 186713

Benignus VA; Coleman T; Eklund CR; Kenyon EM (2006). A general physiological and toxicokinetic (GPAT) model for simulating complex toluene exposure scenarios in humans. Toxicol Mech Meth, 16: 27-36. 151344

Bos PM; Zeilmaker MJ; van Eijkeren JC (2006). Application of physiologically based pharmacokinetic modeling in setting acute exposure guideline levels for methylene chloride. Toxicol Sci, 91: 576-585. 194084

Bruce EN; Bruce MC (2003). A multicompartment model of carboxyhemoglobin and carboxymyoglobin responses to inhalation of carbon monoxide. J Appl Physiol, 95: 1235-1247. 193975

Bruce EN; Bruce MC; Erupaka K (2008). Prediction of the rate of uptake of carbon monoxide from blood by extravascular tissues. Respir Physiol Neurobiol, 161: 142-159. 193977

Bruce MC; Bruce EN (2006). Analysis of factors that influence rates of carbon monoxide uptake, distribution, and washout from blood and extravascular tissues using a multicompartment model. J Appl Physiol, 100: 1171-1180. 193980

Carraway MS; Ghio AJ; Carter JD; Piantadosi CA (2000). Expression of heme oxygenase-1 in the lung in chronic hypoxia. Am J Physiol, 278: L806-L812. 021096

Castillo A; Llapur CJ; Martinez T; Kisling J; Williams-Nkomo T; Coates C; Tepper RS (2006). Measurement of single breath-hold carbon monoxide diffusing capacity in healthy infants and toddlers. Pediatr Pulmonol, 41: 544-550 . 193234

Chakraborty S; Balakotaiah V; Bidani A (2004). Diffusing capacity reexamined: relative roles of diffusion and chemical reaction in red cell uptake of O2, CO, CO2, and NO. J Appl Physiol, 97: 2284-2302. 193759

Cronenberger C; Mould DR; Roethig HJ; Sarkar M (2008). Population pharmacokinetic analysis of carboxyhaemoglobin concentrations in adult cigarette smokers. Br J Clin Pharmacol, 65: 30-39. 194085

Cronje FJ; Carraway MS; Freiberger JJ; Suliman HB; Piantadosi CA (2004). Carbon monoxide actuates O2-limited heme degradation in the rat brain. Free Radic Biol Med, 37: 1802-1812. 180440

De las Heras D; Fernández J; Ginès P; Cárdenas A; Ortega R; Navasa M; Barberá JA; Calahorra B; Guevara M; Bataller R; Jiménez W; Arroyo V; Rodés J (2003). Increased carbon monoxide production in patients with cirrhosis with and without spontaneous bacterial peritonitis. Hepatology, 38: 452-459. 194087

Dutton SJ; Hannigan MP; Miller SL (2001). Indoor pollutant levels from the use of unvented natural gas fireplaces in Boulder, Colorado. J Air Waste Manag Assoc, 51: 1654-1661. 021307

Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at http://epa.gov/hero. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISAs) and the Integrated Risk Information System (IRIS).

Ehlers M; Labaze G; Hanakova M; McCloskey D; Wilner G (2009). Alarming levels of carboxyhemoglobin in banked blood. J Cardiothorac Vasc Anesth, 23: 336-338 . 194089

Gosselin NH; Brunet RC; Carrier G (2009). Determination of carboxyhaemoglobin in humans following low-level exposures to carbon monoxide. Inhal Toxicol, 21: 1077-1091. 190946

Hampson NB; Weaver LK (2007). Carbon monoxide poisoning: a new incidence for an old disease. Undersea Hyperb Med, 34: 163-168. 190272

Hart CL; Smith GD; Hole DJ; Hawthorne VM (2006). Carboxyhaemoglobin concentration, smoking habit, and mortality in 25 years in the Renfrew/Paisley prospective cohort study. Heart, 92: 321-324. 194092

Hsia CC (2002). Recruitment of lung diffusing capacity: Update of concept and application. Chest, 122: 1774-1783. 193857

Johnson FK; Johnson RA; Durante W; Jackson KE; Stevenson BK; Peyton KJ (2006). Metabolic syndrome increases endogenous carbon monoxide production to promote hypertension and endothelial dysfunction in obese Zucker rats. Am J Physiol Regul Integr Comp Physiol, 290: 601-608. 193874

Lamberto C; Nunes H; Le Toumelin P; Duperron F; Valeyre D; Clerici C (2004). Membrane and capillary blood components of diffusion capacity of the lung for carbon monoxide in pulmonary sarcoidosis: relation to exercise gas exchange. Chest, 125: 2061-2068. 193845

Levesque B; Allaire S; Prud'homme H; Dupuis K; Bellemare D (2000). Air quality monitoring during indoor monster truck and car demolition shows. J Expo Sci Environ Epidemiol, 10: 58-65. 011886

Lim S; Groneberg D; Fischer A; Oates T; Caramori G; Mattos W; Adcock I; Barnes PJ; Chung KF (2000). Expression of heme oxygenase isoenzymes 1 and 2 in normal and asthmatic airways: Effect of inhaled corticosteroids. Am J Respir Crit Care Med, 162: 1912-1918. 126969

Mahoney JJ; Vreman HJ; Stevenson DK; Van Kessel AL (1993). Measurement of carboxyhemoglobin and total hemoglobin by five specialized spectrophotometers (CO-oximeters) in comparison with reference methods. Clin Chem, 39: 1693-1700. 013859

Marks GS; Vreman HJ; McLaughlin BE; Brien JF; Nakatsu K (2002). Measurement of endogenous carbon monoxide formation in biological systems. Antioxid Redox Signal, 4: 271-277. 030616

Marvisi M; Bassi E; Bonassi R; Civardi G; Delsignore R (2007). DLCO correlates with intestinal inflammation in ulcerative colitis, but albuminuria does not. Minerva Gastroenterol Dietol, 53: 321-7. 186702

Merx MW; Flogel U; Stumpe T; Godecke A; Decking UK; Schrader J (2001). Myoglobin facilitates oxygen diffusion. FASEB J, 15: 1077-1079. 002006

Monma M; Yamaya M; Sekizawa K; Ikeda K; Suzuki N; Kikuchi T; Takasaka T; Sasaki H (1999). Increased carbon monoxide in exhaled air of patients with seasonal allergic rhinitis. Clin Exp Allergy, 29: 1537-1541. 180426

Morimatsu H; Takahashi T; Maeshima K; Inoue K; Kawakami T; Shimizu H; Takeuchi M; Yokoyama M; Katayama H; Morita K (2006). Increased heme catabolism in critically ill patients: Correlation among exhaled carbon monoxide, arterial carboxyhemoglobin, and serum bilirubin IXalpha concentrations. Am J Physiol Lung Cell Mol Physiol, 290: L114-L119. 194097

Muchova L; Wong RJ; Hsu M; Morioka I; Vitek L; Zelenka J; Schröder H; Stevenson DK (2007). Statin treatment increases formation of carbon monoxide and bilirubin in mice: A novel mechanism of in vivo antioxidant protection. Can J Physiol Pharmacol, 85: 800-810. 194098

Neto CA; Yanagihara JI; Turri F (2008). A carbon monoxide transport model of the human respiratory system applied to urban atmosphere exposure analysis. J Braz Soc Mech Sci & Eng, 30: 253-260. 194672

Paredi P; Biernacki W; Invernizzi G; Kharitonov SA; Barnes PJ (1999). Exhaled carbon monoxide levels elevated in diabetes and correlated with glucose concentration in blood: A new test for monitoring the disease? Chest, 116: 1007-1011. 194102

Paredi P; Shah PL; Montuschi P; Sullivan P; Hodson ME; Kharitonov SA; Barnes PJ (1999). Increased carbon monoxide in exhaled air of patients with cystic fibrosis. Thorax, 54: 917-20. 118798

Pelham TW; Holt LE; Moss MA (2002). Exposure to carbon monoxide and nitrogen dioxide in enclosed ice arenas. Occup Environ Med, 59: 224-233. 025716

Pesola GR; Huggins G; Sherpa TY (2006). Abnormal predicted diffusion capacities in healthy Asians: an inequality with a solution. Respiration, 73: 799-807. 193855

Pesola GR; Sunmonu Y; Huggins G; Ford JG (2004). Measured diffusion capacity versus prediction equation estimates in blacks without lung disease. Respiration, 71: 484-492. 193842

Prommer N; Schmidt (2007). Loss of CO from the intravascular bed and its impact on the optimised CO-rebreathing method. Eur J Appl Physiol, 100: 383-391. 180421

Proudman SM; Stevens WM; Sahhar J; Celermajer D (2007). Pulmonary arterial hypertension in systemic sclerosis: the need for early detection and treatment. J Intern Med, 37: 485-94. 186705

Richardson RS; Noyszewski EA; Saltin B; Gonzalez-Alonso J (2002). Effect of mild carboxy-hemoglobin on exercising skeletal muscle: Intravascular and intracellular evidence. Am J Physiol, 283: R1131-R1139. 037513

Sakamaki F; Oya H; Nagaya N; Kyotani S; Satoh T; Nakanishi N (2002). Higher prevalence of obstructive airway disease in patients with thoracic or abdominal aortic aneurysm. J Vasc Surg, 36: 35-40. 186706

Schachter LM; Dixon J; Pierce RJ; O'Brien P (2003). Severe gastroesophageal reflux is associated with reduced carbon monoxide diffusing capacity. Chest, 123: 1932-8. 186707

Scharte M; Bone HG; Van Aken H; Meyer J (2000). Increased carbon monoxide in exhaled air of critically ill patients. Biochem Biophys Res Commun, 267: 423-426. 194112

Scharte M; von Ostrowski TA; Daudel F; Freise H; Van Aken H; Bone HG (2006). Endogenous carbon monoxide production correlates weakly with severity of acute illness. Eur J Anaesthesiol, 23: 117-122. 194115

Shimazu T (2001). Half-life of blood carboxyhemoglobin. Chest, 119: 661-663. 016331

Shimazu T; Ikeuchi H; Sugimoto H; Goodwin CW; Mason AD Jr; Pruitt BA Jr (2000). Half-life of blood carboxyhemoglobin after short-term and long-term exposure to carbon monoxide. J Trauma, 49: 126-131. 016420

Sylvester KP; Patey RA; Rafferty GF; Rees D; Thein SL; Greenough A (2005). Exhaled carbon monoxide levels in children with sickle cell disease. Eur J Pediatr, 164: 162-165. 191954

Takeuchi A; Vesely A; Rucker J; Sommer LZ; Tesler J; Lavine E; Slutsky AS; Maleck WA; Volgyesi G; Fedorko L; Iscoe S; Fisher JA (2000). A simple "new" method to accelerate clearance of carbon monoxide. Am J Respir Crit Care Med, 161: 1816-1819. 005675

Tarquini R; Masini E; La Villa G; Barletta G; Novelli M; Mastroianni R; Romanelli RG; Vizzutti F; Santosuosso U; Laffi G (2009). Increased plasma carbon monoxide in patients with viral cirrhosis and hyperdynamic circulation. Am J Gastroenterol, 104: 891-897. 194117

Terzano C; Conti V; Petroianni A; Ceccarelli D; De Vito C; Villari P (2009). Effect of Postural Variations on Carbon Monoxide Diffusing Capacity in Healthy Subjects and Patients with Chronic Obstructive Pulmonary Disease. Respiration, 77: 51-57. 108046

Tran TT; Martin P; Ly H; Balfe D; Mosenifar Z (2007). Carboxyhemoglobin and its correlation to disease severity in cirrhotics. J Clin Gastroenterol, 41: 211-215. 194120

Vreman HJ; Wong RJ; Kadotani T; Stevenson DK (2005). Determination of carbon monoxide (CO) in rodent tissue: effect of heme administration and environmental CO exposure. Anal Biochem, 341: 280-289. 193786

Vreman HJ; Wong RJ; Stevenson DK; Smialek JE; Fowler DR; Li L; Vigorito RD; Zielke HR (2006). Concentration of Carbon Monoxide (CO) in Postmortem Human Tissues: Effect of Environmental CO Exposure. J Forensic Sci, 51: 1182-1190. 098272

Weaver LK; Howe S; Hopkins R; Chan K (2000). Carboxyhemoglobin half-life in carbon monoxide-poisoned patients treated with 100% oxygen at atmospheric pressure. Chest, 117: 801-808. 016421

Whincup P; Papacosta O; Lennon L; Haines A (2006). Carboxyhaemoglobin levels and their determinants in older British men. BMC Public Health, 6: 189-197. 195129

Widdop B (2002). Analysis of carbon monoxide. Ann Clin Biochem, 39: 378-391. 030493

Wu L; Wang R (2005). Carbon monoxide: endogenous production, physiological functions, and pharmacological applications. Pharmacol Rev, 57: 585-630. 180411

Yamaya M; Hosoda M; Ishizuka S; Monma M; Matsui T; Suzuki T; Sekizawa K; Sasaki H (2001). Relation between exhaled carbon monoxide levels and clinical severity of asthma. Clin Exp Allergy, 31: 417-422. 180130

Yamaya M; Sekizawa K; Ishizuka S; Monma M; Mizuta K; Sasaki H (1998). Increased carbon monoxide in exhaled air of subjects with upper respiratory tract infections. Am J Respir Crit Care Med, 158: 311-314. 047525

Yasuda H; Sasaki T; Yamaya M; Ebihara S; Maruyama M; Kanda A; Sasaki H (2004). Increased arteriovenous carboxyhemoglobin differences in patients with inflammatory pulmonary diseases. Chest, 125: 2160-2168. 191955

Yasuda H; Yamaya M; Nakayama K; Sasaki H (2005). Blood carbon monoxide will increase from a decline in pulmonary function alone 7. Am J Respir Crit Care Med, 172: 1231-1232. 102183

Yasuda H; Yamaya M; Yanai M; Ohrui T; Sasaki H (2002). Increased blood carboxyhaemoglobin concentrations in inflammatory pulmonary diseases. Thorax, 57: 779-783. 035206

Yerushalmi R; Kramer MR; Rizel S; Sulkes A; Gelmon K; Granot T; Neiman V; Stemmer SM (2009). Decline in pulmonary function in patients with breast cancer receiving dose-dense chemotherapy: a prospective study. Ann Oncol, 20: 437-440. 186711

Zegdi R; Perrin D; Burdin M; Boiteau R; Tenaillon A (2002). Increased endogenous carbon monoxide production in severe sepsis. Intensive Care Med, 28: 793-796. 037461

Annex C. Epidemiology Studies

Table C-1. Studies of CO exposure and cardiovascular morbidity.

Study	Design	Concentrations	CO Effect Estimates (95% CI)
CHANGES IN HEART RATE AND HEART RATE VARIABILITY			
Author: Chan et al. (2005, 088988) **Period of Study:** December 2001-February 2002 **Location:** Taipei, Taiwan	**Health Outcome:** Various measures of HRV via ambulatory ECG (Holter system) **Study Design:** Panel **Statistical Analyses:** Linear regression (mixed effects) **Age Groups Analyzed:** 40-75 yr **Sample Description:** 83 patients from the National Taiwan University Hospital	**Averaging Time:** 1−h ma **Mean (SD) unit:** 1.1 ppm **Range (Min, Max):** 0.1, 7.7 **Copollutant**: NR	**Increment:** NR **RR Estimate** [Lower CI, Upper CI] **Lags examined (-h ma):** 1, 2, 3, 4, 5, 6, 7, 8 CO had no statistically significant effect on SDNN, rMSSD, LF, HF.
Author: Chuang (2008, 155731) **Period of Study:** NR **Location: Boston, MA**	**Health Outcome:** HRV (changes in ST-segment) **Study Design:** Panel **Statistical Analyses:** Linear additive models; Additive mixed logistic regression models **Age Groups Analyzed:** 43-75 **Sample Description:** 48 patients with documented CAD who had undergone percutaneous coronary intervention for acute coronary syndrome (acute MI or unstable angina pectoris) or who had worsened CAD	**Averaging Time:** 12 h, 24 h **Mean (SD) unit:** 12 h: 0.48ppm, 24 h: 0.46ppm **Range (Min, Max):** 12-h: 25th percentile- 0.35, 75th percentile- 0.62, Max- 1.88; 24 h: 25th percentile- 0.37, 75th percentile- 0.62, Max- 1.56 **Copollutant**: NR	**Increment:** NR **RR Estimate** [Lower CI, Upper CI] **Lags examined:** NR **Estimated RR for ST-segment depression ≥0.1 mm (ppm): 12-h:** 0.70 (0.58-0.84) **24 h:** 0.84 (0.68-1.03) **Estimated ST-segment change, mm (ppm):** 12-h mean: 0.013 (0.003-0.024) **24 h mean:** 0.007 (-0.004-0.019) CO not significantly associated with ST-segment depression.
Author: Dales et al. (2004, 099036) **Period of Study:** NR **Location:** Toronto, Canada.	**Health Outcome:** Various measures of HRV via Holter system **Study Design:** Panel **Statistical Analyses:** Linear regression (mixed effects) **Age Groups Analyzed:** 51-88 yr (mean 65 yr) **Sample Description:** 36 subjects with pre-existing CAD	**Averaging Time:** 24 h **Mean (SD) unit:** 2.40 ppm (95th percentile) Personal monitoring **Range (Min, Max):**0.4, 16.5 **Copollutant: correlation** $PM_{2.5}$: r = 0.17	**Increment:** NR **Regression co-efficient** [Lower CI, Upper CI] **Lags examined:** NR CO had no statistically significant effect on LF, HF, HFLFR, SDNN among those taking beta-blockers, whereas CO had a positive effect on SDNN among those not taking beta-blockers. Slope = 0.0111 (0.002-0.020, p = 0.02)

Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at http://epa.gov/hero. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISAs) and the Integrated Risk Information System (IRIS).

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Gold et al. (2000, 011432) **Period of Study:** June-September 1997 **Location:** Boston, MA	**Health Outcome (ICD9 or ICD10):** Heart rate and various measures of HRV via Holter system **Study Design:** Panel/Cohort **Statistical Analyses:** Linear regression (fixed effects/random effects) **Age Groups Analyzed:** 53-87 yr **Sample Description:** 21 active Boston residents observed up to 12 times.	**Averaging Time:** 24 h **Mean (SD) unit:** 0.47 ppm **Range (Min, Max):** 0.12, 0.82 **Copollutant:** NR	**Increment:** 0.6 ppm **% Change [Lower CI, Upper CI]** **Lags examined:** 24 h No significant effect with CO (no results recorded)
Author: Gold et al. (2005, 087558) **Period of Study:** June-September 1999 **Location:** Boston, MA	**Health Outcome:** ST- segment. **Study Design:** Panel **Statistical Analyses:** Linear regression (mixed models) **Age Groups Analyzed:** 61-88 yr **Sample Description:** 24 active Boston residents each observed up to 12 times.	**Averaging Time:** 1 h, 24 h **Mean (SD) unit:** NR **Range (Min, Max):** (ppm) (personal monitoring) 10th = 0.20 90th = 1.08 **Copollutant:** NR	**Increment:** NR **RR Estimate [Lower CI, Upper CI]** **Lags examined:** 1 24 h Although CO was associated with ST-segment depression in single pollutant models, this result did not persist in multiple pollutant models.
Author: Goldberg et al. (2008, 180380) **Period of Study:** July 2002-October 2003 **Location:** Montreal, Quebec	**Health Outcome:** Oxygen saturation and heart rate **Study Design:** Panel **Statistical Analyses:** Mixed regression models **Age Groups Analyzed:** 50-85 yr **Sample Description:** 31 subjects with CHF and limits in physical functioning in the Heart Failure and Heart Transplant Center at the McGill University Health Center	**Averaging Time:** 24 h **Mean (SD) unit:** NR **Range (Min, Max):** NR **Copollutant:** $PM_{2.5}$: r = 0.72 NO_2: r = 0.84 SO_2 and NO_2: r = 0.43	**Increment:** NR **Adjusted Mean Difference [Lower CI, Upper CI]** **Lags examined:** 0, 1, 2 **Oxygen Saturation:** Lag 0: 0.004 ppm (-0.060, 0.067) Lag 1: -0.001 ppm (-0.066, 0.065) 3-day: -0.005 ppm (-0.098. 0.088) **Pulse Rate:** Lag 0: 0.011 ppm (-0.290, 0.312) Lag 1: 0.227 ppm (-0.080,0.535) 3-day: 0.245 ppm (-0.209, 0.700)
Author: Holguin et al. (2003, 057326) **Period of Study:** February-April 2000 **Location:** Mexico City, Mexico	**Health Outcome:** Various measures of HRV via ECG **Study Design:** Panel **Statistical Analyses:** GEE **Age Groups Analyzed:** 60-96 yr (mean age 79 yr) **Sample Description:** 34 patients who were permanent residents of a nursing home in the Northeast metropolitan area.	**Averaging Time:** 24 h **Mean (SD) unit:** 3.3 ppm **Range (Min, Max):** 1.8, 4.8 **Copollutant:** NR	**Increment:** 10 ppm **Regression Coefficients [Lower CI, Upper CI]** **Lags examined:** 0 **Lag 0:** HF: 0.003 (-0.004 to 0.001) LF: 0.001 (-0.006 to 0.008) LF/HF: 0.001 (-0.005 to 0.002)

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Ibald-Mulli et al. (2004, 087415) **Period of Study:** 1998-1999 **Location:** Helsinki, Finland Erfurt, Germany Amsterdam, Netherlands	**Health Outcome:** BP and HR via ECG **Study Design:** Panel **Statistical Analyses:** Linear regression **Age Groups Analyzed:** ≥ 50 yr **Sample Description:** 131 nonsmokers with coronary heart disease	**Averaging Time:** 24 h **Mean (SD) unit:** Amsterdam: 0.6 mg/m^3 Erfurt: 0.4 mg/m^3 Helsinki: 0.4 mg/m^3 **Range (Min, Max):** Amsterdam: 0.4, 1.6 Erfurt: 0.1, 2.5 Helsinki: 0.1, 1.0 **Copollutant:** Amsterdam $PM_{2.5}$: r = 0.58 µg/m^3 NO_2: r = 0.76 µg/m^3 SO_2: r = 0.50 mg/m^3 UFP: r = 0.22 n/cm^3 ACP: r = 0.60 n/cm^3 Erfurt $PM_{2.5}$: r = 0.77 µg/m^3 NO_2: r = 0.86 µg/m^3 SO_2: r = 0.68 mg/m^3 UFP: r = 0.72 n/cm^3 ACP: r = 0.78 n/cm^3 Helsinki $PM_{2.5}$: r = 0.40 µg/m^3 NO_2: r = 0.32 µg/m^3 SO_2: r = 0.19 mg/m^3 UFP: r = 0.35 n/cm^3 ACP: r = 0.51 n/cm^3	**Increment:** NR **RR Estimate [Lower CI, Upper CI]** **Lags examined:** 0, 1, 2, 3 Results presented graphically
Author: Liao et al. (2004, 056590) **Period of Study:** 1996-1998 **Location:** Forsyth County, NC; Selected suburbs of Minneapolis, MN; Jackson, MI	**Health Outcome:** Heart rate & various rates of HRV. **Study Design:** Cohort **Statistical Analyses:** Linear regression **Age Groups Analyzed:** 45-64 yr (mean 62 yr) **Sample Description:** 6,784 study subjects from the atherosclerosis risk in communities study	**Averaging Time:** 24 h **Mean (SD) unit:** 0.65 ppm (0.44) **Range (Min, Max):** NR **Copollutant:** NR	**Increment:** 0.44 ppm **Regression coefficients Lags examined:** 1 **Lag 1:** HF (log transformed): -0.033 LF (log transformed): 0.006 SDNN: -0.274 Heart rate (bpm): 0.404* Confidence intervals: not recorded *p < 0.05

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Min (2009, 199514) **Period of Study:** December 2003 – January 2004 **Location: Tae-in island community in South Korea**	**Health Outcome:** HRV **Study Design:** Panel **Statistical Analyses:** Time-lag model **Age Groups Analyzed:** 20-87 **Sample Description:** 986 subjects, 367 with metabolic syndrome (MetS), 619 without MetS	**Averaging Time:** 8 h **Mean (SD) unit:** 0.454 ppm (0.560) **Range (Min, Max):** 0.100, 7.200 ppm **Copollutant:** PM_{10}	**Increment:** NR **Estimated % Increase in subjects with MetS** [Lower CI, Upper CI] **Lags examined:** 0-1, 1-2, 2-3, 3-4, 4-5, 5-6 Single pollutant: Lag 0-1: Log(SDNN): -0.29 (-0.59, 0.00), p < 0.1 Log(LF): -0.34 (-1.02, 0.33) Log(HF): -0.67 (-1.41, 0.08), p < 0.1 Lag 1-2: Log(SDNN): -0.45 (-0.81, -0.10), p < 0.05 Log(LF): -0.65 (-1.46, 0.17) Log(HF): -1.04 (-1.94, -0.14), p < 0.05 Lag 2-3: Log(SDNN): -0.28 (-0.57, 0.02), p < 0.1 Log(LF): -0.19 (-0.87, 0.48) Log(HF): -0.82 (-1.57, -0.07), p < 0.05 Lag 3-4: Log(SDNN): -0.18 (-0.47, 0.10) Log(LF): -0.14 (-0.80, 0.51) Log(HF): -0.46 (-1.19, 0.27) Lag 4-5: Log(SDNN): -0.20 (-0.49, 0.09) Log(LF): -0.36 (-1.04, 0.31) Log(HF): -0.42 (-1.17, 0.33) Lag 5-6: Log(SDNN): 0.13 (-0.18, 0.44) Log(LF): 0.50 (-0.21, 1.20) Log(HF): -0.03 (-0.81, 0.76) Co-pollutant (with PM_{10}): Lag 0-1: Log(SDNN): -0.25 (-0.56, 0.05) Log(LF): -0.35 (-1.04, 0.31) Log(HF): -0.67 (-1.44, 0.10), p<0.1 Lag 1-2: Log(SDNN): -0.48 (-0.88, -0.09), p<0.05; Log(LF): -0.72 (-1.63, 0.18); Log(HF): -1.09 (-2.09, -0.09), p<0.05 Lag 2-3: Log(SDNN): -0.35 (-0.67, -0.03), p < 0.05 Log(LF): -0.17 (-0.90, 0.56) Log(HF): -0.78 (-1.59, 0.03), p < 0.1 Lag 3-4: Log(SDNN): -0.22 (-0.55, 0.11) Log(LF): -0.11 (-0.86, 0.63) Log(HF): -0.34 (-1.17, 0.49) Lag 4-5: Log(SDNN): -0.18 (-0.48, 0.12); Log(LF): -0.21 (-0.89, 0.48); Log(HF): -0.37 (-1.14, 0.40) Lag 5-6: Log(SDNN): 0.17 (-0.14, 0.49) Log(LF): 0.54 (-0.18, 1.25) Log(HF): 0.00 (-0.80, 0.80) No significant results for subjects without MetS.

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Park et al. (2005, 057331) **Period of Study:** 2000-2003 **Location:** Boston, MA	**Health Outcome:** Various measures of HRV via ECG **Study Design:** Panel/Cohort **Statistical Analyses:** Linear regression **Age Groups Analyzed:** 21-81 yr **Sample Description:** 497 men from the normative aging study in Greater Boston area	**Averaging Time:** 24 h **Mean (SD) unit:** 0.50 ppm **Range (Min, Max):** 0.13, 1.8 **Copollutant:** NR	**Increment:** 0.24 ppm **% Change in HRV [Lower CI, Upper CI]** **Lags examined:** 4-h ma, 24-h ma, 48-h ma Lag 4-h ma: SDNN (Log10): 2.0 (-2.9 to 7.3) HF (Log10): 8.8 (-4.6 to 24.1) LF(Log10): 3.2 (-7.0 to 14.6) LF:HF(Log10): -5.1 (-13.5 to 4.1) Lag 24-h ma: SDNN (Log10): -2.2 (-7.7 to 3.6) HF (Log10): -13.2 (-25.4 to 1.0) LF(Log10): -0.6 (-11.9 to 12.1) LF:HF(Log10): 14.5 (2.9-27.5) Lag 48-h ma: SDNN(Log10): -3.4 (-10.2 to 3.9) HF (Log10): -13.8 (-.28.9 to 4.4) LF (Log10): -2.4 (-16.2 to 13.6) LF:HF (Log10): 13.2 (-1.1 to 29.6)
Author: Peters et al. (1999, 011554) **Period of Study:** 1984-1985 **Location:** Augsburg, Germany	**Health Outcome:** Heart rate **Study Design:** Cohort **Statistical Analyses:** Linear regression (GEE) **Age Groups Analyzed:** 25-64 yr **Sample Description:** 2681 men and women who participated in the MONICA study	**Averaging Time:** 24 h **Mean (SD) unit:** During air pollution episode: 4.54 mg/m^3 Outside air pollution episode: 4.51 mg/m^3 **Range (Min, Max):** During air pollution episode: 2.39, 6.85 Outside air pollution episode: 0.91, 11.51 **Copollutant:** NR	**Increment:** 6.6 mg/m^3 **Mean Change in Heart Rate (beats/min) [Lower CI, Upper CI]** **Lags examined:** 0, 5-day avg All Lag 0: 0.97 (0.02-1.91) Lag 5-day avg: 0.70 (-0.09 to 1.48) Men Lag 0: 0.95 (-0.37 to 2.27) Lag 5-day avg: 0.91 (-0.25 to 2.07) Women Lag 0: 0.98 (-0.37 to 2.34) Lag 5-day avg: 0.52 (-0.55 to 1.59)
Author: Riojas-Rodriguez et al. (2006, 156913) **Period of Study:** December 2001-April 2002 **Location:** Mexico City, Mexico	**Health Outcome:** Various measures of HRV via Holter system **Study Design:** Panel **Statistical Analyses:** Linear regression (mixed effects models) **Age Groups Analyzed:** 25-76 yr (mean 55 yr) **Sample Description:** 30 patients from the Outpatient Clinic of the National Institute of Cardiology of Mexico	**Averaging Time:** 24 h **Mean (SD) unit:** 2.9 ppm (personal monitor) **Range (Min, Max):** 0.1, 18.0 **Copollutant:** NR	**Increment:** 1 ppm **Regression Coefficients [Lower CI, Upper CI]** **Lags examined (per min):** 5, 10 Lag 5 min: HF: -0.006 (-0.023 to 0.010) LF: -0.024 (-0.041 to -0.007) VLF: -0.034 (-0.061 to -0.007) Notes: VLF = Very low frequency
Author: Schwartz et al. (2005, 074317) **Period of Study:** 1999 **Location:** Boston, MA	**Health Outcome:** Measures of HRV via Holter system **Study Design:** Panel **Statistical Analyses:** Linear regression (hierarchical model) **Age Groups Analyzed:** 61-89 yr **Sample Description:** 28 subjects living at or near an apartment complex located on the same street as the Harvard School of Public Health	**Averaging Time:** 24 h **Mean (SD) unit:** NR **Range (Min, Max):** ppm 25th = 0.38; 75th = 0.54 **Copollutant:** correlation $PM_{2.5}$: r = 0.61 NO_2: r = 0.55 SO_2: r = -0.18 O_3: r = 0.21	**Increment:** 0.16 ppm **% Change in HRV [Lower CI, Upper CI]** **Lags examined:** 24 h, 1 h Lag 1 h: SDNN: -2.6 (-5.6 to 0.5); rMSSD: -3.9 (-10.6 to 3.3); PNN50: -3.5 (-13.7 to 8.0); LF:HF: 4.5 (-1.2 to10.5) Lag 24 h: SDNN: -4.2 (-0.6 to -7.7); rMSSD: -10.2 (-2.4 to -17.4); PNN50: -14.8 (-3.0 to -25.2); LF:HF: 6.2 (-0.6 to 13.4)

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Tarkiainen et al. (2003, 053625) **Period of Study:** October 1997-May 1998 **Location:** Kuopio, Finland	**Health Outcome:** Various measures of HRV via Ambulatory ECG (Holter system) **Study Design:** Panel **Statistical Analyses**: ANOVA for repeated errors (GLM) **Age Groups Analyzed:** 55-68 yr **Sample Description:** 6 male patients with angiographically- verified CAD	**Averaging Time:** 24 h **Mean (SD) unit:** 4.6 ppm (max of CO episode) (personal monitoring) **Range (Min, Max):** 0.5, 27.4 (max of CO episode) **Copollutant:** NR	**Increment:** NR **RR Estimate [Lower CI, Upper CI]** **Lags examined:** 5 min prior to CO episode, 5 min during CO episode CO had no statically significant effect on NN, SDNN or rMSSD. However, during high CO exposure (>2.7 ppm), CO was associated with an increase in rMSSD of 2.4ms (p=0.034).
Author: Timonen et al. (2006, 088747) **Period of Study:** 1998-1999 **Location:** 3 Cities in Europe: Amsterdam, Netherlands; Erfert, Germany; Helsinki, Finland	**Health Outcome:** Stable CAD: Various measures of HRV via ambulatory ECG (Holter system) **Study Design: Panel** **Statistical Analyses:** Linear regression (mixed model) **Age Groups Analyzed:** Mean age across 3 cities; 64-71 yr. **Sample Description:** 131 subjects with stable CAD followed for 6 mo with biweekly clinical visits.	**Averaging Time:** 24 h **Mean (SD) unit:** Amsterdam: 0.6 mg/m^3 Erfert: 0.4 mg/m^3 Helsinki: 0.4 mg/m^3 **Range (Min, Max):** Amsterdam: 0.4, 1.6 Erfert: 0.1, 2.5 Helsinki: 0.1, 1.0 **Copollutant:** correlation Amsterdam: $PM_{2.5}$: r = 0.58 NO_2: r = 0.76 Erfert: PM_{10}: r = 0.77 NO_2: r = 0.86 Helsinki: PM_{10}: r = 0.40 NO_2: r = 0.32	**Increment:** 1 mg/m^3 **Regression co-efficient [Lower CI, Upper CI]** **Lags examined (days):** 0, 1, 2, 3, 5-day avg SDNN: Lag 0: -1.21 (-4.44 to 2.03); Lag 1: -1.71 (-6.05 to 2.63); Lag 2: -5.69 (-10.7 to -0.72); Lag 3: 0.66 (-3.83 to 5.15); 5-day avg: -3.60 (-9.88 to 2.68) HF: Lag 0: 5.0 (-15.1 to 25.1); Lag 1: -2.0 (-37.1 to 33.1); Lag 2: -30.7 (-59.8 to -1.5); Lag 3: -9.3 (-35.8 to -17.3); 5-day avg: -15.2 (-53.0 to 22.6) LF/HF: Lag 0: -3.6 (-21.8 to 14.5); Lag 1: -28.6 (-52.0 to -5.3); Lag 2: -10.1 (-36.9 to 16.7); Lag 3: 7.7 (-16.5 to 31.9); 5-day avg: -16.9 (-51.2 to 17.3)
Author: Wheeler et al. (2006, 088453) **Period of Study:** 1999-2000 **Location:** Atlanta, GA	**Health Outcome:** Various measures of HRV via Holter system **Study Design:** Panel **Statistical Analyses:** Linear regression (mixed effects models) **Age Groups Analyzed:** Mean 65 yr;IQR 55-73 yr **Sample Description:** 18 subjects with COPD and 12 subjects with recent MI.	**Averaging Time:** 1 h **Mean (SD) unit:** 362.0 ppb **Range (Min, Max):** 25th = 221.5; 75th = 398.1 **Copollutant:** correlation $PM_{2.5}$: r = 0.43	**Increment:** NR **RR Estimate [Lower CI, Upper CI] ; lag:** **Lags examined (h ma):** 1, 4, 24 No CO results reported.

Study	Design	Concentrations	CO Effect Estimates (95% CI)
ONSET OF CARDIAC ARRHYTHMIA			
Author: Berger et al. (2006, 098702) **Period of Study:** October 2000-April 2001 **Location:** Erfurt, Germany	**Health Outcome:** Runs of supraventricular and ventricular tachycardia recorded via 24-h ECG. **Study Design:** Panel **Statistical Analyses:** Poisson regression (GAM) linear regression **Age Groups Analyzed:** 52-76 yr (mean 76 yr) **Sample Description:** 57 men with CHD	**Averaging Time:** 24 h **Mean (SD) unit:** 0.52 mg/m^3 **Range (Min, Max):** 0.11, 1.93 **Copollutant: correlation** NR	**Increment:** All: 0.27 mg/m^3 5-day avg: 0.22 mg/m^3 **RR Estimate [Lower CI, Upper CI]** **Lags examined (h):** 0, 0-23, 24-47, 48-71, 72-95, 5-day avg Supraventricular extrasystoles: Lag 0: 1.18 (1.00-1.38) Lag 0-23: 1.16 (1.02-1.31); Lag 24-47: 1.13 (1.00-1.28); Lag 48-71: 1.18 (1.03-1.36); Lag 72-95: 1.08 (0.98-1.20); 5-day avg: 1.18 (1.04-1.35) Mean % Change [Lower CI, Upper CI] Hourly Lags examined: 0, 0-23, 24-47, 48-71, 72-95, 5-day avg Ventricular extrasystoles: Lag 0: 0.0 (-4.1 to 4.4); Lag 0-23: 1.1 (-3.3 to 5.7); Lag 24-47: 1.9 (-2.6 to 6.6); Lag 48-71: 4.2 (-0.3 to 8.9); Lag 72-95: 2.7 (-1.3 to 6.9); 5-day avg: 3.0 (-1.8 to 8.0)
Author: Dockery et al. (2005, 078995) **Period of Study:** 1995-2002 **Location:** Boston, MA	**Health Outcome:** Tachyarrhythmias: **Study Design:** Panel **Statistical Analyses:** Logistic regression (GEE) **Age Groups Analyzed:** 19-90 yr; mean 64 yr **Sample Description:** 203 cardiac patients with ICDs within 40km of air monitoring site at Harvard School of Public Health, Boston	**Averaging Time:** 24 h **Mean (SD) unit:** NR **Range (Min, Max):** 25th = 0.53; 75th = 1.02 **Copollutant:** NR	**Increment:** 0.48 ppm **OR for Ventricular Arrhythmia [Lower CI, Upper CI]** **Lags examined (days):** 0, 1, 2, 3 Lag 2-day ma: 1.14 (0.95-1.29) Among those who had an arrhythmia: within 3 days: 1.65 (1.17-2.33) later than 3 days: 1.04 (0.83-1.29)
Author: Metzger et al. (2007, 092856) **Period of Study:** 1993-2002 **Location:** Atlanta, GA	**Health Outcome:** Cardiac arrhythmia, ICD, ventricular tachyarrhythmia **Study Design:** Panel **Statistical Analyses:** Logistic regression (GEE) **Age Groups Analyzed:** 15-88 yr **Sample Description:** 518 patients with ICDs with at least one ventricular tachyarrhythmic event	**Averaging Time:** 1 h **Mean (SD) unit:** 1.7 ppm **Range (Min, Max):** 0.1, 7.7 **Copollutant:** NR	**Increment**: 1 ppm O**R for Tachyarrhythmic event [Lower CI, Upper CI]** **Lags examined (days):** 0 Results for all events Lag 0: 0.999 (0.970-1.028) Events resulting in cardiac pacing or defibrillation Lag 0: 1.008 (0.964-1.054) Events resulting defibrillation Lag 0: 1.012 (0.925-1.10.7)

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Peters et al. (2000, 011347) **Period of Study:** 1995-1997 **Location:** Eastern Massachusetts	**Health Outcome:** Defibrillated discharges for ventricular tachycardia or fibrillation **Study Design:** Panel **Statistical Analyses:** Conditional logistic regression **Age Groups Analyzed:** Mean 62 yr **Sample Description:** 100 patients with ICDs	**Averaging Time:** 24 h **Mean (SD) unit:** 0.58 ppm **Range (Min, Max):** 25th = 0.43; 75th = 0.66 **Copollutant: correlation** PM_{10}: r = 0.51 $PM_{2.5}$: r = 0.56 NO_2: r = 0.71 SO_2: r = 0.41 O_3: r = -0.40	**Increment:** 0.65 ppm (Lags 0, 1, 2, 3); 0.42 ppm (Lag 5-day mean) **OR for Defibrillated Discharge [Lower CI, Upper CI]** Lags examined (days): 0, 1, 2 ,3, 5-day mean At least one discharge: Lag 0: 1.07 (0.62-1.86); Lag 1: 1.06 (0.61-1.85); Lag 2: 1.05 (0.62-1.77); Lag 3: 0.09 (0.65-1.83); Lag 5-day mean: 1.23 (0.71- 2.12) At least 10 discharges: Lag 0: 1.12 (0.54-2.32); Lag 1: 1.13 (0.54-2.33); Lag 2: 1.62 (0.85-3.09); Lag 3: 1.98 (1.05-3.72); Lag 5-day mean: 1.94 (1.01-.75)
Author: Rich et al. (2004, 055631) **Period of Study:** February-December 2000 **Location:** Vancouver, Canada	**Health Outcome:** Cardiac arrhythmia via patients ICD **Study Design:** Case crossover **Statistical Analyses:** Conditional logistic regression **Age Groups Analyzed:** 15-85 yr **Sample Description:** 34 patients who experienced at least 1 ICD discharge (8,201 person days)	**Averaging Time:** 24 h **Mean (SD) unit:** 553.8 ppb **Range (Min, Max):** IQR: 162.7 **Copollutant: correlation** PM_{10}: r = 0.40 SO_2: r =0.75 NO_2: r =0.68 O_3: r = -0.56	**Increment: NR** **RR Estimate [Lower CI, Upper CI]** **Lags examined (days):** 0, 1, 2, 3 No significant effect (results not reported in table).
Author: Rich et al. (2005, 079620) **Period of Study:** 1995-1999 **Location:** Boston, MA	**Health Outcome:** Ventricular arrhythmias via ICD **Study Design:** Panel/Case crossover **Statistical Analyses:** Conditional logistic regression **Age Groups Analyzed:** All **Sample Description:** 203 patients with implanted ICD at the New England Medical Center	**Averaging Time:** 1 h and 24 h **Mean (SD) unit:** NR **Range (percentiles):** 1 h: 25th = 0.46 75th = 1.04 24 h: 25th = 0.52 75th = 1.03 **Copollutant:** NR	**Increment:** 0.56 ppm; 0.54; 0.51; 0.49 respectively for results shown below **OR Estimate [Lower CI, Upper CI]** Ventricular arrythmia Hours prior to event: 0-2: 1.01 (0.87-1.18) 0-6: 1.00 (0.85-1.17) 0-23: 1.03 (0.84-1.25) 0-47: 1.11 (0.88-1.40)
Author: Rich et al. (2006, 089814) **Period of Study:** 2001 & 2002 **Location:** St. Louis, MO	**Health Outcome:** Ventricular arrhythmia **Study Design:** Case crossover **Statistical Analyses:** Conditional logistic regression **Age Groups Analyzed:** All **Sample Description:** 60 subjects with at least 1 ICD recorded arrhythmia who lived within 40 km of St. Louis – Midwest supersite.	**Averaging Time:** 24 h **Mean (SD) unit:** NR **Range (Min, Max):** 25th = 0.4; 75th = 0.6 **Copollutant:** NR	**Increment:** 0.2 ppm **OR for Ventricular Arrhythmia [Lower CI, Upper CI]** **Lags examined:** 0 to 23-h ma: 0- to 23-h ma: 0.99 (0.80-1.21)

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Rich et al. (2006, 088427) **Period of Study:** 1995-1999 **Location:** Boston, MA	**Health Outcome:** ICD episode of atrial fibrillation **Study Design:** Panel/case crossover **Statistical Analyses:** Conditional logistic regression **Age Groups Analyzed:** All **Sample Description:** 203 patients with ICDs at the New England Medical Center	**Averaging Time:** 1 h and 24 h **Mean (SD) unit:** NR **Range (Min, Max):** 1 h: 25th = 0.46; 75th = 1.04 24 h: 25th = 0.52; 75th = 1.03 **Copollutant:** NR	**Increment:** Lag (hrs) 0: 0.58 ppm Lag (hrs) 0-23: 0.51 ppm **OR for episode of atrial fibrillation [Lower CI, Upper CI]** Lags (h): 0, 0-23 Lag 0: 0.87 (0.56-1.37) Lag 0-23: 0.71 (0.39-1.28)
Author: Sari et al. (2008, 190315) **Period of Study:** June 2007 **Location:** Gaziantep, Turkey	**Health Outcome:** P-wave dispersion (predictors of atrial fibrillation, ventricular arrhythmias and sudden death) via ECG **Study Design:** Case control **Statistical Analyses:** Pearson correlation analysis **Age Groups Analyzed:** Barbecue workers mean age: 33.66 ± 9.43 yr Control group mean age: 35.15 ± 6.78 yr **Sample Description:** 48 healthy males working at various indoor barbecue restaurants for at least 3 yr (avg:15.6 ± 7.1 yr), 51 age-matched healthy men for control group	**Averaging Time:** NR **Mean (SD) unit:** COHb% Indoor barbecue workers: 6.48% ± 1.43 **Control Group:** 2.19% ± 1.30 **Range (Min, Max):** NR **Copollutant:** NR	**Increment:** NR Correlation coefficient for COHb [p-value] **Lags examined:** NR Pmin: -0.132 (0.245) Pmax: 0.215 (0.057) Pd: 0.315 (0.005) QTmin: 0.080 (0.454) QTmax: 0.402 (<0.001) QTd: 0.573 (<0.001) cQTd: 0.615 (<0.001)
Author: Sarnat et al. (2006, 090489) **Period of Study:** 24 wk during the summer and fall of 2000 **Location:** Steubenville, OH	**Health Outcome:** Arrhythmia via ECG measurements **Study Design:** Panel **Statistical Analyses:** Logistic regression **Age Groups Analyzed:** 53-90 yr (mean age 71) **Sample Description:** 32 nonsmoking older adults	**Averaging Time:** 24 h **Mean (SD) unit:** 0.02 ppm **Range (Min, Max):** -0.1, 1.5 **Copollutant:** correlation $PM_{2.5}$: r = 0.45 SO_2: r = 0.62 NO_2: r = 0.66 O_3: r = -0.37	**Increment:** 0.2 ppm **RR Estimate** [Lower CI, Upper CI] ; **lag:** **Lags examined (days):** 1, 2, 3, 4, 5, 5-day ma Lag 5-day ma: Supraventricular ectopy SVE: 0.99 (0.76-1.29) Ventricular ectopy VE: 1.05 (0.75-1.46)
Author: Vedal et al. (2004, 055630) **Period of Study:** 1997-2000 **Location:** Vancouver, Canada	**Health Outcome:** Cardiac arrythmia via patients with ICD **Study Design:** Panel **Statistical Analyses:** Logistic regression (GEE) **Age Groups Analyzed:** Range from 12-77 yr (mean age 53 yr) **Sample Description:** 50 patients who experienced 1 or more arrhythmia event during the 4yr	**Averaging Time:** 24 h **Mean (SD) unit:** 0.6 ppm **Range (Min, Max):** 0.3, 1.6 **Copollutant:** correlation PM_{10}: r = 0.43 SO_2: r = 0.62 NO_2: r = 0.74 O_3: r = -0.52	**Increment:** 0.2 ppm **RR Estimate** [Lower CI, Upper CI] **Lags examined (days):** 0, 1, 2, 3 No significant effect for CO (results shown in plots)

Study	Design	Concentrations	CO Effect Estimates (95% CI)
CARDIAC ARREST			
Author: Levy et al. (2001, 017171) **Period of Study:** 1988-1994 **Location:** Seattle, WA	**Health Outcome:** Out-of-hospital primary cardiac arrest **Study Design:** Case crossover **Statistical Analyses:** Conditional logistic regression **Age Groups Analyzed:** 25-75 yr Sample Description: 362 cases	**Averaging Time:** 24 h **Mean (SD) unit:** 1.79 ppm **Range (Min, Max):** 0.52, 5.92 **Copollutant:** correlation PM_{10}: r = 0.81 SO_2: r = 0.29	**Increment:** NR **RR Estimate** [Lower CI, Upper CI] **Lags examined (days):** 0, 1 Lag 1: 0.99 (0.83-1.18)
Author: Sullivan et al. (2003, 043156) **Period of Study:** 1985-1994 **Location:** Washington State	**Health Outcome:** Out-of-Hospital cardiac arrest **Study Design:** Case crossover **Statistical Analyses:** Conditional logistic regression **Age Groups Analyzed:** All **Sample Description:** 1,542 members of a large health maintenance organization	**Averaging Time:** 24 h **Mean (SD) unit:** 1.92 ppm **Range (Min, Max):** 0.52, 7.21 **Copollutant:** NR	**Increment:** 1.02 ppm **OR Estimate** [Lower CI, Upper CI] **Lags examined (days):** 0, 1, 2 Lag 0: 0.95 (0.85-1.05) Lag 1: 0.97 (0.87-1.08) Lag 2: 0.99 (0.89-1.11)
MYOCARDIAL INFARCTION			
Author: Peters et al. (2001, 016546) **Period of Study:** 1995-1996 **Location:** Boston, MA	**Health Outcome:** Onset of MI **Study Design:** Case crossover **Statistical Analyses:** Conditional logistic regression **Age Groups Analyzed:** All **Sample Description:** 772 participants	**Averaging Time:** 24 h **Mean (SD) unit:** 1.09 **Range (percentiles):** ppm 5th = 0.49 95th = 1.78 **Copollutant:** NR	**Increment:** 2 H-1 ppm; 24 h – 0.6 ppm **OR Estimate** [Lower CI, Upper CI] **Onset of MI:** 2-h prior: 1.22 (0.89-1.67) 24 h prior: 0.98 (0.70-1.36)
Author: Rosenlund et al. (2006, 089796) **Period of Study:** 1992-1994 **Location:** Stockholm, Sweden	**Health Outcome:** MI **Study Design:** Case control **Statistical Analyses:** Logistic regression **Age Groups Analyzed:** 45-70 yr **Sample Description:** 1,397 cases;1,870 controls	**Averaging Time:** **Mean (SD) unit:** 66.8 µg/m^3 (Estimated 30-yr residential exposure) **Range (percentiles):** 5th = 13.9; 95th = 295.7 **Copollutant:** NR	**Increment:** 300 µg/m^3 **OR Estimate** [Lower CI, Upper CI] ; lag: Estimated 30-yr avg exposure All cases: 1.04 (0.89-1.21) Nonfatal cases: 0.98 (0.82-1.16) Fatal cases: 1.22 (0.98-1.52) In-hospital death: 1.16 (0.89-1.51) Out-of-hospital death: 1.36 (1.01-1.84)
Author: Rosenlund et al. (2009, 190309) **Period of Study:** NR **Location:** Stockholm County, Sweden	**Health Outcome:** Fatal and nonfatal MI **Study Design:** Case control **Statistical Analyses:** Various multiple regression models **Age Groups Analyzed:** 15-79 yr **Sample Description:** 43,275 MI cases during 1985-1996; 511,065 controls	**Averaging Time:** 1 yr **Mean (SD) unit:** **Cases:** 64.2 µg/m^3 **Controls:** 55.8 µg/m^3 **Range (percentiles):** Cases: 5th = 7.3; 95th =267.4 Controls: 5th =6.1;95th=261.8 **Copollutant:** PM_{10}, NO_2	**Increment:** NR **OR Estimate** [Lower CI, Upper CI] 5-yr avg exposure All subjects (n = 301,273) All cases: 1.01 (0.97-1.05) Nonfatal cases: 0.94 (0.89-1.00) Fatal cases: 1.14 (1.07-1.21) In-hospital death: 1.00 (0.91-1.10) Out-of-hospital death: 1.23 (1.14-1.32) Restriction to subjects who did not move between population census (n = 80,155) All cases: 1.04 (0.94-1.14) Nonfatal cases: 0.96 (0.87-1.06) Fatal cases: 2.03 (1.59-2.60) In-hospital death: 2.04 (1.35-3.08) Out-of-hospital death: 2.03 (1.50-2.74)

Study	Design	Concentrations	CO Effect Estimates (95% CI)
CHANGES IN BLOOD PRESSURE			
Author: Ibalde-Mulli et al. (2001, 016030) **Period of Study:** 1984-1985 **Location:** Augsburg, Germany	**Health Outcome:** BP–SPB **Study Design:** Cohort **Statistical Analyses:** Gaussian regression for repeated measures **Age Groups Analyzed:** 25-64 yr **Sample Description:** 2,607 men and women 25-64 yr	**Averaging Time:** 24 h **Mean (SD) unit:** 4.1 mg/m^3 **Range (Min, Max):** 1.7, 8.2 **Copollutant:** NR	**Increment:** Lag 0: 5.6 mg/m^3 5-day prior avg **Mean Change** [Lower CI, Upper CI] SPB mmHg Lag 0 (days): All: 0.53 (-0.66 to 1.72); Men: 0.68 (-0.94 to 2.31); Women: 0.51 (-1.31 to 2.19) 5-day prior avg: All: 1.06 (-0.17 to 2.29); Men: 0.92 (-0.87 to 2.70); Women: 0.91 (-0.87 to 2.70)
Author: Zanobetti et al. (2004, 087489) **Period of Study:** 1999-2001 **Location:** Boston, MA	**Health Outcome:** BP **Study Design:** Cohort/Panel **Statistical Analyses:** Random effects **Age Groups Analyzed:** 39-90 yr **Sample Description:** 62 subjects with 631 total visits	**Averaging Time:** 1 h and 120 h avg **Mean (SD) unit:** Same h: 0.81 ppm 120-h avg: 0.66 ppm **Range (Min, Max):** Same h: 10th = 0.48; 90th = 1.22 120-h avg: 10th = 0.48; 90th = 0.86 **Copollutant:** NR	**Increment:** NR **RR Estimate** [Lower CI, Upper CI] CO had no significant effect on BP
CHANGES IN BLOOD MARKERS OF COAGULATION AND INFLAMMATION			
Author: Baccarelli et al. (2007, 090733) **Period of Study:** 1995-2005 **Location:** Milan, Italy	**Health Outcome:** Prothrombin time (PT) and activated partial thromboplastin time (APTT) **Study Design:** Panel **Statistical Analyses:** GAMS **Age Groups Analyzed:** 11-84 yr (mean 43 yr) **Sample Description:** 1,218 healthy individuals who were partners or friends of patients with thrombosis who attended the thrombosis center of the University of Milan.	**Averaging Time:** 1 h **Mean (SD) unit:** NR **Range (percentiles):** Sept-Nov: 25th = 1.36; 75th = 3.52 Dec-Feb: 25th = 2.00; 75th = 4.31 Mar-May: 25th = 1.03; 75th = 2.14 Jun-Aug: 25th = 0.73; 75th = 1.58 **Copollutant:** NR	**Increment:** NR **Regression co-efficient** [Lower CI, Upper CI] **Lags examined (time of blood sampling – avg):** 0, 7, 30 PT: Lag 0: -0.11 (-0.18 to -0.05); Lag 7: -0.07 (-0.14 to 0.01); Lag 30: -0.05 (-0.13 to 0.02) APTT: Lag 0: 0.03 (-0.04 to 0.10); Lag 7: 0.04 (-0.04 to 0.11); Lag 30: 0.06 (-0.01 to 0.14) Notes: CO had no effect on fibrinogen, functional antithrombin, functional protein C, protein C antigen, functional protein S, or free protein S for all lag periods.

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Delfino et al. (2008, 156390) **Period of Study:** 2005-2006 **Location:** Los Angeles, CA	**Health Outcome:** Biomarkers of systemic inflammation **Study Design:** Panel **Statistical Analyses:** Linear mixed-effects models **Age Groups Analyzed:** ≥ 65 yr (mean 85.7 yr) **Sample Description:** 29 nonsmoking subjects with history of CAD living in retirement communities	**Averaging Time:** 24 h **Mean (SD) unit:** 0.78 ± 0.30 ppb **Range (Min, Max):** 0.22, 1.97 **Copollutant (Outdoor):** EC: r = 0.84 OC: r = 0.69 OCprimary: r = 0.73 NO_2: r = 0.78 O_3: r = -0.35 $PM_{0.25}$: r = 0.84 $PM_{0.25-2.5}$: r = 0.14 $PM_{2.5-10}$: r = 0.51	**Increment:** NR Estimated coefficient **Relationship to outdoor air pollutants:** CRP (ng/mL): Lag 0: 847.52; 3-day avg: 728.79; 9-day avg: 236.51 IL-6 (pg/mL): Lag 0: 0.52; 3-day avg: 0.51; 9-day avg: 0.50 sTNF-RII (pg/mL): Lag 0: 154.05; 3-day avg: 139.45; 9-day avg: 225.60 **Relationship to indoor air pollutants:** CRP (ng/mL): Lag 0: 695.39; 3-day avg: 527.37; 9-day avg: 760.15 IL-6 (pg/mL): Lag 0: 0.54; 3-day avg: 0.47; 9-day avg: 0.77 sTNF-RII (pg/mL): Lag 0: 114.22; 3-day avg: 107.95; 9-day avg: 273.38 **Relationship of sP-selction (ng/mL) to:** Indoor air pollutants: Lag 0: 0.77; 5-day avg: 1.40; 9-day avg: 2.19 Outdoor air pollutants: Lag 0: 0.84; 5-day avg: 1.23; 9-day avg: 4.29 **Relationship of Cu, Zn-SOD (U/g Hb) to:** Indoor air pollutants: Lag 0: -145.54; 5-day avg: -238.72; 9-day avg: -70.10 Outdoor air pollutants: Lag 0: -105.73; 5-day avg: -176.72; 9-day avg: -41.92

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Delfino et al. **(2009, 200844)** **Period of Study:** Jul-midOct and midOct-Feb of 2005-2006 and 2006-2007 **Location:** Los Angeles, CA	**Health Outcome:** Biomarkers of inflammation **Study Design:** Panel **Statistical Analyses**: Linear mixed effects models adjusted for confounders **Age Groups:** 65+ (84.1 ± 5.60) yr **Sample Description:** 60 subjects with confirmed CAD history, nonsmoker, unexposed to environmental tobacco smoke	**Averaging Time:** 24 h **Mean (SD) unit:** 0.50 (0.25) ppm **Range (min, max):** 0.11, 1.30 **Copollutant:** NO_2, NO_X, O_3, $PM_{0.25}$, $PM_{0.25-2.5}$, $PM_{2.5-10}$, EC_3 OC, BC, OCpri, SOC, PN/cm^3	Increment: NR Regression coefficients (95% CI) Subjects with positive responses: Cu,Zn-SOD (U/g Hb): 1-day avg: 1441 (97, 2786), 3-day avg: 2634 (1416, 3854), 5-day avg: 4227 (2078, 6376), 7-day avg: 3474 (914, 6034), 9-day avg: 2954 (737, 5172) GPx-1 (U/g HB): 1-day avg: -0.97 (-4.45, 2.50), 3-day avg: -2.21 (-6.48, 2.06), 5-day avg: 4.71 (-2.90, 12.33), 7-day avg: 4.20 (-3.29, 11.68), 9-day avg: 4.76 (-1.58, 11.10) Subjects with negative responses: Cu,Zn-SOD (U/g Hb): 1-day avg: -195 (-338, -52), 3-day avg: -242 (-399, -85), 5-day avg: -242 (-440, -44), 7-day avg: -315 (-664, 34), 9-day avg: -176 (-508, 156) GPx-1 (U/g HB): 1-day avg: -0.82 (-1.55, -0.08), 3-day avg: -0.85 (-1.66, -0.04), 5-day avg: -0.84 (-1.88, 0.21), 7-day avg: -1.04 (-2.85, 0.78), 9-day avg: -0.47 (-2.19, 1.26) All subjects: IL-6 (pg/mL): 1-day avg.: 0.35 (0.17, 0.54), 3-day avg.: 0.40 (0.20, 0.61), 5-day avg.: 0.54 (0.27, 0.80), 7-day avg.: 0.34 (-0.06, 0.74), 9-day avg.: 0.31 (-0.07, 0.70) P-selectin (ng/mL): 1-day avg.: 3.33 (0.94, 5.73), 3-day avg.: 3.65 (1.02, 6.29), 5-day avg.: 5.28 (1.86, 8.70), 7-day avg.: 11.2 (5.39, 17.0), 9-day avg.: 10.4 (4.83, 16.0) TNF-RII (pg/mL): 1-day avg: 112 (13, 211), 3-day avg: 136 (29, 243), 5-day avg: 229 (88, 371), 7-day avg: 132 (-86, 349), 9-day avg: 220 (19, 421) TNF-α (pg/mL): 1-day avg: 0.05 (-0.05, 0.16), 3-day avg: 0.09 (-0.03, 0.20), 5-day avg: 0.14 (-0.01, 0.29), 7-day avg: 0.07 (-0.19, 0.33), 9-day avg: 0.14 (-0.11, 0.39) CRP (ng/mL): 1-day avg: 780 (343, 1217), 3-day avg: 739 (255, 1222), 5-day avg: 1117 (485, 1749), 7-day avg: 126 (-800, 1052), 9-day avg: 41 (-840, 923) SOD (U/g Hb): 1-day avg: -62 (-231, 108), 3-day avg: -53 (-244, 138), 5-day avg: -37 (-285, 211), 7-day avg: 98 (-314, 509), 9-day avg: 208 (-173, 590) GPx-1 (U/g Hb): 1-day avg: -0.69 (-1.41, 0.03), 3-day avg: -0.69 (-1.48, 0.11), 5-day avg: -0.56 (-1.60, 0.48), 7-day avg: -0.56 (-2.34, 1.21), 9-day avg: 0.05 (-1.63, 1.72) Effect modification by medication use: TNF-RII (pg/mL): 1-day avg: All subjects: 125 (11, 239), Statins: 48 (-105, 201), No Statins: 199 (47, 352); 3-day avg: All subjects: 161 (39, 283), Statins: 1 (-170, 171), No Statins: 306 (141, 472) ; 5-day avg: All subjects: 257 (100, 413), Statins: 15 (-210, 240), No Statins: 445 (240, 649); 7-dayay avg: All subjects: 176 (-68, 419), Statins: 43 (-297, 382), No Statins: 283 (-23, 589); 9-dayay avg: 265 (41, 489), Statins: 160 (-158, 478), No Statins: 355 (65, 646) sP-selectin (ng/mL): 1-day avg: All subjects: 1.84 (-0.62, 4.30), Clopidogrel: 0.00 (-2.80, 2.81), No Clopidogrel: 1.72 (-0.42, 3.86); 3-day avg: All subjects: 1.90 (-0.79, 4.60), Clopidogrel: -0.67 (-3.95, 2.60), No Clopidogrel: 1.60 (-0.76, 3.96); 5-day avg: All subjects: 2.97 (-0.47, 6.41), Clopidogrel: -0.18

Study	Design	Concentrations	CO Effect Estimates (95% CI)
			(-4.38, 4.01), No Clopidogrel: 3.04 (0.06, 6.01); 7-day avg: All subjects: 6.74 (0.75, 12.73), Clopidogrel: 2.24 (-4.22, 8.71), No Clopidogrel: 6.78 (1.60, 3.96); 9-day avg: All subjects: 6.96 (1.20, 12.72), Clopidogrel: 2.0 (-4.40, 8.48), No Clopidogrel: 5.54 (0.46, 10.6)
Author: Liao et al. (2005, 088677) **Period of Study:** 1996-1998 **Location:** Forsyth County, NC; Selected suburbs of Minneapolis, MN; Jackson, MI	**Health Outcome:** Various measures of hemostasis/ inflammation **Study Design:** Cohort **Statistical Analyses:** Linear regression **Age Groups Analyzed:** 45-64 yr **Sample Description:** 10,208 subjects from the Atherosclerosis Risk in Communities Study	**Averaging Time:** 24 h **Mean (SD) unit:** NR **Range (Min, Max):** NR **Copollutant:** NR	Increment: 0.6 ppm Regression coefficients [SE] Lags examined (days): 1 Lag 1: Fibrinogen (mg/dL): -0.16 (0.67) Factor VIII –C (%): 0.45 (0.42) vWF %: -0.29 (0.50) WBC (x 103/mm3): 0.003 (0.017) Albumin (g/dL): -0.018 (0.003)** ** p < 0.01
Author: Ljungman et al. (2009, 191983) **Period of Study:** May 2003-July 2004 **Location:** Athens, Greece; Augsberg, Germany; Barcelona, Spain; Helsinki, Finland; Rome, Italy; Stockholm, Sweden	**Health Outcome:** Plasma Interleukin-6 (IL-6), Fibrinogen **Study Design:** Panel/Field **Statistical Analyses:** Linear Mixed Effects Model **Age Groups Analyzed:** 35-80 yr (mean = 62.2 yr) **Sample Description:** 955 subjects who had experienced MI between 4 mo and 6 yr before start of the study	**Averaging Time:** 24 h **Mean (SD) unit:** **Individual cities:** 0.29-1.48 mg/m^3 **Mean for all cities:** 0.78 mg/m^3 **Range (percentiles):** 25th = 0.56; 75th = 0.90 (for mean of all cities) **Copollutant:** (mean for all cities) NO_2: r = 0.69 PM_{10}: r = 0.47 $PM_{2.5}$: r = 0.55 PNC: r = 0.67	**Increment:** 0.34 mg/m^3 Change of IL-6 % of overall mean per IQ range increase **Genotypes:** 1 1, 1 2, 2 2 IL6 rs2069832 1 1: 2.0 (0.3, 3.6); 1 2: -0.2 (-1.7, 1.3); 2 2: -2.0 (-4.7, 0.8); p-value: 0.03 IL6 rs2069840 1 1: 2.0 (0.3, 3.8); 1 2: 0.4 (-0.9, 1.7); 2 2: -1.2 (-3.4, 1.1); p-value: 0.04 IL6 rs2069845 1 1: 1.9 (0.2, 3.5); 1 2: -0.1 (-1.5, 1.4); 2 2: -1.6 (-4.3, 1.2); p-value: 0.31 FGA rs2070011 1 1: 1.0 (-0.7, 2.7); 1 2: 0.7 (0.6, 2.0); 2 2: 0.4 (-1.9, 2.7); p-value: 0.64 FGB rs1800790 1 1: -0.2 (-1.8, 1.3); 1 2: 2.1 (0.4, 3.8); 2 2: 4.5 (1.1, 8.0); p-value: 0.02
Author: Pekkanen et al. (2000, 013250) **Period of Study:** 1991-1993 **Location:** London, England	**Health Outcome:** Fibrinogen **Study Design:** Cohort **Statistical Analyses:** Logistic regression **Age Groups Analyzed:** 35-55 yr **Sample Description:** 7,205 office workers	**Averaging Time:** 8 h **Mean (SD) unit:** 1.4 mg/m^3 **Range (Min, Max):** Min = NR, Max = 9.9 **Copollutant correlation:** PM_{10}: r = 0.57 NO_2: r = 0.81 SO_2: r = 0.61 O_3: r = -0.45	**Increment:** 1.6 mg/m^3 % Change in fibrinogen concentration [p value] ; **Lags examined:** 0, 1, 2, 3 Lag 0: 1.43 (<0.01); Lag 1: 1.49 (<0.01); Lag 2: 1.59 (<0.01); Lag 3: 1.26 (<0.01) OR for having Fibrinogen above 3.19 g/l [p value] **Lags examined**: 0, 1, 2, 3 Lag 0: 1.17 (0.05); Lag 1: 1.09 (0.31); Lag 2: 1.14 (0.11); Lag 3: 1.22 (<0.01)

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Ruckerl et al. (2006, 088754) **Period of Study:** 2000-2001 **Location:** Erfert, Germany	**Health Outcome:** Blood markers of inflammation and coagulation **Study Design:** Panel **Statistical Analyses:** Linear and logistic regression (fixed effects) **Age Groups Analyzed:** 51-76 yr (mean = 66 yr) **Sample Description:** 57 male patients with CHD	**Averaging Time:** 24 h **Mean (SD) unit:** 0.52 mg/m^3 **Range (Min, Max):** 0.11, 1.93 **Copollutant correlation:** NO_2: r = 0.82	**Increment:** 0.27 mg/m^3 **OR Estimate for blood marker** >90th percentile **[Lower CI, Upper CI]** **Lags examined (h):** 0-23, 24-47, 48-71, 5-day avg CRP (C-reactive protein) 0-23: 0.9 (0.7-1.2); 24-47: 1.0 (0.7-1.5); 48-71: 1.5 (1.1-2.1); 5-day avg 1.1 (0.8-1.6) ICAM-1 (Intercellular adhesion molecule 1) 0-23: 0.8 (0.6-1.0); 24-47: 1.5 (1.2-1.9); 48-71: 1.7 (1.3-2.3); 5-day avg 1.2 (1.0-1.6) % of change from the mean of blood marker vWF (von Willebrand factor antigen) 0-23: 4.4 (1.4- 7.5); 24-47: 2.7 (-0.8 to 6.1); 48-71: 2.0 (-1.7 to 5.8); 5-day avg: 4.9 (1.0-8.8) FVII (Factor VII) 0-23: -1.4 (-3.8 to 1.1); 24-47: -2.6 (-4.8 to 0.3); 48-71: -2.8 (-5.1 to -0.4); 5-day avg: -3.0 (-5.5 to -0.4)
Author: Ruckerl et al. (2007, 156931) **Period of Study:** May 2003-July 2004 **Location:** 6 cities across Europe: Athens, Greece; Augsburg, Germany; Barcelona, Spain; Helsinki, Finland; Rome, Italy; Stockholm, Sweden	**Health Outcome:** Interleukin-6, C-reactive protein, Fibrinogen **Study Design:** Panel/Cohort **Statistical Analyses:** Linear regression (mixed effects) **Age Groups Analyzed:** 37-81 yr **Sample Description:** 1,003 MI survivors who had at least 2 valid repeated blood samples	**Averaging Time:** 24 h **Mean (SD) unit:** Athens: 1.48 mg/m^3 Augsburg: 0.58 mg/m^3 Barcelona: 0.59 mg/m^3 Helsinki: 0.31 mg/m^3 Rome: 1.40 mg/m^3 Stockholm: 0.29 mg/m^3 **Range (Min, Max):** NR **Copollutant:** NR	**Increment:** 0.34 mg/m^3 % Change in mean [Lower CI, Upper CI] **Lags examined:** 0, 1, 2, 5-day avg (Pooled estimates) Interleukin-6 Lag 0: 0.57 (-0.63 to 1.79) Lag 1: 0.44 (-0.79 to 1.68); Lag 2: -2.36 (-4.82 to 0.17) 5-day avg: -0.28 (-2.53 to 2.02) C-reactive protein Lag 0: -0.01 (-1.72 to 1.73 Lag 1: -1.51 (-3.30 to 0.32) Lag 2: -2.35 (-6.84 to 2.36); 5-day avg: -0.85 (-.5.37 to 3.90) Fibrinogen Lag 0: 0.24 (-0.54 to 0.92) Lag 1: 0.32 (-0.35 to 1.00); Lag 2: -0.44 (-1.11 to 0.23) 5-day avg: 0.12 (-0.81 to 1.05)

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Rudez et al. (2009, 193783) **Period of Study:** January 2005-December 2006 **Location:** Rotterdam, the Netherlands	**Health Outcome:** Platelet aggregation, thrombin generation, Fibrinogen, C-reactive protein **Study Design:** Panel **Statistical Analyses:** Linear regression **Age Groups Analyzed:** Mean = 41 yr **Sample Description:** 40 healthy individuals	**Averaging Time:** 24 h **Median (SD) unit:** 333 µg/m^3 **Range (percentiles):** 25th = 276; 75th = 412 **Copollutant:** PM_{10}: r >0.6 NO: r >0.6 NO_2: r >0.6 O_3: -0.4 ≥ r ≥ -0.6	**Increment:** NR **Estimated Changes** [Lower CI, Upper CI] Platelet Aggregation Parameters Maximal Platelat Aggregation: D0-6: -3.6 (-9.3, 2.1); D0-12: -4.7 (-11.0, 1.5); D0-24: -2.6 (-7.9, 2.7); I24-48: -1.1 (-7.2, 4.9); I48-72: 8.4 (2.5, 14.3); I72-96: -0.1 (-5.1, 5.0); D+I0-96: 9.5 (1.6, 17.4) Late Aggregation: D0-6: 10.5 (0.8, 20.3); D0-12: 11.6 (1.2, 21.9); D0-24: 11.2 (1.4, 21.0); I24-48: 7.5 (-2.2, 17.1); I48-72: 18.1 (8.4, 27.8); I72-96: 4.2 (-5.5, 13.9); D+I0-96: 20.4 (8.4, 32.4) Thrombin Generation ETP D0-6: -1.51 (-3.7, 0.80); D0-12: -1.1 (-3.4, 1.1); D0-24: -1.5 (-3.9, 0.9); I24-48: -0.7 (-3.4, 2.0); I48-72: 0.8 (-1.9, 3.4); I72-96: 3.5 (0.8, 6.2); D+I0-96: 0.8 (-2.7, 4.3) Peak D0-6: -2.5 (-6.3, 1.3) D0-12: -1.9, (-5.7, 1.9); D0-24: -3.3 (-7.3, 0.7); I24-48; -1.3 (-6.1, 3.6); I48-72: -0.5 (-5.0, 4.0) I72-96: 3.8 (-0.8, 8.4) D+I0-96: -1.7 (-7.5, 4.2) Lag Time D0-6: 1.0 (-0.5, 2.5); D0-12: 1.0 (-0.5, 2.5); D0-24: 1.6 (0.1, 3.1); I24-48; 0.4 (-1.3, 2.2); I48-72: -1.0 (-2.7, 0.7); I72-96: -1.5 (-3.2, 0.2); D+I0-96: 0.1 (-2.1, 2.2) Inflammatory Markers Fibrinogen I24-48; 0.0 (-1.7, 1.8); I48-72: 0.0 (-1.8, 1.9) I72-96: -0.1 (-1.9, 1.7) CRP I24-48; 3.2 (-6.4, 12.8); I48-72: -1.9 (-12.5, 8.7); I72-96: -4.5 (-15.3, 6.3)
Author: Steinvil et al. (2008, 188893) **Period of Study:** 2003-2006 **Location:** Tel Aviv, Israel	**Health Outcome:** Various measures of inflammation sensitive biomarkers **Study Design:** Cohort **Statistical Analyses:** Linear regression **Age Groups Analyzed:** Mean = 46 yr **Sample Description:** 3,659 subjects living within 11 km of monitoring site	**Averaging Time:** 24 h **Mean (SD) unit:** 0.8 ppm **Range (percentiles):** 25th = 0.7; 75th = 1.0 **Copollutant:** correlation PM_{10}: r = 0.75 NO_2: r = 0.857 SO_2: r = 0.671 O_3: r = -0.656	**Increment:** 0.3 ppm **Regression co-efficient** [Lower CI, Upper CI] **Lags examined (days):** 0, 1, 2, 3, 4, 5, 6, 7, last wk avg Fibrinogen: Men Lag 0: -3.3 (-6.1 to -0.6); Lag 1: -2.6 (-5.5 to 0.4); Lag 2: -3.4 (-6.6 to -0.3); Lag 3: -3.4 (-6.5 to -0.2); Lag 4: -5.9 (-8.9 to -2.9); Lag 5: -4.7 (-7.8 to -1.6); Lag 6: -2.0 (-5.1 to 1.0); Lag 7: -2.7 (-5.7 to 0.2); Last wk avg: -7.7 (-12.1 to -3.3) **Notes:** No effect on fibrinogen among women. CO had no effect on CRP among men and no effect on CRP and WBC among women for all Lag times examined.
VARIOUS MEASURES OF CARDIOVASCULAR HEALTH			
Author: Briet et al. (2007, 093049) **Period of Study:** NR **Location:** Paris, France	**Health Outcome:** Endothelial function, Reactive Hyperemia **Study Design:** Case-crossover **Statistical Analyses:** Multiple regression models **Age Groups Analyzed:** 18-35 yr **Sample Description:** 40 healthy white male nonsmokers	**Averaging Time:** 24 h **Mean (SD) unit:** NR **Range (Min, Max):** NR **Copollutant:** $PM_{2.5}$, PM_{10}, NO, NO_2, SO_2	**Increment:** NR β-Coefficient [Lower CI, Upper CI] **Flow-mediated Brachial Artery Dilatation:** -0.68 (-1.22, -0.15) **Small Artery Reactive Hyperemia:** 10.46 (1.73, 19.31)

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Nautiyal et al. (2007, 190301) **Period of Study:** August 1999-May 2000 **Location:** Mandi Gobindgarh, India Morinda, India	**Health Outcome:** Various measures of cardiovascular health via ECG (Minnesota Code) **Study Design:** Cross-sectional **Statistical Analyses:** NR **Age Groups Analyzed:** +15 yr **Sample Description:** 200 total survey participants (100/town)	**Averaging Time:** NR **Mean (SD) unit:** NR **Range (Min, Max):** Morinda Pure residential Site: 0-1 ppm GT Road Site: 2-3 ppm Mandi Gobindgarh Mixed Habitat Site: 0-3 ppm GT Road Site: 1-3 ppm Co**pollutant:** $PM_{2.5}$, PM_{10}, NO_X, SO_X	**Increment:** NR **RR Estimate** [Lower CI, Upper CI] **Lags examined:** NR No quantitative results presented
Author: Wellenius et al. (2007, 092830) **Period of Study:** February 2002-March 2003 **Location:** Boston, MA	**Health Outcome:** Congestive heart failure **Study Design:** Cohort (retrospective) **Statistical Analyses:** Linear mixed models **Age Groups Analyzed:** 33-88 yr. Tai Chi Group mean age (n=14): 66 ± 13 yr. Control Group mean age (n=14): 63 ± 14 yr. **Sample Description:** 28 patients with CHF and impaired systolic function	**Averaging Time:** 24 h **Mean (SD) unit:** 0.44 ppm **Range (IQ):** 0.20 ppm **Copollutant:** $PM_{2.5}$: r = 0.35 NO_2, SO_2, O_3, BC	**Increment:** NR **RR Estimate** [Lower CI, Upper CI] **Lags examined:** 0, 1, 2, 3 Results presented graphically

Table C-2. Studies of CO exposure and cardiovascular hospital admissions and ED visits.

Study	Design	Concentrations	CO Effect Estimates (95% CI)
STROKE			
Author: Chan et al. (2006, 090193) **Period of Study:** 1997-2002 **Location:** Taipei, Taiwan	**ED Visits** **Health Outcome** (ICD9): Cerebrovascular disease (430-437); Strokes (430-434); Hemorrhagic stroke (430-432); Ischemic stroke (433-434) **Study Design:** Time-series **Statistical Analyses:** GAM **Age Groups Analyzed:** All **Sample Description:** NR	**Averaging Time:** 8 h **Mean (SD) unit:** 1.7 ppm **Range (Min, Max):** 0.6, 4.4 **Copollutant:** correlation O_3: r = 0.30 SO_2:r = 0.63 NO_2: r = 0.77 $PM_{2.5}$: r = 0.44 PM_{10}: r = 0.47	**Increment:** 0.8 ppm **OR Estimate** [Lower CI, Upper CI] **Lags (days) examined** 0, 1, 2, 3 Cerebrovascular disease: Lag 2, 1.03 (1.01, 1.06) Stroke: Lag 2, 1.03 (1.01, 1.05) Ischemic and Hemorrhagic stroke: not significant. Cerebrovascular 2 pollutant model: CO + O_3: Lag 2, 1.03 (1.01-1.05) CO + $PM_{2.5}$: Lag 2, 1.02 (1.00-1.04) CO + PM_{10}: Lag 2, 1.03 (1.01-1.05)
Author: Henrotin et al. (2007, 093270) **Period of Study:** 1994-2004 **Location:** Dijon, France	**Health Outcome** (ICD9 or ICD10): Stroke (Ischemic & Hemorrhagic) **Study Design:** Bidirectional case crossover **Statistical Analyses:** Conditional logistic regression **Age Groups Analyzed:** ≥ 40 yr **Sample Description:** NR	**Averaging Time:** 24 h **Mean (SD) unit:** 683 μg/m^3 **Range (Min, Max):** 0, 4014 **Copollutant:** NR	**Increment:** 10 μg/m^3 **OR Estimate [Lower CI, Upper CI]** **Lags (days) examined:** 0, 1, 2, 3. Ischemic: Lag 0: 0.999 (0.997-1.001) Lag 1: 0.998 (0.997-1.001) Lag 2: 0.999 (0.998-1.001) Lag 3: 1.000 (0.998-1.001) Hemorrhagic: Lag 0: 1.000 (0.996-1.004) Lag 1: 1.001 (0.997-1.005) Lag 2: 0.999 (0.995-1.004) Lag 3: 0.998 (0.994-1.002) Also not significant when stratified by sex.

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Maheswaran et al. (2005, 090769) **Period of Study:** 1994-1998 **Location:** Sheffield, UK	**Health Outcome** (ICD9 or ICD10): Stroke deaths (ICD9: 430-438); Stroke Hospital admissions (ICD10: I60-I69) **Study Design:** Ecological **Statistical Analyses:** Poisson regression **Age Groups Analyzed:** ≥ 45 yr **Sample Description:** 1,030 census districts	**Averaging Time:** NR **Mean (SD) unit:** Quintiles **Range (Min, Max):** NR **Copollutant:** NR	**Increment:** NR – Quintiles of exposure **RR Estimate** [Lower CI, Upper CI] Adjusted for sex, age, deprevation, smoking. Quintiles: 2nd: 1.04 (0.94-1.16) 3rd: 1.01 (0.91-1.13) 4th: 1.10 (0.99-1.23) 5th: 1.11 (0.99-1.25) Adjusted for sex, age: 2nd: 1.11 (1.01-1.22) 3rd: 1.15 (1.04-1.27) 4th: 1.29 (1.17-1.42) 5th: 1.37 (1.24-1.52)
Author: Tsai et al. (2003, 080133) **Period of Study:** 1997-2000 **Location:** Kaohsiung, Taiwan	**Study Design:** Case-crossover **Health Outcome (ICD9 or ICD10):** Cerebrovascular diseases: ICD9: 430 to 438 (Subarachnoid hemorrhagic stroke 430, Primary intracerebral hemorrhage (PIH): 431-432, Ischemic stroke (IS): 433-435). **Statistical Analyses:** NR **Age Groups Analyzed:** All **Sample Description:** NR	**Averaging Time:** 24 h **Mean (SD) unit:** 0.79 ppm **Range (Min, Max):** 0.24, 1.72 **Copollutant:** NR	**Increment:** 0.8 ppm (IQR) **RR Estimate** [Lower CI, Upper CI] **Lag (days):** 0-2 >20ºC PIH: OR 1.21 (1.09-1.34) IS: OR 1.21 (1.14-1.28) <20ºC PIH: OR 1.18 (0.80-0.72) IS: OR 1.77 (1.31-2.39) Notes: 2-pollutant models: PIH results persisted when adjusting for SO_2 and O_3 IS results persisted when controlling for PM_{10}, SO_2 and O_3
Author: Villeneuve et al. (2006, 090191) **Period of Study:** 1992-2002 **Location:** Edmonton, Canada	ED Visits (within 5 hospitals) **Health Outcome (ICD9):** Stroke (430-438); Ischemic (434-436) Hemorrhagic (430-432); Transient Ischemic Attack (435) **Study Design:** Case-crossover **Statistical Analyses:** Conditional logistic regression **Age Groups Analyzed:** 65+ yr **Sample Description:** 12,422 visits	**Averaging Time:** 24 h **Mean (SD) unit:** 0.8 ppm **Range (percentiles):** 25th = 0.5; 75th = 1.0 **Copollutant correlation:** O_3: r = -0.54 $PM_{2.5}$: r = 0.43 PM_{10}: r = 0.30	**Increment:** 0.5 ppm **OR Estimate** [Lower CI, Upper CI] **Lags (days) examined:** 0, 1 & 0-2 Ischemic (April-Sept) Lag 0: 1.16 (1.00, 1.33) Lag 1: 1.17 (1.01, 1.36) Lag 0-2: 1.32 (1.09, 1.60) Notes: - Not significant for all seasons or Oct-Mar. - Hemorrhagic: Not significant for all seasons or Oct-Mar, Apr-Sept. - Transient Ischemic Attack: Not significant for all seasons or Oct-Mar, Apr-Sept.
Author: Wellenius et al. (2005, 088685) **Period of Study:** NR **Location:** 9 U.S. cities: Chicago, Detroit, Pittsburgh, Cleveland, Birmingham, New Haven, Seattle, Minneapolis, Salt Lake City	ED Visits **Health Outcome:** Stroke among Medicare beneficiaries: (Ischemic, hemorrhagic) **Study Design:** Time-series **Statistical Analyses:** Logistic regression **Age Groups Analyzed:** ≥ 65 yr **Sample Description:** 155,503 visits	**Averaging Time:** NR **Mean (SD) unit:** NR **Range (percentiles):** 25th = 0.73; 50th = 1.02; 75th = 1.44 (ppm) **Copollutant:** correlation PM_{10}: r = 0.43	**Increment:** 0.71 ppm **% Change** [Lower CI, Upper CI] **Lag:** 0 Ischemic: 2.83 (1.23-4.46) Hemorrhagic: -1.61 (-4.79 to 1.68)

Study	Design	Concentrations	CO Effect Estimates (95% CI)
ISCHEMIC HEART DISEASE			
Author: D'Ippoliti et al. (2003, 074311) **Period of Study:** 1995-1997 **Location:** Rome, Italy	Hospital Admissions **Health Outcome (ICD9):** MI (410) **Study Design:** Case-crossover **Statistical Analyses:** Conditional logistic regression **Age Groups Analyzed:** 18+ yr **Sample Description:** 6,531 patients.	**Averaging Time:** 24 h **Mean (SD) unit:** 4.4 mg/m^3 **Range (percentiles):** 25th = 2.8; 75th = 4.3 **Copollutant:** correlation TSP: r = 0.35 SO_2: r = 0.56 NO_2: r = 0.31	**Increment:** 1 mg/m^3 **OR Estimate** [Lower CI, Upper CI] ; lag: **Lags examined (days):** 0, 1, 2, 3, 4, 0-2 Acute MI Lag 0: 1.021 (0.988-1.054) Lag 1: 1.020 (0.988-1.054) Lag 2: 1.033 (1.001-1.066) Lag 3: 1.010 (0.982-1.040) Lag 4: 1.025 (0.996-1.055) Lag 0-2: 1.044 (1.000- .089
Author: Hosseinpoor et al. (2005, 087413) **Period of Study:** 1996-2001 **Location:** Tehran, Iran	**Health Outcome:** Angina Pectoris (ICD9: 413; ICD10: I20) **Study Design:** Time series **Statistical Analyses:** Poisson regression **Age Groups Analyzed:** All **Sample Description:** NR	**Averaging Time:** 24 h **Mean (SD) unit:** 10.8 mg/m^3 **Range (Min, Max):** 1.6, 57.8 **Copollutant:** NR	**Increment:** 1 mg/m^3 **RR Estimate** [Lower CI, Upper CI] **Lags examined (days):** 0, 1, 2, 3 Lag 1: 1.00957 (1.00600-1.01315)
Author: Lanki et al. (2006, 089788) **Period of Study:** 1994-2000 **Location:** 5 European cities: Augsburg, Germany Barcelona, Spain Helsinki, Finland Rome, Italy Stockholm, Sweden	**Health Outcome:** First AMI (ICD9: 410; ICD10: I21, I22) **Study Design:** Time series **Statistical Analyses:** Poisson regression (GAM) **Age Groups Analyzed:** 35+ yr **Sample Description:** 26,854 Hospital Admissions	**Averaging Time:** 24 h **Mean (SD) unit:** NR Unit: mg/m^3 **Range (percentiles):** Augsburg, Germany 25th = 0.7; 75th = 1.1 Barcelona, Spain 25th = 0.6; 75th = 1.4 Helsinki, Finland 25th = 0.3; 75th = 0.5 Rome, Italy 25th = 1.7; 75th = 2.9 Stockholm, Sweden 25th = 0.3; 75th = 0.5 **Copollutant:** correlation PM_{10}: r = 0.21 – 0.56 NO_2: r = 0.43 – 0.75 O_3: r = -.023 – 020	**Increment:** 0.2 mg/m^3 **RR Estimate** [Lower CI, Upper CI] ; lag: **Lags examined:** 0, 1, 2, 3 All 5 cities: Lag 0: 1.005 (1.000-1.010) Lag 1: 1.002 (0.996-1.007) Lag 2: 1.002 (0.997-1.007) Lag 3: 0.998 (0.992-1.003) 3 cities with Hospital Discharge Register(HDR): Lag 0: 1.007 (1.001-1.012) Lag 1: 1.002 (0.996-1.008) Lag 2: 1.003 (0.998-1.009) Lag 3: 1.004 (0.988-1.020) 3 cities with HDR – ≤ 75years Fatal: Lag 0: 1.027 (1.006-1.048) Lag 1: 1.021 (1.000-1.042) Lag 2: 1.018 (0.997-1.039) Lag 3: 1.015 (0.994-1.037) Non-Fatal: Lag 0: 1.001 (0.995-1.008) Lag 1: 1.000 (0.994-1.007) Lag 2: 1.004 (0.998-1.011) Lag 3: 0.999 (0.992-1.006) 3 cities with HDR – ≥ 75years Fatal: Lag 0: 1.009 (0.992-1.006) Lag 1: 1.001 (0.985-1.018) Lag 2: 1.006 (0.990-1.023) Lag 3: 1.000 (0.983-1.017) Non-Fatal: Lag 0: 1.015 (1.004-1.086) Lag 1: 1.006 (0.995-1.017) Lag 2: 0.995 (0.983-1.006) Lag 3: 0.998 (0.987-1.009)

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Lee et al. (2003, 095552) **Period of Study:** 1997-1999 **Location:** Seoul, Korea	**Study Design:** Time-series **Health Outcome (ICD9 or ICD10):** Angina: ICD10: 120 AMI: ICD10: I21-I23 Other Acute IHDs: ICD10: I24 **Statistical Analyses:** Poisson regression, GAM **Age Groups Analyzed:** 64+ yr **Sample Description:** 822 days	**Averaging Time:** Daily max **Mean (SD) unit:** 1.8 ppm **Range (percentiles):** 25th = 1.2 75th = 2.2 **Copollutant:** correlation PM_{20}: 0.60 SO_2: 0.81 NO_2: 0.79 O_3: -0.39	**Increment:** 1 ppm (IQR) **RR Estimate** [Lower CI, Upper CI] **Lags examined (days):** 0, 1, 2, 3, 4, 5, 6 All yr: Lag 5: All ages: 0.94 (0.91 0.98) Lag 5: 64+ age: 1.07 (1.01-1.13) Summer: Lag 5: All ages: 1.19 (1.02-1.38) Lag 5: 64+ age: 1.60 (1.27-2.03) 2-pollutant model: Lag 5: 64+ age: CO + PM_{10}: 1.04 (0.98-1.11)
Author: Maheswaran et al. (2005, 090769) **Period of Study:** 1994-1998 **Location:** Sheffield, UK	Emergency Hospital Admission **Health Outcome (ICD9):** CHD (410-414) **Study Design:** Ecological **Statistical Analyses:** Poisson regression **Age Groups Analyzed:** 45+ yr **Sample Description:** 11,407 Emergency Hospital Admissions for CHD in patients 45+ yr (within 1,030 census districts)	**Averaging Time:** NR **Mean (SD) unit:** Quintiles **Range (Min, Max):** NR **Copollutant:** NR	**Increment:** NA **RR Estimate** [Lower CI, Upper CI] Lowest quintile reference category Adjusted for sex, age, deprivation, smoking: 2nd: 0.97 (0.89-1.07) 3rd: 0.94 (0.86-1.04) 4th: 0.96 (0.97-1.06) 5th: 0.88 (0.79- 0.98) Adjusted for sex, age: 2nd: 1.09 (1.00-1.19) 3rd: 1.15 (1.05-1.26) 4th: 1.19 (1.09-1.30) 5th: 1.20 (1.09-1.32)
Author: Mann et al. (2002, 036723) **Period of Study:** 1988-1995 **Location:** Southern California	**Health Outcome (ICD9):** IHD (IHD) (410-414); MI (410) **Study Design:** Time series **Statistical Analyses:** Poisson regression, GAM **Age Groups Analyzed:** All **Sample Description:** 54,863 IHD admissions among Southern California Kaiser- Permanente members (within 20km of monitor)	**Averaging Time:** 8 h **Mean (SD) unit:** 2.07 ppm **Range (Min, Max):** 0.30, 11.8 **Copollutant:** correlation Ranging across 7 regions: NO_2: r = 0.64, 0.86 O_3: r = -0.37, 0.28 PM_{10}: r = 0.15, 0.40	**Increment:** 1 ppm **% Change** [Lower CI, Upper CI] **Lags examined (days):** 0, 1, 2, 2 ma, 3 ma, 4 ma With arrythmia: Lag 0: 2.99 (1.80-4.99) Lag 1: 1.51 (0.37-2.66) Lag 2: 1.26 (0.15-2.38) 2 ma: 2.66 (1.40-3.94) 3 ma: 2.59 (1.27-3.92) 4ma: 2.25 (0.90-3.63) With CHF: Lag 0: 3.60 (1.620-5.63) Lag 1: 3.34 (1.48-5.22) Lag 2: 1.90 (0.11-3.72) 2 ma: 4.23 (2.13-6.37) 3 ma: 4.14 (1.96-6.37) 4 ma: 4.07 (1.81-6.38) Without secondary diagnosis: Lag 0: 1.62 (0.65-2.59) Lag 1: 1.45 (0.54-2.37) Lag 2: 0.92 (0.04-1.82) 2 ma: 1.83 (0.80-2.86) 3 ma: 1.79 (0.72-2.87) 4 ma: 1.82 (0.71-2.94)
Author: Szyszkowicz (2007, 193793) **Period of Study:** 1997-2003 **Location:** Montreal, Canada	**Study Design:** Time-series **Health Outcome (ICD9 or ICD10):** ED Visits. IHD: ICD9: 410-414 **Statistical Analyses:** Poisson regression (GLMM) **Age Groups Analyzed:** All **Sample Description:** 4,979 ED Visits	**Averaging Time:** 24 h **Mean (SD) unit:** 0.5 ppm **Range (Min, Max):** 0.1, 3.1 **Copollutant:** NR	**Increment:** 0.2 ppm **% Change** [Lower CI, Upper CI] ; lag: **Lags examined (days):** 0, 1 All Patients: Lag 0: 5.4 (2.3-8.5) Males: Lag 0: 7.5 (3.6-11.6) Females: Lag 0: 2.7 (-2.0 to 7.6) Ages ≥ 64 All Patients: Lag 0: 4.9 (1.3-8.7) Males: Lag 0: 7.5 (2.6-12.6) Females: Lag 0: 2.4 (-3.0 to.0) Lag 1 not significant for all results

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: von Klot et al. (2005, 088070) **Period of Study:** 1992-2001 **Location:** 5 European cities: Augsburg, Germany Barcelona, Spain Helsinki, Finland Rome, Italy Stockholm, Sweden	**Health Outcome:** Hospital cardiac (mi), angina, dysrythmia, heart failure) re-admissions **Study Design:** Prospective Cohort **Statistical Analyses:** Poisson regression **Age Groups Analyzed:** All **Sample Description:** 22,006 survivors of first MI	**Averaging Time:** 24 h **Unit:** mg/m^3 **Mean (SD) unit:** Augsburg, Germany: 0.93 Barcelona, Spain: 1.00 Helsinki, Finland: 0.42 Rome, Italy: 2.21 Stockholm, Sweden: 0.43 **Range (Min, Max):** NR **Copollutant:** correlation PM_{10}: r = 0.21 – 0.57 NO_2: r = 0.44 – 0.75 O_3: r = -.027 – 0.47	**Increment:** 0.2 mg/m^3 (0.172 ppm) **RR Estimate** [Lower CI, Upper CI] **Lags examined (days):** 0, 1, 2, 3 Lag 0: MI:1.022 (0.998-.047) Angina: 1.009 (0.992-.02) Cardiac: 1.014 (1.001-.026)
HEART FAILURE			
Author: Lee et al. (2007, 090707) **Period of Study:** 1996-2004 **Location:** Kaohsiung City, Taiwan	Hospital Admissions **Health Outcome (ICD9):** CHF (428) **Study Design:** Case-crossover **Statistical Analyses:** Conditional logistic regression **Age Groups Analyzed:** All **Sample Description:** 13,475 Hospital Admissions (63 Hospitals)	**Averaging Time:** 24 h **Mean (SD) unit:** 0.76 ppm **Range (Min, Max):** 0.14, 1.72 **Copollutant:** NR	**Increment:** 0.31 ppm **OR Estimate** [Lower CI, Upper CI] **Lag examined (days):** 0-2 ≥ 25°C: 1.19 (1.09-1.31) <25°C: 1.39 (1.24-1.54) Adjusted for PM_{10}: ≥ 25°C; 1.15 (1.04-1.27) <25°C; 1.21 (1.206-1.38) Adjusted for SO_2: ≥ 25°C: 1.23 (1.11-1.36) <25°C: 1.39 (1.24-1.55) Adjusted for NO_2: ≥ 25°C: 1.22 (1.08-1.39) <25°C: 0.94 (0.81-1.10) Adjusted for O_3: ≥ 25°C: 1.17 (1.07-1.28) <25°C: 1.36 (1.22-1.51)
Author: Symons et al. (2006, 091258) **Period of Study:** 2002 (April-November) **Location:** Johns Hopkins Bayview Medical Center, Baltimore, MD	Hospital Admissions **Health Outcome:** NR **Study Design:** Case-crossover **Statistical Analyses:** Conditional logistic regression **Age Groups Analyzed:** All **Sample Description:** 398 Hospital Admissions for CHF	**Averaging Time:** 24 h **Mean (SD) unit:** 0.4 ppm **Range (Min, Max):** 0.1, 1.0 **Copollutant:** NR	**Increment:** 0.2 ppm **OR Estimate** [Lower CI, Upper CI] **Lags examined (days):** 0, 1, 2, 3, cum 1, cum 2, cum 3 Lag 0: 0.86 (0.67-1.11) Lag 1: 0.90 (0.70-1.17) Lag 2: 0.96 (0.73-1.26) Lag 3: 0.88 (0.67-1.16) Cum. Lag1: 0.82 (0.60-1.13) Cum. Lag2: 0.80 (0.54-1.17) Cum. Lag3: 0.27 (0.46-1.14)
Author: Wellenius et al. (2005, 087483) **Period of Study:** 1987-1999 **Location:** Pittsburgh, PA	Hospital Admissions **Health Outcome (ICD9):** CHF (428, 428.1) **Study Design:** Case-crossover **Statistical Analyses:** Conditional logistic regression **Age Groups Analyzed:** 65+ yr **Sample Description:** 54,019 Hospital Admissions among Medicare beneficiaries	**Averaging Time:** 24 h **Mean (SD) unit:** 1.03 ppm **Range (percentiles):** 25th = 0.68; 75th = 1.23 **Copollutant:** correlation PM_{10}: r = 0.57 NO_2: r = 0.70 O_3: r = -0.25 SO_2: r = 0.54	**Increment:** 0.55 ppm **% Change** [Lower CI, Upper CI] **Lags examined (days):** 0, 1, 2, 3 Lag 0: Single pollutant model: 4.55 (3.33-5.79) Adjusted for PM_{10}: 5.18 (3.49-6.89) Adjusted for NO_2: 4.84 (3.06-6.66) Adjusted for O_3: 4.35 (3.08-5.64) Adjusted for SO_2: 4.51 (3.15-5.90)

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Yang (2008, 157160) **Period of Study:** 1996-2004 **Location:** Taipei, Taiwan	Hospital Admissions **Health Outcome:** CHF **Study Design:** Case-crossover **Statistical Analyses:** NR **Age Groups Analyzed:** NR **Sample Description:** 24,240 CHF HA from 47 hospitals	**Averaging Time:** 24 h **Mean (SD) unit:** 1.26 ppm **Range (Min, Max):** 0.12, 3.66 **Copollutant:** PM_{10}, NO_2, O_3, SO_2	**Increment:** NR **OR Estimate** [Lower CI, Upper CI] **Lags examined (days):** 0, 1, 2 **Single Pollutant Model** Warm days (>20o C): 1.24 (1.16, 1.33) Cool days (<20o C): 1.05 (0.96, 1.15) **Two Pollutant Models** Warm days (≥20°C) Adjusted for PM_{10}: 1.16 (1.08, 1.26) Adjusted for NO_2: 1.02 (0.92, 1.13) Adjusted for O_3: 1.25 (1.17, 1.34) Adjusted for SO_2: 1.32 (1.22, 1.42) Cool days (<20°C) Adjusted for PM_{10}: 1.09 (0.97, 1.21) Adjusted for NO_2: 1.07 (0.92, 1.25) Adjusted for O_3: 0.89 (0.80, 0.99) Adjusted for SO_2: 1.03 (0.92, 1.16)
CARDIOVASCULAR DISEASES – NON-SPECIFIC			
Author: Ballester et al. (2001, 013257) **Period of Study:** 1994-1996 **Location:** Valencia, Spain	ED Visits **Health Outcome** (ICD9: CVD (390-459); Heart diseases (410-414, 427, 428); cerebrovascular disease (430-438) **Study Design:** Time series **Statistical Analyses:** Poisson regression **Age Groups Analyzed:** All **Sample Description:** NR	**Averaging Time:** 24 h **Mean (SD) unit:** 6.2 mg/m^3 **Range (Min, Max):** 0.6, 17.8 **Copollutant:** correlation BS: r = 0.64 NO_2: r = 0.03 SO_2: r = 0.74 O_3: r = -0.26	**Increment:** 1 mg/m^3 **RR Estimate** [Lower CI, Upper CI] ; lag: **Lags examined (days):** 0, 1, 2, 3, 4, 5 All cardiovascular: Lag 2: 1.0077 (0.9912-1.0138) Heart Disease: Lag 1: 1.0092 (0.9945-1.0242) Cerebrovascular Disease: Lag 1: 0.9874 (0.9646-1.0107)
Author: Ballester et al. (2006, 088746) **Period of Study:** 1995-1999 **Location:** 14 Cities in Spain	**Health Outcome** (ICD9: All CVD (390-459);Heart diseases (410-414, 427, 428) **Study Design:** Time series **Statistical Analyses:** GAM **Age Groups Analyzed:** All **Sample Description:** NR	**Averaging Time:** 8 h **Mean (SD) unit:** Range across 14 cities, 1.4-2.8 mg/m^3 **Range (percentiles):** 10th = 0.4-1.7; 90th = 2.0-3.9 **Copollutant:** NR	**Increment:** 1 mg/m^3 **% Change** [Lower CI, Upper CI] **Lags examined (days):** 0-1 All CVD: Lag 0-1: 2.06 (0.65-3.48) Heart Disease: Lag 0-1: 4.15 (1.31-7.08)
Author: Barnett et al. (2006, 089770) **Period of Study:** 1998-2001 **Location:** Brisbane, Canberra, Melbourne, Perth, Sydney Australia Auckland & Christchurch, New Zealand	Hospital Admissions with CVDs **Health Outcome** (ICD9: Arrythmia (247); Cardiac Disease (390-429); Cardiac Failure (428); IHD (410-413); MI (410); Total CVD (390-459) **Study Design:** Case-crossover **Statistical Analyses:** Conditional logistic regression **Age Groups Analyzed**: 15-64 yr & ≥ 65 yr **Sample Description:** NR	**Averaging Time:** 8 h **Mean (SD) unit:** ppm Brisbane: 1.7 Canberra: 0.9 Melbourne: 1.0 Perth: 1.0 Sydney: 0.8 Auckland: 2.1 Christchurch: 0.5 **Range (Min, Max):** ppm Brisbane: 0.0, 7.0 Canberra: 0.0, 5.8 Melbourne: 0.1, 8.0 Perth: 0.1, 4.0 Sydney: 0.0, 4.5 Auckland: 0.2, 7.9 Christchurch: 0.0, 5.4 **Copollutant** NR	**Increment:** 0.9 ppm **% Change** [Lower CI, Upper CI] **Lags examined (days):** 0-1 15-64 yr Arrythmia: 2.5 (0.1-4.9) Cardiac: 1.7 (0.5-2.9) Cardiac Failure: 4.2 (0.6-7.8) IHD: 1.6 (-0.6 to 3.9) MI: 1.8 (-0.7 to 4.3) Total CVD: 1.2 (0.3-2.1) ≥ 65 yr Arrythmia: 0.1 (-1.8 to 2.1) Cardiac: 2.8 (1.3-4.4) Cardiac Failure: 6.0 (3.5-8.5) IHD: 2.3 (0.9-3.8) MI: 2.9 (0.8-4.9) Total CVD: 2.2 (0.9-3.4)

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Bell et al. (2009, 193780) **Period of Study:** 1999-2005 **Location:** 126 U.S. urban counties	Hospital Admissions with CVDs **Health Outcome (ICD9):** Cardiac failure (428); cerebrovascular events (430-438); heart rhythm disturbances (426-427); ihd (410-414,429); peripheral vascular disease (440-448) **Study Design:** Time series **Statistical Analyses:** Log-linear over-dispersed Poisson regression **Age Groups Analyzed:** ≥ 65 yr **Sample Description:** >9.3 million Medicare subjects	**Averaging Time:** 1 h **Mean (SD) unit**: 1.6 ppm **Median (SD) unit:** 1.3 ppm **Median Range** (Min, Max): 0.2, 9.7 **Copollutant:** $PM_{2.5}$: r = 0.26 NO_2: r = 0.56 EC: r = 0.48	**Increment:** 1 ppm **% Change** [Lower CI, Upper CI] **Lags examined (days):** 0-2 Lag 0: Single pollutant model: 0.96 (0.79-1.12) Adjusted for $PM_{2.5}$: 0.76 (0.57-0.96) Adjusted for NO_2: 0.55 (0.36-0.74) Adjusted for EC: 0.97 (0.38-1.57)
Author: Chang et al. (2005, 080086) **Period of Study:** 1997-2001 **Location:** Taipei, Taiwan	**Health Outcome (ICD9):** CVD Hospital Admissions (410-429) **Study Design:** Case-crossover **Statistical Analyses:** Conditional logistic regression **Age Groups Analyzed:** All **Sample Description:** 74,509 CVD hospital admissions (47 Hospitals)	**Averaging Time:** 24 h **Mean (SD) unit:** 1.37 ppm **Range (Min, Max):** 0.37, 3.66 **Copollutant:** NR	**Increment:** 0.49 ppm **OR Estimate** [Lower CI, Upper CI] **Lag examined (days):** 0-2 ≥ 20°C: 1.090 (1.064-1.118) <20°C: 0.984 (0.927-1.044) Adjusted for PM_{10}: ≥ 20°C: 1.171 (1.132-1.211) <20°C: 0.946 (0.892-1.003) Adjusted for SO_2: ≥ 20°C: 1.232 (1.194-1.272) <20°C: 1.098 (1.034-1.165) Adjusted for NO_2: ≥ 20°C: 1.048 (1.003-1.095 <20°C: 0.983 (0.914-1.058) Adjusted for O_3: ≥ 20°C: 1.196 (1.161-1.232) <20°C: 1.092 (1.031-1.157)
Author: Filhol. (2008, 190260) **Period of Study:** January 2001-July 2003 **Location:** Sao Paulo, Brazil	ED Visits **Health Outcome (ICD10):** Hypertension and Cardiac Ischemic Disease (I10-I25) **Study Design:** Time series **Statistical Analyses:** Linear Poisson regression models **Age Groups Analyzed:** >18 yr **Sample Description:** 45,000 Cardiovascular emergency room visits from diabetic and non-diabetic patients (tertiary referral teaching hospital)	**Averaging Time:** 8 h **Mean (SD) unit:** 2.7 ppm **Range (Min, Max):** 0.7, 12.1 **Copollutant:** correlation PM_{10}: r = 0.69 NO_2: r = 0.58 SO_2: r = 0.52 O_3: r = 0.07	**Increment:** 1.2 ppm **Regression Coefficients** [SEM] **Lags examined (days):** 0, 1, 2 **CVD Visits/Diabetes:** Lag 0: 0.0575 (0.0410) Lag 1: - 0.0056 (0.0418) Lag 2: -0.0324 (0.0426) 2-day moving avg: 0.0324 (0.0470) 3-day moving avg: 0.0074 (0.0528) 4-day moving avg: -0.0025 (0.0582) **CVD Visits/Non-Diabetes:** Lag 0: 0.0286 (0.0095) Lag 1: 0.0098 (0.0091) Lag 2: 0.0102 (0.0089) 2-day moving avg: 0.0271 (0.0108) 3-day moving avg: 0.0281 (0.0120) 4-day moving avg: 0.0306 (0.0131)
Author: Fung et al. (2005, 074322) **Period of Study:** 1995-2000 **Location:** Windsor, Ontario, Canada	Hospital Admissions of CVDs **Health Outcome (ICD9):** CHF (428); IHD (410-414); dysrythmias (427) **Study Design:** Time series Statistical Analyses: GLM **Age Groups Analyzed:** All **Sample Description:** 11,632 Cardiac hospital admissions	**Averaging Time:** 24 h **Mean (SD) unit:** 1.3 ppm **Range (Min, Max):** 0.0, 11.8 **Copollutant:** correlation PM_{10}: r = 0.21 NO_2: r = 0.38 SO_2: r = 0.16 O_3: r = 0.10	**Increment:** 1.2 ppm **% Change** [Lower CI, Upper CI] **Lags examined (days):** 0, 0-1, 0-2 <65 yr Lag 0: -3.1 (-7.4 to 1.4) Lag 0-1: -2.7 (-8.1 to 3.0) Lag 0-2: -0.5 (-6.7 to 6.0) ≥ 65 yr Lag 0: 0.5 (-2.2 to 3.3) Lag 0-1: 2.3 (-1.1 to 5.9) Lag 0-2: 2.8 (-1.1 to 7.0)

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Jalaludin et al. (2006, 189416) **Period of Study:** 1997-2001 **Location:** Sydney, Australia	ED Visits **Health Outcome (ICD9):** All cardiovascular (390-459); cardiac disease (390-429); IHD (410-413); cerebrovascular or stroke (430-438) **Study Design:** Time series **Statistical Analyses:** GLM & GAM **Age Groups Analyzed:** 65+ yr **Sample Description:** NR	**Averaging Time:** 8 h **Mean (SD) unit:** 0.82 ppm **Range (Min, Max):** 0.02, 4.63 **Copollutant:** correlation PM_{10}: r = 0.31 NO_2: r = 0.71 SO_2: r = 0.51 O_3: r = 0.19	**Increment:** 0.69 ppm **% Change** [Lower CI, Upper CI] **Lags examined (days):** 0, 1, 2, 3, 0-1 All Cardiovascular: Lag 0: 2.32 (1.45-3.19) Lag 1: 1.33 (0.47-2.20) Lag 0-1: 2.35 (1.39-3.32) Cardiac Disease: Lag 0: 2.52 (1.50-3.54) Lag 1: 1.85 (0.83-2.88) Lag 2: 1.11 (0.0-2.15) Lag 0-1: 2.85 (1.71-4.01) IHD: Lag 0: 2.83 (1.22-4.48) Lag 1: 1.58 (0.01-3.19) Lag 0-1: 2.86 (1.07-4.68) Stroke: No results were significant for Stroke. All CVD: Cool period: Lag 0: 3.26 (2.00-4.53) Cardiac Disease: Cool period: Lag 0: 3.43 (1.95-4.93) IHD: Cool period: Lag 0: 3.64 (1.28-6.06) Warm period: Lag 0: 2.29 (0.01-4.62) Stroke: Cool period: Lag 0: 3.54 (0.78-6.37) Notes: Cool: May to October Warm: November to April
Author: Koken et al. (2003, 049466) **Period of Study:** 1993-1997 **Location:** Denver, CO	Hospital Admissions for CVD **Health Outcome (ICD9:** MI (410-410.92); coronary atherosclerosis (414-414.05); pulmonary heart disease (416-416.9); cardiac dysrythmia (427-427.9); CHF (428) **Study Design:** Time series **Statistical Analyses:** GLM **Age Groups Analyzed:** >65 yr **Sample Description:** NR	**Averaging Time:** 24 h **Mean (SD) unit:** 0.9 ppm **Range (Min, Max):** 0.3, 1.6 **Copollutant:** correlation PM_{10}: r = 0.25 NO_2: r = 0.73 SO_2: r = 0.21 O_3: r = -0.40	**Increment:** 0.3 ppm **% Change** [Lower CI, Upper CI] **Lags examined (days):** 1, 2, 3, 4 CHF: Lag 3: 10.5 (0.1-22.0) CO not significantly associated with other Lag periods.
Author: Linn et al. (2000, 002839) **Period of Study:** 1992-1995 **Location:** Los Angeles, CA	**Health Outcome:** Hospital Admissions for Cardiovascular, Cerebrovascular, Pulmonary. **Study Design:** Time series **Statistical Analyses:** Ordinary least squares regression; Poisson regression **Age Groups Analyzed:** >30 yr **Sample Description:** NR	**Averaging Time:** 24 h **Mean (SD) unit:** Winter: 1.7; Spring: 1.0; Summer: 1.2; Fall: 2.1 **Range (Min, Max):** Winter: 0.5, 5.3; Spring: 0.4, 2.2; Summer: 0.3, 2.7; Fall: 0.2, 4.3 **Copollutant: correlation** Winter: PM_{10}: r = 0.78; NO_2: r = 0.89; O_3: r = -0.43; Spring: PM_{10}: r = 0.54; NO_2: r = 0.92; O_3: 0.29 Summer: PM_{10}: r = 0.72; NO_2: r = 0.94; O_3: 0.03 Fall: PM_{10}: r = 0.58; NO_2: r = 0.84; O_3: r = -0.36	**Increment:** 1 ppm Co-efficient [SE] **Lags examined (lags):** 0, 1 Lag 0: Cardiovascular All: 0.032 (0.003)* (e.g. 3.2% increase) Winter: 0.038 (0.006)* Spring: 0.010 (0.015) Summer: 0.035 (0.014)* Fall: 0.027 (0.006)* Cerebrovascular All: 0.009 (0.007) Winter: -0.008 (0.014) Spring: 0.107 (0.033)* Summer: 0.030 (0.033) Fall: 0.008 (0.012) MI All: 0.040 (0.009) * CHF All: 0.025 (0.009)* Cardiac Arrythmia All: 0.023 (0.009)* Stroke All: 0.044 (0.009)* Notes:* $p < 0.05$

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Metzger et al. (2004, 044222) **Period of Study:** 1993-2000 **Location:** Atlanta, GA	ED Visits (from 31 hospitals) **Health Outcome (ICD9:** Cardiovascular: IHD (410-414); Acute MI (410); Dysrythmia (427); Cardiac Arrest (427.5); CHF (428); Peripheral Vascular & Cereberovascular Disease (PVCD) (433-437, 440, 443, 444, 451-453); Atherosclerosis (440); Stroke (436) **Study Design:** Case-crossover **Statistical Analyses:** Poisson regression (GLM) **Age Groups Analyzed:** All **Sample Description:** 4,407,535 visits	**Averaging Time:** 1 h **Median (SD) unit:** 1.5 ppm **Range (percentiles):** 10th = 0.5; 90th = 3.4 **Copollutant:** correlation PM_{10}: r = 0.47 NO_2: r =0.68 SO_2: r =0.26 O_3: r =0.20	**Increment:** 1 ppm RR Estimate [Lower CI, Upper CI] **Lags examined (days):** 0-2ma All CVD: 1.017 (1.008-1.027) Dysrythmia: 1.012 (0.993-1.031) CHF: 1.010 (0.988-1.032) IHD: 1.016 (0.999-1.034) PVCD: 1.031 (1.010-1.052)
Author: Peel et al. (2007, 090442) **Period of Study:** 1993-2000 **Location:** Atlanta, GA	ED Visits (from 31 hospitals) **Health Outcome (ICD9:** Cardiovascular: IHD (410-414); Dysrythmia (427); CHF (428); PVCD (433-437, 440, 443, 444, 451-453) **Study Design:** Case-crossover **Statistical Analyses:** Conditional logistic regression **Age Groups Analyzed:** All **Sample Description:** 4,407,535 visits	**Averaging Time:** 1-h **Mean (SD) unit:** 1.8 ppm **Range (SD):** SD: 1.2 **Copollutant:** NR	**Increment:** 1.2 ppm OR Estimate [Lower CI, Upper CI] **Lags examined (days):** 0-2ma IHD: Without Diabetes: 1.023 (1.004-1.420) Without CHF: 1.024 (1.006-1.042) Dysrythmias: With Hypertension: 1.065 (1.015-1.118) PVCD: With Hypertension: 1.038 (1.004-1.074) Without Hypertension: 1.027 (1.002-1.054) With Diabetes: 1.065 (1.012-1.121) Without Diabetes: 1.025 (1.003-1.048) With COPD: 1.113 (1.027-1.205) Without COPD: 1.026 (1.004-1.047) Without CHF: 1.029 (1.008-1.051) With Dysrythmias: 1.072 (1.011-1.138) Without Dysrythmias: 1.026 (1.004-1.048) CHF: With COPD: 1.058 (1.003-1.115)
Author: Slaughter et al. (2005, 073854) **Period of Study:** 1995-2001 **Location:** Spokane, WA	Health Outcome (ICD9: Cardiac Hospital Admissions: (390-459) **Study Design:** Time series **Statistical Analyses:** Poisson regression (GLM & GAM) **Age Groups Analyzed:** All **Sample Description:** NR	**Averaging Time:** 24 h **Mean (SD) unit:** 0.42-1.82 **Range (Min, Max):** NR **Copollutant correlation:** PM_{10}: r = 0.32 $PM_{2.5}$: r = 0.62	**Increment:** NR **RR Estimate [Lower CI, Upper CI] ;** lag: **Lags examined (days):** 1, 2, 3 No significant association. Results not reported.
Author: Tolbert et al. (2007, 090316) **Period of Study:** 1993-2004 **Location:** Atlanta, GA	ED Visits (from 41 hospitals) **Health Outcome (ICD9):** IHD (410-414), cardiac dysrhythmias (427), CHF (428), peripheral vascular and cerebrovascular diseases (433-437, 440, 443-445 and 451-453) **Study Design:** Time series **Statistical Analyses:** Poisson generalized linear model **Age Groups Analyzed:** NR **Sample Description:** 10,234,490 ED Visits (238,360 CVD group)	**Averaging Time:** 1 h **Mean (SD) unit:** 1.6 ppm **Range (Min, Max):** 0.1, 7.7 **Copollutant:** PM_{10}: r = 0.51 NO_2: r =0.70 SO_2: r =0.28 O_3: r =0.27 $PM_{2.5}$: r = 0.47	**Increment:** NR RR Estimate [Lower CI, Upper CI] **Lags examined (days):** 1, 2, 3 Single-Pollutant Model 3-day ma: 1.020 (1.010, 1.030) Results for multi-pollutant models presented graphically

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Yang et al. (2004, 094376) **Period of Study:** 1997-2000 **Location:** Kaohsiung City, Taiwan	**Health Outcome (ICD9:** CVDs (410-429) **Study Design:** Case-crossover **Statistical Analyses:** Conditional logistic regression **Age Groups Analyzed:** All **Sample Description:** 29,661 Cardiovascular hospital admissions (63 hospitals)	**Averaging Time:** 24 h **Mean (SD) unit:** 0.79 ppm **Range (Min, Max):** 0.24, 1.72 **Copollutant:** NR	**Increment:** 0.28 ppm OR Estimate [Lower CI, Upper CI] **Lag examined (days):** 0-2 ≥ 25°C: 1.264 (1.205-1.326) <25°C: 1.448 (1.357-1.545) Adjusted for PM_{10}: ≥ 25°C: 1.206 (1.146-1.270) <25°C: 1.314 (1.213-1.423) Adjusted for SO_2: ≥ 25°C: 1.406 (1.327-1.489) <25°C: 1.3450 (1.352-1.555) Adjusted for NO_2: ≥ 25°C: 1.246 (1.166-1.332) <25°C: 0.905 (0.819-0.999) Adjusted for O_3: ≥ 25°C: 1.250 (1.191-1.311) <25°C: 1.447 (1.356-1.545)

Table C-3. Studies of CO exposure and neonatal and postneonatal outcomes.

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Bell et al. (2007, 091059) **Period of Study:** 1999-2002 **Location:** Connecticut and Massachusetts	**Health Outcome:** Birth weight and LBW **Study Design:** Retrospective cohort **Statistical Analyses:** Linear and logistic regression **Age Groups Analyzed:** NA **Sample Description:** 358,504 full-term live singleton births (32-44 wk)	**Averaging Time:** 24 h **Mean (SD) unit:** 0.65 ppm (0.18) **Range (Min, Max):** NR **Copollutant:** NR	**Increment:** Interquartile range – 0.30 ppm Regression co-efficient for birth weight (g) [Lower CI, Upper CI] Entire pregnancy: -16.2 (-19.7 to -12.6) Stratified by race. Black mother: -10.9 (-20.2 to -1.6) White mother: -17.5 (-21.3 to -13.7) OR for LBW [Lower CI, Upper CI] Entire pregnancy: 1.028 (0.983-1.074)
Author: Brauer et al. (2008, 156292) **Period of Study:** 1999-2004 **Location:** Vancouver, Canada	**Health Outcome:** LBW, PTB and SGA **Study Design:** Retrospective cohort **Statistical Analyses:** Logistic regression **Age Groups Analyzed:** NA **Sample Description:** 70,249 live singleton births	**Averaging Time:** LUR model **Mean (SD) unit:** 633 $\mu g/m^3$ **Range (Min, Max):** 124, 1409 **Copollutant: correlation:** PM_{10}: r = 0.73 NO_2: r = 0.75 SO_2: r = 0.82 O_3: r = -0.39	**Increment:** 100 $\mu g/m^3$ OR for SGA [Lower CI, Upper CI] ; Entire pregnancy: 1.06 (1.03-1.08) OR for term LBW [Lower CI, Upper CI] ; Entire pregnancy: 1.02 (0.96-1.09) OR PTB [Lower CI, Upper CI] ; Entire pregnancy: 1.16 (1.01-1.33)
Author: Chen et al. (2002, 024945) **Period of Study:** 1991-1999 **Location:** Northern Nevada	**Health Outcome:** Birth weight & LBW **Study Design:** Retrospective cohort **Statistical Analyses:** Linear and logistic regression **Age Groups Analyzed:** NA **Sample Description:** 39,338 full term live singleton births (37-44 wk)	**Averaging Time:** 8 h **Mean (SD) unit:** 0.98 ppm **Range (Min, Max):** 0.25, 4.87 **Copollutant:** NR	**Increment:** NR Regression co-efficient for birth weight (g) [SE] Trimesters: First: -1.02 (6.68) Second: -0.07 (6.58) Third: -3.95 (6.76) Entire pregnancy: -8.28 (14.9) **Notes:** CO not associated with LBW

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Conceicao et al. (2001, 016628) **Period of Study:** 1994-1997 **Location:** Sao Paulo, Brazil	**Health Outcome:** Child mortality, under 5 yr of age **Study Design:** Time series **Statistical Analyses:** Poisson regression (GAM) **Age Groups Analyzed:** NA **Sample Description:** NR	**Averaging Time:** 24 h **Mean (SD) unit:** 4.4 ppm (2.2) **Range (Min, Max):** NR **Copollutant:** NR	**Increment:** NR Regression co-efficient for Child mortality – under 5 yr of age [SE] ; **Lags examined:** 0, 1, 2, 3 Lag 2: 0.0306 (0.0076) ($p < 0.01$) Lag chosen for best fitting model
Author: Gilboa et al. (2005, 087892) **Period of Study:** 1997-2000 **Location:** Texas	**Health Outcome:** Birth defects (heart defects and orofacial clefts) **Study Design:** Case control **Statistical Analyses:** Conditional Logistic regression **Age Groups Analyzed:** NA **Sample Description:** NR	**Averaging Time:** NR **Mean (SD) unit:** NR **Range (Min, Max):** NR **Copollutant:** NR	**Increment:** Exposure categories (ppm):<0.4; 0.4 – 0.5; 0.5 – 0.7; >0.7 OR for Birth Defects [Lower CI, Upper CI] ; Exposure period: wk 3 to 8 of pregnancy Conotruncal defects: 1.00; 1.38 (0.97-1.97); 1.17 (0.81-1.70); 1.46 (1.03-2.08) Tetralogy of Fallot: 1.00; 0.92 (0.52-1.62); 1.27 (0.75-2.14); 2.04 (1.26-3.29) Notes: CO was not associated with the following defects: Aortic artery and valve, atrial septal, pulmonary artery and valve, ventricular septal, endocardial cushion and mitral valve , cleft lip, cleft palate, aortic valve stenosis, coarctation of the aorta, ostium secundum.
Author: Gouveia et al. (2004, 055613) **Period of Study:** 1997 **Location:** Sao Paulo, Brazil	**Health Outcome:** Birth weight & LBW **Study Design:** Retrospective cohort **Statistical Analyses:** Linear and logistic regression **Age Groups Analyzed:** NA **Sample Description:** 179,460 live singleton term births (>37 wk)	**Averaging Time:** 8 h **Mean (SD) unit:** 3.7 ppm **Range (Min, Max):** 1.1, 11.4 **Copollutant:** NR	**Increment:** 1 ppm Regression co-efficient for birth weight (g) [Lower CI, Upper CI] Trimesters: First: -23.1 (-41.3 to -4.9) Second: 3.2 (-18.2 to 24.5) Third: 1.9 (-18.2 to 22.0) OR for LBW) [Lower CI, Upper CI] 4th quartile exposure (compared to lowest quartile): First: 1.02 (0.82-1.27); Second: 1.07 (0.88-1.30); Third: 0.93 (0.76-1.12)
Author: Ha et al. (2001, 019390) **Period of Study:** 1996-1997 **Location:** Seoul, South Korea	**Health Outcome:** LBW **Study Design:** Retrospective cohort **Statistical Analyses:** Logistic regression (GAM) **Age Groups Analyzed:** NA **Sample Description:** 276 763 full-term live singleton births (>37 wk)	**Averaging Time:** 24 h **Mean (SD) unit:** NR **Range (Min, Max):** Percentiles: 25th: 0.99 ppm 75th: 1.41 ppm **Copollutant correlation:** TSP: r = 0.73 NO_2: r = 0.75 SO_2: r = 0.82 O_3: r = -0.39	**Increment:** 0.42 ppm RR for LBW [Lower CI, Upper CI] Trimesters: First: 1.08 (1.04, 1.12) Third: 0.91 (0.87, 0.96)
Author: Ha et al. (2003, 042552) **Period of Study:** 1995-1999 **Location:** Seoul, South Korea	**Health Outcome:** Post-neonatal mortality (1 mo-1 yr) (also looked at older age groups) **Study Design:** Time series **Statistical Analyses:** Poisson regression (GAM) **Age Groups Analyzed:** NA **Sample Description:** NR	**Averaging Time:** 24 h **Mean (SD) unit:** 1.2 ppm **Range (Min, Max):** 0.39, 3.38 **Copollutant correlation:** PM_{10}: r = 0.63 NO_2: r = 0.72 SO_2: r = 0.75 O_3: r = -0.46	**Increment:** 0.57 ppm RR for Post–neonatal mortality (1 mo-1 yr) [Lower CI, Upper CI] **Lags examined:** 0 Total mortality: Lag 0: 1.020 (0.976-1.067) Respiratory mortality: Lag 0: 1.388 (1.009-1.911)

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Hajat et al. (2007, 093276) **Period of Study:** NR **Location:** Birmingham, Bristol, Leeds, Liverpool, London, Manchester, Middlesbrough, Newcastle, Nottingham, Sheffield England	**Health Outcome:** Neonatal and postneonatal mortality **Study Design:** Time series **Statistical Analyses:** Poisson regression (GLM) **Age Groups Analyzed:** NA **Sample Description:** 22,288 total infant deaths between 1990 and 2000	**Averaging Time:** 3 days **Mean (SD) unit:** (mg/m^3) Birmingham: 0.64; Bristol: 1.01; Leeds: 0.73; Liverpool: 0.51; London: 0.77; Manchester: 0.63; Middlesbrough: 0.37; Newcastle: 0.67; Nottingham: 0.62; Sheffield: 0.60 **Range (Min, Max):** Birmingham: 0.4, 0.8; Bristol: 0.6, 1.2; Leeds: 0.5, 0.9; Liverpool: 0.3, 0.6; London: 0.5, 0.9; Manchester: 0.4, 0.7; Middlesbrough: 0.2, 0.4; Newcastle: 0.5, 0.8; Nottingham: 0.4, 0.7; Sheffield: 0.3, 0.7 **Copollutant:** SO_2, NO_2, NO, O_3, PM_{10}	**Increment:** 1 mg/m^3 **RR Estimate** [Lower CI, Upper CI] **Lags examined (days):** 0, 1, 2 All infant deaths: 1.02 (0.96, 1.09) Neonatal deaths: 0.99 (0.92, 1.07) Post-neonatal deaths: 1.09 (0.94, 1.25) City-specific results of all infant mortality displayed graphically
Author: Huynh et al. (2006, 091240) **Period of Study:** 1999-2000 **Location:** California	**Health Outcome:** PTB (24-36 wk gestation) **Study Design:** Case-control **Statistical Analyses:** Conditional Logistic regression **Age Groups Analyzed:** Cases = 24- to 36-wk gestation; Controls = 39- to 44-wk **Sample Description:** 10,673 PTBs (cases); 32,119 term births (controls)	**Averaging Time:** NR **Mean (SD) unit:** NR **Range (Min, Max):** NR **Copollutant:** NR	**Increment:** 1 ppm Exposure level – Quartiles of exposure for first mo and last two wk of gestation (mg/m^3) First: <0.61; Second: 0.61 – 0.82; Third: 0.82 – 1.07; Fourth: >1.07 Quartiles for entire pregnancy and last two wk of pregnancy were similar. OR for PTB [Lower CI, Upper CI] First mo of gestation: Per 1 ppm increase: 1.10 (0.99-1.20) Second quartile: 0.94 (0.88-1.01) Third quartile: 1.04 (0.97-1.11) Fourth quartile: 1.05 (0.96-1.14) Last two wk of gestation: Per 1 ppm increase: 1.00 (0.93-1.09) Second quartile: 1.03 (0.97-1.10) Third quartile: 1.04 (0.97-1.12) Fourth quartile: 0.99 (0.91-1.08) Entire pregnancy: Per 1 ppm increase: 1.06 (0.95-1.18) Second quartile: 0.97 (0.91-1.04) Third quartile: 0.99 (0.92-1.05) Fourth quartile: 1.02 (0.94-1.09) Lowest quartile used as reference group
Author: Hwang and Jaakkola (2008, 193794) **Period of Study:** 2001-2003 **Location:** Taiwan	**Health Outcome:** Oral clefts (with or without palate) **Study Design:** Case control **Statistical Analyses:** Logistic regression **Age Groups Analyzed:** NA **Sample Description:** 6,530 cases from 721,289 newborns	**Averaging Time:** 8 h **Mean (SD) unit:** 0.69 (0.4) **Range (Min, Max):** 0.25, 2.7 **Copollutant correlation:** PM_{10}: r = -0.19 NO_X: r = 0.82 SO_2: r = 0.24 O_3: r = -0.19	**Increment:** 100 ppb **RR for oral cleft** [Lower CI, Upper CI] Month 1: 1.00 (0.96-1.04) Month 2: 1.00 (0.96-1.03) Month 3: 1.00 (0.96-1.03)
Author: Jalaludin et al. (2007, 156601) **Period of Study:** 1998-2000 **Location:** Sydney, Australia	**Health Outcome:** PTB **Study Design:** Retrospective cohort **Statistical Analyses:** Logistic regression **Age Groups Analyzed:** NA **Sample Description:** 123,840 full term live singleton births (<42 wk)	**Averaging Time:** 8 h **Mean (SD) unit:** 0.9 ppm (0.68) **Range (Min, Max):** NR **Copollutant correlation:** PM_{10}: r = 0.28 NO_2: r = 0.60 SO_2: r = 0.24 O_3: r = -0.21	**Increment:** 1 ppm **RR for PTB** [Lower CI, Upper CI] First mo: All of Sydney: 0.89 (0.84-0.95) Within 5km of site: 1.03 (0.68-1.54) First trimester: All of Sydney: 0.77 (0.71-0.83) Within 5km of site: 1.24 (0.81-1.91) 1 mo prior to birth: All of Sydney: 0.96 (0.88-1.04) Within 5km of site: 1.00 (0.86-1.15) 3 mo prior to birth: All of Sydney: 0.99 (0.90-1.09) Within 5km of site: 1.11 (0.94-1.31)

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Lee et al. (2003, 043202) Period of Study: 1996-1998 **Location:** Seoul, South Korea	**Health Outcome:** LBW **Study Design:** Retrospective cohort **Statistical Analyses:** Logistic regression **Age Groups Analyzed:** NA **Sample Description:** 388,105 full-term live singleton births (37-44 wk)	**Averaging Time:** 24 h **Mean (SD) unit:** 1.2 ppm **Range (Min, Max):** 0.4, 3.4 **Copollutant correlation:** PM_{10}: r = 0.47 NO_2: r = 0.77 SO_2: r = 0.79	**Increment:** 0.5 ppm **OR for LBW** [Lower CI, Upper CI] First: 1.04 (1.01-1.07) Second: 1.03 (1.00-1.06) Third: 0.96 (0.93-0.99) Entire pregnancy: 1.05 (1.01-1.09)
Author: Leem et al. (2006, 089828) **Period of Study:** 2001-2002 **Location:** Incheon, Korea	**Health Outcome:** PTB **Study Design:** Retrospective cohort **Statistical Analyses:** Logistic regression **Age Groups Analyzed:** NA **Sample Description:** 52,113 live singleton births	**Averaging Time:** Kriging was used to estimate exposure **Mean (SD) unit:** NR **Range (Min, Max):** NR **Copollutant correlation:** PM_{10}: r = 0.27 NO_2: r = 0.63 SO_2: r = 0.31	**Increment:** Exposure level – Quartiles of exposure for first trimester (mg/m^3) First: 0.47-0.63; Second: 0.6 -0.77; Third: 0.78-0.90; Fourth: 0.91-1.27 - exposure groups for third trimester was similar OR for PTB [Lower CI, Upper CI] First Trimester: Second quartile: 0.92 (0.81-1.05) Third quartile: 1.14 (1.01-1.29) Fourth quartile: 1.26 (1.11-1.44) Third Trimester: Second quartile: 1.07 (0.95-1.21) Third quartile: 1.07 (0.94-1.22) Fourth quartile: 1.16 (1.01-1.34) Lowest quartile used as reference group.
Author: Lin et al. (2004, 095787) **Period of Study:** 1998-2000 **Location:** Sao Paulo, Brazil	**Health Outcome:** Neonatal death (within first 28 days of life) **Study Design:** Time series **Statistical Analyses:** Poisson regression (GAM) **Age Groups Analyzed:** NA Sample Description: NR	**Averaging Time:** 24 h **Mean (SD) unit:** 2.83 ppm **Range (Min, Max):** 0.54, 10.25 **Copollutant correlation:** PM_{10}: r = 0.71 NO_2: r = 0.67 SO_2: r = 0.55 O_3: r = 0.03	**Increment:** NR Regression coefficent for neonatal death [SE] **Lags examined:** 0 Lag 0: 0.0061 (0.0110)
Author: Lin et al. (2004, 089503) **Period of Study:** 1995-1997 **Location:** Taipei & Kaoshiung, Taiwan	**Health Outcome:** LBW **Study Design:** Retrospective cohort **Statistical Analyses:** Logistic regression **Age Groups Analyzed:** NA **Sample Description:** 92,288 full-term live singleton births (>37 wk) within 3 km of monitoring site.	**Averaging Time:** 24 h **Mean (SD) unit:** Taipei (avg over 5 sites) 0.84-1.31 Kaohsiung (avg over 5 sites) 5.56-10.05 **Range (Min, Max):** NR **Copollutant:** NR	**Increment:** Exposure groups M = Median exposure 1.1-14.2 ppm H = High exposure >14.2 ppm OR for LBW [Lower CI, Upper CI] Trimesters: First: M 1.01 (0.89, 1.16), H 0.90 (0.75, 1.09) Second: M 1.02 (0.90, 1.16), H 1.00 (0.82, 1.22) Third: M 0.88 (0.77, 1.00), H 0.86 (0.71, 1.03) Entire pregnancy: M 0.89 (0.77, 1.01), H 0.77 (0.63, 0.94) **Notes:** Cut off for exposures groups for second and third trimester were similar to those presented above.

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Liu et al. (2003, 089548) **Period of Study:** 1985-1998 **Location:** Vancouver, BC, Canada	**Health Outcome:** PTB, IUGR, LBW **Study Design:** Retrospective cohort **Statistical Analyses:** Logistic regression **Age Groups Analyzed:** NA **Sample Description:** 229,085 live singleton births	**Averaging Time:** 24 h **Mean (SD) unit:** 1.0 ppm **Range (Min, Max):** 25th: 0.7; 75th: 1.2 **Copollutant:** NR	**Increment:** 1.0 ppm OR for LBW [Lower CI, Upper CI] Month of pregnancy: First mo: 1.01 (0.93-1.09) Last mo: 0.96 (0.88-1.04) OR for PTB [Lower CI, Upper CI] First mo: 0.95 (0.89-1.01) Last mo: 1.08 (1.01-1.15) OR for IUGR [Lower CI- Upper CI] First mo: 1.06 (1.01-1.10) Last mo: 0.98 (0.94-1.03) Trimester 1: 1.05 (1.00-1.10) Trimester 2: 0.97 (0.92-1.01) Trimester 3: 0.97 (0.93-1.02)
Author: Liu et al. (2007, 090429) **Period of Study:** 1995-2000 **Location:** Calgary, Edmonton, and Montreal, Canada	**Health Outcome:** IUGR **Study Design:** Retrospective cohort **Statistical Analyses:** Logistic regression **Age Groups Analyzed:** NA **Sample Description:** 386,202 live singleton births	**Averaging Time:** 24 h **Mean (SD) unit:** 1.1 ppm **Range (Min, Max):** 25th: 0.6; 75th: 1.3 **Copollutant correlation:** $PM_{2.5}$: r = 0.31 NO_2: r = 0.71 SO_2: r = 0.21 O_3: r = -0.42	**Increment:** 1 ppm **RR for LBW** [Lower CI, Upper CI] **Notes:** CO was associated with an increased risk of IUGR of approximately 16% and 23% in the first and nine mo of pregnancy. (All results presented in Figures)
Author: Maisonet et al. (2001, 016624) **Period of Study:** 1994-1996 **Location:** Northeastern USA	**Health Outcome:** Live birth weight **Study Design:** Retrospective cohort **Statistical Analyses:** Logistic regression **Age Groups Analyzed:** NA **Sample Description:** 89,557 live singleton term births (37-44 wk)	**Averaging Time:** 24 h **Mean (SD) unit:** NR **Range (Min, Max):** Percentiles: 25th: 0.93 ppm; 75th: 1.23 ppm **Copollutant:** NR	**Increment:** 1 ppm **OR for LBW [Lower CI, Upper CI]** Trimester: First: 1.08 (0.91-1.28); Second: 1.14 (0.83-1.58); Third: 1.31 (1.06-1.62) Stratified results among African-Americans: First: 1.43 (1.18-1.74); Second: 1.27 (0.87-1.86); Third: 1.75 (1.50-2.04) **Notes**: CO had no effect on whites or Hispanics
Author: Mannes et al. (2005, 087895) **Period of Study:** 1998-2000 **Location:** Sydney, Australia	**Health Outcome:** Birth weight and SGA **Study Design:** Retrospective cohort **Statistical Analyses:** Linear and logistic regression **Age Groups Analyzed:** NA **Sample Description:** 138,056 full-term all singleton births (including stillbirths) (at least 20-wk gestation)	**Averaging Time:** 8 h **Mean (SD) unit:** 0.8 ppm **Range (Min, Max):** 0.0, 4.6 **Copollutant: correlation** PM_{10}: r = 0.26 NO_2: r = 0.57 O_3: r = -0.20	**Increment:** 1 ppm Regression coefficients for birth weight (g) [Lower CI, Upper CI] All births: First trimester: 1.86 (-8.31 to 12.03) Second trimester: -10.72 (-23.09 to 1.65) Third trimester: -6.63 (-18.57 to 5.31) One mo prior to birth: -15.28 (-25.59 to -4.97) Births within 5 km of monitor: First trimester: -8.56 (-28.60 to 10.68) Second trimester: -28.87 (-50.98 to -6.76) Third trimeste: -22.88 (-44.58 to -1.18) One mo prior to birth: -10.41 (-30.03 to 9.21) OR for SGA [Lower CI, Upper CI] All births: First trimester: 0.95 (0.88-1.04) Second trimester: 0.99 (0.90-1.10) Third trimester: 1.01 (0.91-1.11) One mo prior to birth: 1.06 (0.98-1.16) Births within 5km of monitor: First trimester 0.99 (0.86-1.14) Second trimester: 1.06 (0.90-1.25) Third trimester: 1.05 (0.90-1.23) One mo prior to birth: 1.10 (0.96-1.27)

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Medeiros et al. (2005, 089824) **Period of Study:** 1998-2000 **Location:** Sao Paulo, Brazil	**Health Outcome:** Birth weight and LBW **Study Design:** Retrospective cohort **Statistical Analyses:** Linear and logistic regression **Age Groups Analyzed:** NA **Sample Description:** 311,735 full-term live singleton births (37-41 wk)	**Averaging Time:** 24 h **Mean (SD) unit:** Daily mean shown in Figure (see paper) **Range (Min, Max):** NR **Copollutant:** NR	**Increment:** 1 ppm **Regression coefficient for birth weight (g) [Lower CI, Upper CI]** Trimesters: First: -11.9 (-15.5 to -8.2); Second: 4.9 (0.5-9.3); Third: 12.1 (7.6-16.6) OR for LBW [Lower CI, Upper CI] 4th quartile exposure (compared to lowest quartile) First: 0.98 (0.91-1.06); Second: 0.97 (0.90-1.05); Third: 1.03 (0.96-1.11)
Author: Mortimer et al. (2008, 187280) **Period of Study:** November 2000-April 2005 **Location:** Central Valley of Californinia	**Health Outcome:** Allergic sensitization **Study Design:** Cohort **Statistical Analyses:** Chi-square tests **Age Groups Analyzed:** 6-11 yrs. **Sample Description:** 170 children with asthma from the FACES-LiTE study	**Averaging Time:** 8 h **Mean (SD) unit:** NR **Range (Min, Max):** NR **Copollutant:** Entire Prenatal: PM_{10}: r = 0.32 NO_2: r = 0.74 O_3: r = -0.40 Trimester 2: PM_{10}: r = 0.32 NO_2: r = 0.68 O_3: r = -0.26	**Increment:** NR Trimester specific results presented graphically Single-pollutant Model for "sensitized to at least one outdoor allergen" **OR adjusted for yr of birth and sex [Lower CI, Upper CI]** Entire Pregnancy 24-h avg: 1.45 (1.02, 2.07) Daily max: 1.53 (1.01, 2.33) 8-h max: 1.55 (1.01, 2.37) 2nd Trimester 24-h avg: 1.52 (0.93, 2.47) Daily max: 1.50 (0.92, 2.45) 8-h max: 1.45 (0.90, 2.35) Coefficient adjusted for yr of birth and sex [SE] Entire Pregnancy 24-h avg: 1.33 (0.68) Daily max:0.54 (0.27) 8-h max: 0.84 (0.42) 2nd Trimester 24-h avg: 0.57 (0.34) Daily max: 0.21 (0.13) 8-h max: 0.32 (0.21)
Author: Parker et al. (2005, 087462) **Period of Study:** 2000 **Location:** California	**Health Outcome:** Birth weight & SGA **Study Design:** Retrospective cohort **Statistical Analyses:** Linear and logistic regression **Age Groups Analyzed:** NA **Sample Description:** 18,247 full-term live singleton births (40 wk) within 5 mi of a monitor	**Averaging Time:** 24 h **Mean (SD) unit:** 0.78 ppm **Range (Min, Max):** NR **Copollutant:** NR	**Increment:** Quartiles of exposure for first trimester First: <0.57; Second: 0.57-0.76 ; Third: 0.76- 0.93; Fourth: >0.93 - exposure groups for other trimesters were similar Regression co-efficient for birth weight (g) [Lower CI, Upper CI] Trimesters: 4th quartile exposure (compared to lowest quartile) First: -7.3 (-29.7 to 15.0); Second: 14.2 (-8.9 to 37.3); Third: -8.4 (-32.2 to 15.3); Entire pregnancy: -20.5 (-40.1 to -0.8) OR for SGA [Lower CI, Upper CI] 4th quartile exposure (compared to lowest quartile) First: 0.91 (0.76-1.09); Second: 0.80 (0.66-0.97); Third: 0.90 (0.75-1.10); Entire pregnancy: 0.95 (0.81-1.12)

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Ritz et al. (2000, 012068) **Period of Study:** 1989-1993 **Location:** Southern California	**Health Outcome:** PTB **Study Design:** Retrospective Cohort **Statistical Analyses:** Logistic regression **Age Groups Analyzed:** Eligible study subjects were singletons born at 26- to 44-wk gestation **Sample Description:** 97,518 neonates born in Southern California	**Averaging Time:** 6-9 a.m. **Mean (SD) unit:** 2.70 ppm **Range (Min, Max):** 0.36, 9.12 **Copollutant correlation:** PM_{10}: r = 0.37 NO_2: r = 0.60 O_3: r = -0.44	**Increment:** 3 ppm **RR for PTB [Lower CI, Upper CI]** Adjusted for various risk factors and season of birth and conception 6 wk prior to birth: 1.04 (0.99-1.10) 1st mo of pregnancy: 1.04 (0.99-1.09) Adjusted for various risk factors 6 wk prior to birth: 1.06 (1.02-1.10) 1st mo of pregnancy: 1.01 (0.97-1.04)
Author: Ritz et al. (2002, 023227) **Period of Study:** 1987-1993 **Location:** Southern California	**Health Outcome:** Birth defects (heart defects and orofacial clefts) **Study Design:** Case control **Statistical Analyses:** Logistic regression **Age Groups Analyzed:** NA **Sample Description:** NR	**Averaging Time:** NR **Mean (SD) unit:** NR **Range (Min, Max):** NR **Copollutant:** NR	**Increment:** Exposure categories: ppm <1.14; 1.14-1.57; 1.57- 2.39; >2.39 **OR for Birth defects [Lower CI, Upper CI]:** Period of exposure: Second mo of pregnancy. Aortic artery and valve defects: 1.00 (ref group); 1.10 (0.73-1.66); 1.25 (0.74-2.13); 0.93 (0.47-1.85) Pulmonary artery and valve anomalies: 1.00 (ref group); 1.09 (0.69-1.73); 0.92 (0.50-1.70); 1.00 (0.46-2.17) Ventricular septal defects: 1.00 (ref group); 1.62 (1.05-2.48); 2.09 (1.19-3.67); 2.95 (1.44-6.05) Conotruncal defects: 1.00 (ref group); 0.79 (0.47-1.32); 0.73 (0.36-1.47); 0.95 (0.38-2.38) **Notes:** Results also presented for more specific defects, however CO showed no association (see paper Table 3.). CO not associated with orofacial clefts)
Author: Ritz et al. (2006, 089819) **Period of Study:** 1989-2000 **Location:** Southern California	**Health Outcome:** Postneonatal mortality (28 days to 1 yr); all causes; SIDS **Study Design:** Case control **Statistical Analyses:** Conditional Logistic regression **Sample Description:** Mothers residing within 16 km of monitoring site	**Averaging Time:** 24 h **Mean (SD) unit:** 1.63 ppm **Range (Min, Max):** 0.38, 3.44 **Copollutant:** correlation PM_{10}: r = 0.33 NO_2: r = 0.72 O_3: r = -0.57	**Increment:** 1 ppm OR for Post-neonatal death [Lower CI, Upper CI] Exposure period: 2 wk prior to death, 1 mo prior to death, 2 mo prior to death, 6 mo prior to death All causes: 2 wk prior to death: 1.14 (1.03-1.25) 2 mo prior to death: 1.11 (1.06-1.16) SIDS: 2 mo prior to death: 1.19 (1.10-1.28) Term/normal weight births 2 mo prior to death: All causes: 1.12 (1.05-1.19) SIDS: 1.17 (1.07-1.29) Respiratory: 1.14 (0.95-1.36) Preterm &/or LBW births 2 mo prior to death: All causes: 1.12 (1.01-1.25) SIDS: 1.46 (1.09-1.94) Respiratory: 1.03 (0.83-1.27) Notes: These results did not persist in multipollutant models (CO, NO_2, PM_{10}, O_3)

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Ritz et al. (2007, 096146) Period of Study: January-December 2003 **Location:** Los Angeles, CA	**Health Outcome:** PTB **Study Design:** Nested case-control **Statistical Analyses:** Logistic regression **Age Groups Analyzed:** NA **Sample Description:** A survey of 2,543 of 6,374 women sampled from a cohort of 58,316 eligible births in Los Angeles county.	**Averaging Time:** 24 h **Mean (SD) unit:** NR **Copollutant correlation:** TSP: r = 0.73 NO_2: r = 0.75 SO_2: r = 0.82 O_3: r = -0.39	**Increment: Exposure categories (ppm):** Less than 0.58: 0.59-0.91; 0.92-1.25; >1.25 RR for LBW [Lower CI, Upper CI] First trimester: 1.00 (Ref group); 1.17 (1.08-1.26); 1.15 (1.05-1.26); 1.25 (1.12-1.38) 6 wk prior to birth 1.00 (Ref group); 1.00 (0.93-1.08); 1.08 (0.98-1.20); 1.03 (0.93-1.14) Entire pregnancy: 1.00 (Ref group); 0.76 (0.70-0.82); 0.84 (0.77-0.91); 1.03 (0.91-1.17)
Author: Salam et al. (2005, 087885) **Period of Study:** 1975-1987 **Location:** California	**Health Outcome:** Birth weight, LBW , IUGR **Study Design:** Retrospective cohort **Statistical Analyses:** Linear and logistic regression **Age Groups Analyzed:** NA **Sample Description:** 3,901 infants from the California Children's Health Study	**Averaging Time:** 24-h **Mean (SD) unit:** 1.8 ppm (0.9) (Entire pregnancy) **Range:** NR **Copollutant: correlation** PM_{10}: r = 0.41 NO_2: r = 0.69 O_3: r = -0.27	**Increment:** Entire pregnancy 1.2 ppm Trimesters: First: 1.4 ppm; Second: 1.4 ppm; Third: 1.3 ppm **Regression co-efficient for birth weight (g) [Lower CI, Upper CI]** Trimesters: First: -21.7 (-42.3 to -1.1); Second: 11.3 (-9.7 to 32.3); Third: 11.8 (-8.4 to 32.1); Entire pregnancy: 2.2 (-20.1 to 24.4) OR for LBW [Lower CI, Upper CI] Trimesters: First: 1.0 (0.7-1.5); Second: 0.9 (0.6-1.3); Third: 0.7 (0.5-1.1); Entire pregnancy: 0.8 (0.6-1.3) OR for IUGR [Lower CI, Upper CI] Trimesters: First: 1.2 (1.0-1.4); Second: 1.0 (0.9-1.1); Third: 1.0 (0.8-1.1); Entire pregnancy: 1.0 (0.9-1.2)
Author: Son et al. (2008, 190323) **Period of Study:** NR **Location:** Seoul, Korea	**Health Outcome:** Postneonatal mortality from all causes **Study Design:** Case crossover and time series **Statistical Analyses:** Conditional logistic regression **Age Groups Analyzed:** NA **Sample Description:** 1,286 first-born birth and infant death records from 1999-2003 (only postneonatal deaths)	**Averaging Time:** 8 h **Mean (SD) unit:** 1.01 ppm **Range (Min, Max):** 0.29, 3.54 **Copollutant:** PM_{10}, NO_2, O_3, SO_2	**Increment**: NR **RR Estimate** [Lower CI, Upper CI] **Lags examined (days):** 0-7 Time Series: 1.323 (1.077, 1.625) Case-crossover(1:6): 1.029 (0.833, 1.271) CLR Analyses using different control selection schemes 1:2: 1.076 (0.839, 1.379) 1:4: 0.981 (0.784, 1.228) 1:6: 1.029 (0.833, 1.271)
Author: Strickland et al. (2009, 190324) **Period of Study:** NR **Location:** Atlanta, GA	**Health Outcome:** Cardiovascular malformations **Study Design:** Retrospective cohort **Statistical Analyses:** Poisson GLM **Age Groups Analyzed:** NA **Sample Description:** Pregnancies reaching at least 20-wk gestation that were conceived during January 1, 1986-March 12, 2003	**Averaging Time:** 24-h **Mean (SD) unit:** By season of conception: March-May: 0.9 ppm June-August: 0.8 ppm Sept.-Nov.: 0.9 ppm Dec.-Feb.: 0.7ppm By yr of conception: 1986-1991: 0.7 ppm 1992-1997: 0.8 ppm 1998-2003: 0.7 ppm **Range (IQR):** 0.3 **Copollutant:** PM_{10} (24 h): r = 0.32 NO_2 (24 h): r = 0.41 O_3 (8 h): r = 0.07 SO_2 (24 h): r = 0.23	**Increment:** NR **RR Estimate** [Lower CI, Upper CI] Atrial septal defect, secundum: 1.16 (0.67, 2.00) Coarctation of the aorta: 1.15 (0.65, 2.06) Hypoplastic left heart syndrome: 0.82 (0.37, 1.84) Patent ductus arteriosus: 1.39 (0.72, 2.68) Pulmonary stenosis, valvar: 0.97 (0.53, 1.75) Tetralogy of Fallot: 1.09 (0.59, 2.00) Transposition of the great arteries: 1.29 (0.58, 2.85) Ventricular septal defect, muscular: 1.08 (0.77, 1.50) Ventricular septal defect, perimembranous: 1.06 (0.67, 1.68) Conotruncal defect: 1.22 (0.81, 1.85) Left ventricular outflow tract defect: 1.09 (0.70, 1.68) Right ventricular outflow tract defects: 0.73 (0.44, 1.22)

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Tsai et al. (2006, 090709) **Period of Study:** 1994-2000 **Location:** Kaoshiung, Taiwan	**Health Outcome:** Postneonatal death (27 days-1 yr old) **Study Design:** Case crossover **Statistical Analyses:** Poisson regression **Age Groups Analyzed:** NA **Sample Description:** NR	**Averaging Time:** 24 h **Mean (SD) unit:** 8.27 ppm x10 **Range (Min, Max):** 2.26, 17.7 **Copollutant**: NR	**Increment: Interquartile range:** 0.31 ppm OR for Post-neonatal mortality [Lower CI, Upper CI] **Lag examined:** 0-2 Lag 0-2: 1.051 (0.304-3.630)
Author: Wilhelm et al. (2005, 088668) **Period of Study:** 1994-2000 **Location:** Los Angeles, CA	**Health Outcome:** Term LBW and PTB **Study Design:** Retrospective cohort **Statistical Analyses:** Logistic regression **Age Groups Analyzed:** NA **Sample Description:** 518,254 births within 4 mi of a monitoring station. Varied according to analyses.	**Averaging Time:** 24 h **Mean (SD) unit**: Trimester 1: 1.42 ppm Results for third trimester and 6 wk prior to birth were similar to first trimester **Range (Min, Max):** 0.26, 2.82 **Copollutant correlation:** First Trimester: PM_{10}: r = 0.12 $PM_{2.5}$: r = 0.57 NO_2: r = 0.81 SO_2: r = -0.31	**Increment:** 1 ppm **RR for PTB** [Lower CI, Upper CI] First trimester: <1 mile: 1.06 (1.00-1.12) 1-2 miles: 1.06 (1.03-1.10) 2-4 miles: 1.08 (1.06-1.09) ZIP code level: 1.04 (1.01-1.07) 6 wk prior to birth: <: 1.04 (0.98-1.09) 1-2 miles: .04 (1.01-1.08) 2-4 miles: 1.01 (0.99-1.02) ZIP code level: 1.03 (1.00-1.06) **Notes:** All results above did not persist in multipollutant model (CO, NO_2, O_3, PM_{10}) OR for term LBW [Lower CI, Upper CI] Third trimester: <1 mile: 1.10 (0.98-1.23) 1-2 miles: 1.05 (0.99-1.13) 2-4 miles: 1.06 (1.02-1.10) ZIP code level: 1.12 (1.05-1.19) **Notes:** All results above did not persist in multipollutant model (CO, NO_2, O_3, PM_{10}) See paper for results based on exposure category groupings.
Author: Woodruff et al. (2008, 098386) **Period of Study:** 1999-2002 **Location:** U.S. counties with >250,000 residents	**Health Outcome:** Postneonatal deaths all causes; respiratory; SIDS; ill-defined + SIDS; other causes. **Study Design:** Retrospective cohort **Statistical Analyses:** Logistic regression (GEE) **Age Groups Analyzed:** NA **Sample Description:** NR	**Averaging Time:** 24 h **Mean (SD) unit:** All causes: 0.70 ppm **Range (Min, Max):** Percentiles: 25th: 0.48; 75th: 0.87 **Copollutant correlation:** PM_{10}: r = 0.18 SO_2: r = 0.27 O_3: r = -0.46	**Increment:** 0.39 ppm **OR for Post-neonatal mortality [Lower CI, Upper CI]** Avg exposure over the first 2 mo of life: All causes: 1.01 (0.95-1.07) Respiratory: 1.14 (0.93-1.40) SIDS: 0.88 (0.76-1.03) Ill-defined + SIDS: 0.93 (0.84-1.02) Other causes: 1.02 (0.97-1.07)
Author: Yang et al. (2004, 094376) **Period of Study:** 1994-2000 **Location:** Taipei, Taiwan	**Health Outcome:** Postneonatal mortality (27 days-1 yr old) **Study Design:** Case crossover **Statistical Analyses:** Poisson regression **Age Groups Analyzed:** NA **Sample Description:** NR	**Averaging Time:** 24-h **Mean (SD) unit:** 15.8 ppm x10 **Range (Min, Max):** 3.20, 48.4 **Copollutant:** NR	**Increment:** Interquartile range: 0.56 ppm OR for Post-neonatal mortality [Lower CI, Upper CI] **Lag examined**: 0-2 Lag 0-2: 1.038 (0.663-1.624)

Table C-4. Studies of short-term CO exposure and respiratory morbidity

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Andersen et al. (2008, 096150) **Period of Study:** Dec 1998-Dec 2004 **Location:** Copenhagen, Denmark	**Health Outcome:** Wheezing symptoms **Study Design:** Panel **Statistical Analyses**: Logistic regression (GEE) **Age Groups Analyzed:** 0-3 yrs **Sample Description:** 205 children of mothers with asthma	**Averaging Time:** 24h **Mean (SD) unit:** 0.29 (0.10) ppm **Range (percentiles):** 25th = 0.22; 75th = 0.34 **Copollutant: correlation** PM_{10}: r = 0.45 $PM_{2.5}$: r = 0.45 UFPNC: r = 0.52 NO_2: r = 0.75 NO_X: r = 0.74 O_3: r = -0.63	**Increment:** NR **OR Estimate [Lower CI, Upper CI] ;** lag: **Lags examined:** 0, 1, 2, 3, 4, 2-4 Lag 0: 0.96 (0.80, 1.15) Lag 1: 0.92 (0.77, 1.10) Lag 2: 1.08 (0.92, 1.28) Lag 3: 1.07 (0.90, 1.26) Lag 4: 1.02 (0.84, 1.23) 3d mean: 1.07 (0.87, 1.32)
Author: Bhattacharyya et al. (2009, 180154) **Period of Study:** 1997-2006 **Location:** NR (National Health Interview Survey as aggregated in the Integrated Health Interview Series served as data source)	**Health Outcome:** Respiratory morbidity **Study Design:** Cross-sectional study **Statistical Analyses:** SPSS version 14.0, univariate linear regression analysis **Age Groups Analyzed:** 18+ yr (avg: 45.2 yr) **Sample Description:** Hay fever, weak/failing kidneys, sinusitis all in past 12 mo	**Averaging Time:** NR **Mean (SD) unit:** NR **Range (Min, Max):** 2.209-4.157ppm (decreased with increasing yr) **Copollutant:** NR	**Increment:** NR Linear regression analysis for disease condition prevalence: Hayfever: Standardized B- 0.012, p-value- <0.001; Sinusitis: Standardized B- 0.027, p-value- <0.001; Kidney Weak/Failin: Standardized B- -0.001, p-value- <0.001 **Lags examined:** NR
Author: Chen et al. (1999, 011149) **Period of Study:** 5/1995-1/1996 **Location:** 3 Taiwan communities	**Health Outcome:** Lung function (FVC, FEV_1, FEV_1/FVC, $FEF_{25-75\%}$, PEF) **Study Design:** Cross-sectional survey **Statistical Analyses:** Multivariate linear model **Population:** 941 children (Boys: 453; Girls: 488) **Age Groups Analyzed:** 8-13 yr	**Pollutant:** CO **Averaging Time:** 1-h max; 24-h avg **Mean (SD) unit**: NR **Range (Min, Max):** 1-h max: (0.4, 3.6) **Copollutant correlation:** NO_2: r = 0.86 – 0.98 **Note:** To represent the schoolchildren's exposure the daytime avg and peak concentrations were measured from 0800 to 1800.	**Increment:** NR **β Coefficient (SE); lag:** FVC (mL) 24-h avg -66.6 (40.73); 1 -147.71 (64.48); 2 2.2 (48.13); 7 1-h max -33.25 (20.74); 1 -16.48 (19.67); 2 -5.18 (16.48); 7 FEV_1 (mL) 24-h avg 20.55 (38.24); 1 -82.42 (60.95); 2 48.23 (45.58); 7 1-h max 1.2 (19.48); 1 -1.44 (18.57); 2 20.96 (15.67); 7
Author: Chen et al. (2000, 011931) **Period of Study:** 8/1996-6/1998 **Location:** Washoe County, NV	**Health Outcome:** School absenteeism **Study Design:** Time series **Statistical Analyses:** Maximum likelihood **Population:** 1st to 6th grade children: 27,793 **Age Groups Analyzed:** 1st to 6th grade children	**Pollutant:** CO **Averaging Time:** 1-h max **Mean (SD) unit:** 2.73 (1.154) ppm **Range (Min, Max):** (0.65, 2.73) **Copollutant correlation:** PM_{10}: r = 0.721 O_3: r = -0.204	**Increment:** 1.0 ppm **% Increase (Lower CI, Upper CI);** lag: 3.79% (1.04-6.55); 0

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: de Hartog et al. (2003, 001061) **Period of Study:** 1998-1999 **Location:** Amsterdam, Netherlands; Erfurt, Germany; Helsinki, Finland	**Health Outcome:** Respiratory symptoms (shortness of breath, being awakened by breathing problems, phlegm, wheezing, tripping heart) **Study Design:** Time series **Statistical Analyses:** Logistic regression **Population:** Nonsmoking individuals with CHD: Amsterdam: 37 Erfurt: 47 Helsinki: 47 **Age Groups Analyzed:** ≥ 50 yr	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** Amsterdam: 0.6 mg/m^3 Erfurt: 0.4 mg/m^3 Helsinki: 0.4 mg/m^3 **Range (Min, Max):** Amsterdam: (0.4, 1.6) Erfurt: (0.1, 2.5) Helsinki: (0.1, 1.0) **Copollutant:** $PM_{2.5}$; NO_2	**Increment:** 0.25 mg/m^3 **Odds Ratio (Lower CI, Upper CI); lag:** Incidence of symptoms Shortness of breath 1 (0.92-1.1); 0 0.96 (0.88-1.05); 1 1 (0.92-1.09); 2 1.07 (0.98-1.16); 3 1.03 (0.9-1.18); 0-4 Being awakened by breathing problems 1.02 (0.92-1.14); 1 1.03 (0.93-1.15); 2 1.11 (1-1.22); 3 1.16 (0.98-1.37); 0-4 Phlegm 1.05 (0.93-1.19); 0 1.02 (0.91-1.14); 1 1.08 (0.96-1.22); 2 1.09 (0.97-1.22); 3 1.13 (0.94-1.35); 0-4 Prevalence of symptoms Shortness of breath 1 (0.94-1.06); 0 0.99 (0.94-1.05); 1 0.99 (0.93-1.05); 2 1.01 (0.95-1.07); 3 0.98 (0.9-1.07); 0-4 Being awakened by breathing problems 1.01 (0.93-1.1); 1 0.99 (0.91-1.08); 2 1.1 (1.02-1.19); 3 1.13 (1-1.29); 0-4
Author: Delfino et al. (2003, 050460) **Period of Study:** 11/1999-1/2000 **Location:** Los Angeles, CA	**Health Outcome:** Asthma symptoms (Cough, wheeze, sputum production, shortness of breath, chest tightness) (symptom scores >1, symptoms scores >2); Lung function (PEF) **Study Design:** Panel study **Statistical Analyses:** Asthma symptoms: GEE Lung function: Generalized linear mixed model **Population:** 22 asthmatic Hispanic children **Age Groups Analyzed:** 10-15 yr	**Pollutant:** CO **Averaging Time:** 1-h max; 8-h max **Mean (SD) unit:** 1-h max: 7.7 (3.1) ppb 8-h max: 5.0 (2.0) ppb **Range (Min, Max):** 1-h max: (2, 17) 8-h max: (1, 10) **Copollutant correlation:** NO_2: r = 0.65; O_3: r = -0.17; Acetaldehyde: r = 0.51; Acetone: r = 0.28; Formaldehyde: r = 0.41; Benzene: r = 0.50; Ethylbenzene: r = 0.62; Tetrachloroethylene: r = 0.63; Toluene: r = 0.71; m,p - Xylene: r = 0.72; PM_{10}: r = 0.50; EC: r = 0.60; OC: r = 0.55; SO_2: r = 0.69	**Increment:** 5.0 ppb & 3.0 ppb **Odds Ratio (Lower CI, Upper CI); lag:** 1-max Increment: 5.0 ppb Symptom scores >1 0.95 (0.52-1.75); 0 1.11 (0.75-1.65); 1 Symptom scores >2 0.48 (0.07-3.53); 0 .28 (0.53-3.12); 1 8-h max Increment: 3.0 ppb Symptom scores >1 0.95 (0.55-1.62); 0 1.2 (0.77-1.86); 1 Symptom scores >2 0.53 (0.10-2.92); 0 1.43 (0.41-5.00); 1
Author: Estrella et al. (2005, 099124) **Period of Study:** 1/2000-4/2000 **Location:** Quito, Ecuador	**Health Outcome:** Acute respiratory infection **Study Design:** Prospective study **Statistical Analyses:** Logistic regression; Poisson **Population:** 960 children **Age Groups Analyzed:** 6-11 yr	**Pollutant:** CO **Averaging Time: NR** **Mean (SD) unit**: NR **Range (Min, Max):** NR **Copollutant:** NR	**Increment:** NR **Odds Ratio (Lower CI, Upper CI); lag:** Acute respiratory infection ARI in children COHb >2.5% vs. COHb <2.5%: Adjusted Logistic Regression Model 3.25 (1.65-6.38) ARI in children COHb >2.5% vs. COHb <2.5%: Crude Logistic Regression Model 2.06 (1.30-3.20) Log-Linear Model (Each Percent Increase in COHb above 2.5%) 1.15 (1.03-1.28)

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Fischer et al. (2002, 025731) **Period of Study:** NR **Location:** Utrecht, Netherlands	**Health Outcome:** Lung function (FVC, FEV_1, PEF, MMEF) **Study Design:** Panel study **Statistical Analyses:** Restricted max likelihood linear model **Population:** 68 children **Age Groups Analyzed:** 10-11	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 921 $\mu g/m^3$ **Range (Min, Max):** (319, 1540) **Copollutant:** PM_{10}; BS; NO_2; NO	**Increment:** 100 $\mu g/m^3$ mL (SE); lag: FVC: 0.5 (0.4); 1; 0.1 (0.2); 2 FEV1: -0.4 (0.5); 1; -0.2 (0.2); 2 m/s (SE); lag: PEF: -1.1 (2.8); 1; -0.6 (1.1); 2 MMEF: -0.5 (1.4); 1; -0.3 (0.6); 2
Author: Ho et al. (2007, 093265) **Period of Study:** Oct 1995-Mar 1996 **Location:** Taipei, Taiwan	**Health Outcome:** Asthma **Study Design:** Panel **Statistical Analyses:** Logistic regression (GEE) **Age Groups Analyzed:** 10-17 yr **Sample Description:** A stratified cluster random sample of students (n=69,367) from 1,139,452 students sampled nationwide	**Averaging Time:** 8 h **Mean (SD) unit:** NR **Range (min, max):** NR **Copollutant:** NO, NO_2, NO_X, O_3, SO_2, PM_{10}, PSI	**Increment:** very high, high, med, low, very low OR Estimate [Lower CI, Upper CI] ; lag: **Lags examined:** NR Females: 1.984 (1.536, 2.561) Males: 1.780 (1.377, 2.302) Monthly attack rate vs single air pollutant concentrations Estimate (p-value): 0.0750 (0.3336)
Author: Lagorio et al. (2006, 089800) Period of Study: 5/1999-6/1999; 11/1999-12/1999 **Location:** Rome, Italy	**Health Outcome:** Lung function (FVC, $FEV_{1)}$ **Study Design:** Time-series panel study **Statistical Analyses:** Generalized estimating equations (GEE) **Population:** COPD panel: 11 Asthma panel: 11 IHD panel: 7 **Age Groups Analyzed:** COPD panel: 50-80 yr Asthma panel: 18-64 yr IHD panel: 40-64 yr **Notes:** Asthma panel was restricted to never smokers, while COPD and IHD panels include former smokers if smoking cessation occurred at least 1 yr prior to enrollment.	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** Overall: 7.4 (6.2) mg/m^3 Spring: 2.1 (0.3) mg/m^3 Winter: 12.3 (4.9) mg/m^3 **Range (Min, Max):** Overall: (1.6, 28.9) **Copollutant correlation:** $PM_{2.5}$: r = 0.67 $PM_{10-2.5}$: r = -0.09 PM_{10}: r = 0.55 NO_2: r = 0.05 O_3: r = -0.87 SO_2: r = 0.65	**Increment:** 1 mg/m^3 **β Coefficient (SE); lag:** COPD panel FVC (% of predicted) -0.14 (0.15);0 -0.13 (0.18); 0-1 0.15 (0.23); 0-2 FEV1 (% of predicted) -0.05 (0.13); 0 -0.12 (0.16); 0-1 -0.03 (0.2); 0-2 Asthma panel FVC (% predicted) 0.02 (0.12); 0 -0.001 (0.13); 0-1 -0.06 (0.16); 0-2 FEV1 (% predicted) -0.05 (0.14); 0 -0.16 (0.15); 0-1 -0.28 (0.18); 0-2 IHD panel FVC (% of predicted) 0.176 (0.101); 0 0.132 (0.120); 0-1/ 0.132 (0.165); 0-2 FEV1 (% of predicted) 0.204 (0.120); 0 0.114 (0.142); 0-1 0.159 (0.194); 0-2
Author: Moon et al. (2009, 190297) **Period of Study:** Apr 2003-May 2003 **Location:** Seoul, Incheon, Busan, & Jeju, Korea	**Health Outcome:** Respiratory symptoms **Study Design:** Panel **Statistical Analyses:** Logistic regression (GEE) **Age Groups Analyzed:** < 13 yr **Sample Description:** 696 children	**Averaging Time:** 24h **Mean (SD) unit:** NR **IQ Range:** 0.12ppm **Copollutant:** PM_{10}, SO_2, NO_2, O_3	**Increment:** 0.12 ppm (IQR) **OR Estimate [Lower CI, Upper CI] ; lag:** **Lags examined:** lag days 0-3 Lower resp. symptoms: 1.005 (1.003, 1.008), lag 0 Upper resp. symptoms: 1.006 (1.003, 1.008), lag 0-2 Irritation symptoms: 1.004 (1.001, 1.006), lag 1-3

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Mortimer et al. (2008, 187280) **Period of Study:** Nov 2000-Apr 2005 **Location:** Fresno, California	**Health Outcome:** Allergic sensitization **Study Design:** Panel **Statistical Analyses:** Multistep modeling **Age Groups Analyzed:** 6-11 yr **Sample Description:** 170 children with physician diagnosed asthma	**Averaging Time:** 24-h avg, 24-h max, 8-h max **Mean (SD) unit:** NR **IQ Range (24-h avg, 24-h max, 8-h max):** 0.28, 0.79, 0.52 **Copollutant:** entire prenatal correlation NO_2: r = 0.74 O_3: r = -0.40 PM_{10}: r = 0.32	**Increment:** IQR **OR Estimate [Lower CI, Upper CI] ; lag:** **Lags examined:** NR Entire Pregnancy: CO 24-h avg: 1.45 (1.02, 2.07) CO 24-h max: 1.53 (1.01, 2.33) CO 24-h avg: 1.55 (1.01, 2.37)
Author: Nkwocha et al. (2008, 190304) **Period of Study:** Feb 2005-Jul 2006 **Location:** Port Harcourt, Nigeria	**Health Outcome:** Respiratory symptoms **Study Design:** Panel **Statistical Analyses:** Mixed Effects models **Age Groups Analyzed:** 0-5 yr **Sample Description:** 250 children	**Averaging Time:** 8 h **Mean (SD) unit:** NR **Range (min, max):** 1.3 µg/m^3, 1.83 µg/m^3 **Copollutant:** NO_2, SO_2, PM_{10}	**Increment:** NR **Lags examined:** NR **R Estimate:** Dry season: 0.13 Wet season: 0.25
Author: O'Connor et al. (2008, 156818) **Period of Study:** Aug 1998-Jul 2001 **Location:** Boston, MA; the Bronx, NY; Chicago, IL; Dallas, TX; New York, NY; Seattle, WA; Tuscon, AZ	**Health Outcome:** respiratory symptoms **Study Design:** panel **Statistical Analyses:** Mixed Effects Models **Age Groups Analyzed:** 5-12 yr **Sample Description:** 861 children with persistent asthma and atopy living in low-income census tracts	**Averaging Time:** 8 h **Mean (SD) unit:** NR **Range (10th-90th):** 872.1 ppb **Copollutant:** PM_{10}, SO_2, NO_2, O_3	**Increment:** 872.1 ppb **Lags examined:** NR **Change Estimate [Lower CI, Upper CI]:** FEV_1: -0.56 (-1.31, 0.20) PEFR: -0.49 (-1.24, 0.27) Pollution Impact*[Lower CI, Upper CI]: Wheeze-cough: 1.26 (1.03, 1.55) Nighttime asthma: 1.35 (1.07, 1.71) Slow play: 1.28 (1.04, 1.59) OR [Lower CI, Upper CI]: Missed School: 1.08 (0.76, 1.53) *Coefficients from the negative binomial model and indicate the multiplicative effect per unit change
Author: Park et al. (2002, 093798) **Period of Study:** 3/1996-12/1999 **Location:** Seoul, Korea	**Health Outcome:** School absenteeism **Study Design:** Time series **Statistical Analyses:** Poisson GAM, LOESS **Population:** ~1,264 children (671 Boys, 593 girls) **Age Groups Analyzed:** 1st through 6th grade students	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 1.11 (0.40) ppm **Range (Min, Max):** (0.39, 2.97) **Copollutant correlation:** PM_{10}: r = 0.56; NO_2: r = 0.70; SO_2: r = 0.67; O_3: r = -0.46	**Increment:** 0.52 ppm **Relative Risk (Lower CI, Upper CI); lag:** Total Absences: 0.95 (0.94-0.97); 0 Non-Illness Related Absences: 0.99 (0.96-1.02); 0 Illness-Related Absences: 0.96 (0.94-0.98); 0
Author: Park et al. (2005, 088673) **Period of Study:** 3/2002-6/2002 **Location:** Incheon, Korea	**Health Outcome:** Lung function (PEF variability (>20%), Mean PEF); Respiratory symptoms (night respiratory symptoms, cough, inhaler use) **Study Design:** Panel study **Statistical Analyses:** GEE; Poisson GAM **Population:** 64 bronchial asthmatics **Age Groups Analyzed:** 16-75 yr	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** Control days: 0.6368 (0.1522) ppm Dust days: 0.6462 (0.0945) ppm **Range (Min, Max):** NR **Copollutant:** NR	**Increment:** NR **Relative Risk (Lower CI, Upper CI); lag:** PEF variability (>20%): 1.43 (0.54-3.75) Night respiratory symptoms: 0.98 (0.51-1.86) β Coefficient (SE); lag: PEF variability (>20%): 0.9737 (0.3187) Mean PEF (L/min): -10.103 (2.7146) Night respiratory symptoms: -0.018 (0.3654) Cough: 0.0855 (0.1826) Inhaler Use: 0.0796 (0.1733)

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Penttinen et al. (2001, 030335) **Period of Study:** 11/1996-4/1997 **Location:** Helsinki, Finland	**Health Outcome:** Lung function (PEF) **Study Design:** Panel study **Statistical Analyses:** First order autoregressive linear model **Population:** 57 nonsmoking adult asthmatics **Age Groups Analyzed:** NR	**Pollutant:** CO **Averaging Time:** 24-h avg **Median unit:** 0.4 mg/m^3 **Range (Min, Max):** (0.1, 1.1) mg/m^3 **Copollutant correlation:** PM_{10}: r = -0.03 $PM_{10-2.5}$: r = -0.30 $PM_{2.5}$: r = 0.32 PM_1: r = 0.39 PNC: r = 0.44 NC0.01-0.1: r = 0.43 NC0.1-1: r = 0.47 NO: r = 0.60 NO_2: r = 0.44	**Increment:** 0.2 mg/m^3 β Coefficient (SE); lag: PEF Deviations (L/min) Morning 0.27 (0.38); 0 -1.08 (0.36); 1 0.23 (0.38); 2 -1.11 (1.19); 5-day avg Afternoon -0.4 (0.43); 0 -0.13 (0.41); 1 -0.71 (0.41); 2 -3.03 (1.06); 5-day avg Evening -0.7 (0.45); 0; -0.31 (0.44); 1 0.3 (0.44); 2 -3.62 (1.19); 5-day avg Co-pollutant models with PNC Morning: -0.67 (0.64); 1 Afternoon: -0.46 (0.69); 0 Evening: -0.46 (0.73); 0
Author: Rabinovitch et al. (2004, 096753) **Period of Study:** 11/1999-3/2000; 11/2000-3/2001; 11/2001-3/2002 **Location:** Denver, CO	**Health Outcome:** Lung function (FEV_1); asthma exacerbation; bronchodilator use **Study Design:** Panel study **Statistical Analyses:** Pulmonary function: Mixed effects model; Asthma exacerbation and medication use: GLM **Population:** Urban poor asthmatic children: 1999-2000: 41 2000-2001: 63 2001-2002: 43 **Age Groups Analyzed:** 6-12 yr	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 1.0 (0.4) ppm **Range (Min, Max):** (0.3, 3.5) **Copollutant:** $PM_{2.5}$; PM_{10}; NO_2; SO_2; O_3	**Increment:** 0.4 ppm β Coefficient (SE); lag: FEV1 AM: -0.001 (0.008); 3-day ma PM: 0.015 (0.01); 3-day ma Odds Ratio (Lower CI, Upper CI); lag: Asthma exacerbation: 1.012 (0.913-1.123); 3-day ma Bronchodilator use: 1.065 (1.001-1.133); 3-day ma
Author: Ranzi et al. (2004, 089500) **Period of Study:** 2/1999-5/1999 **Location:** Emilia-Romagna, Italy	**Health Outcome:** Lung function; respiratory symptoms, medication use **Study Design:** Panel study **Statistical Analyses:** GLM **Population:** 120 "asthma-like" school children **Age Groups Analyzed:** 6-11 yr	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** Urban area: 1.54 mg Rural area: 1.22 mg **Range (Min, Max):** NR **Copollutant: NO2;** TSP; $PM_{2.5}$	The study did not present quantitative results for CO.
Author: Rodriguez et al. (2007, 092842) **Period of Study:** 1996-2003 **Location:** Perth, Australia	**Health Outcome:** Respiratory symptoms (body temperature, cough, wheeze/rattle chest, runny/blocked nose) **Study Design:** Panel study **Statistical Analyses:** Logistic regression, GEE **Population:** 263 children at high risk of developing asthma **Age Groups Analyzed:** 0-5 yr	**Pollutant:** CO **Averaging Time:** 8-h avg **Mean (SD) unit:** 1.408 ppm **Range (Min, Max):** (0.012, 8.031) **Copollutant:** NR	**Increment:** NR **Odds Ratio (Lower CI, Upper CI); lag:** Body Temperature 1.024 (0.911-1.151); 0 1.056 (0.943-1.184); 5 0.991 (0.962-1.021); 0-5 Cough 1.001 (0.996-1.005); 0 1.064 (0.941-1.02); 5 1.028 (0.996-1.061); 0-5 Wheeze/Rattle Chest 1.089 (0.968-1.226); 0 1.136 (1.016-1.26); 5 1.035 (1.005-1.066); 0-5 Runny/Blocked Nose 1.094 (0.824-1.453); 0 1.38 (1.028-1.853); 5 1.101 (1.025-1.183); 0-5

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Schildcrout et al. (2006, 089812) **Period of Study:** 11/1993-9/1995 **Location:** 8 North American cities: Albuquerque, NM Baltimore, MD Boston, MA Denver, CO San Diego, CA Seattle, WA St. Louis, MO Toronto, ON, Canada	**Health Outcome:** Asthma symptoms; rescue inhaler use **Study Design:** Panel study **Statistical Analyses:** Asthma symptoms: Logistic regression; Rescue Inhaler Use: Poisson regression **Population:** 990 asthmatic children **Age Groups Analyzed:** 5-12 yr	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** NR **Range (Min, Max):** NR **Copollutant:** NO_2; O_3; PM_{10}; SO_2	**Increment:** 1.0 ppm **Odds Ratio (Lower CI, Upper CI); lag:** Asthma Symptoms 1.08 (1.01-1.14); 0 1.07 (0.99-1.16); 1 1.08 (1.02-1.15); 2 1.05 (1.01-1.09); 0-2 Asthma Symptoms + 20 ppb increase in NO_2 1.07 (1-1.14); 0 1.04 (0.96-1.11); 1 1.09 (1.02-1.16); 2 1.04 (1-1.08); 0-2 + 25 µg/m^3 increase in PM_{10} 1.08 (1.01-1.15); 0 1.06 (0.99-1.14); 1 1.08 (1.02-1.14); 2 1.05 (1.01-1.08); 0-2 + 10 ppb increase in SO_2 1.07 (0.99-1.16); 0 1.06 (0.96-1.19); 1 1.1 (1.02-1.18); 2 1.05 (1-1.09); 0-2 Rescue Inhaler Use 1.07 (1.01-1.13); 0 1.05 (0.99-1.1); 1 1.06 (1.01-1.1); 2 1.04 (1.01-1.07); 0-2 Rescue Inhaler Use + 20 ppb increase in NO_2 1.05 (0.99-1.12); 0 1.04 (0.98-1.11); 1 1.07 (1.02-1.12); 2 1.04 (1-1.07); 0-2 + 25 µg/m^3 increase in PM_{10} 1.06 (0.99-1.13); 0 1.05 (0.99-1.11); 1 1.05 (1.01-1.09); 2 1.03 (1-1.07); 0-2 + 10 ppb increase in SO_2 1.04 (0.96-1.12); 0 1.04 (0.97-1.1); 1 1.08 (1.03-1.13); 2 1.04 (1-1.08); 0-2
Author: Silkoff et al. (2005, 087471) **Period of Study:** 11/11/1999-3/31/2000; 11/1/2000-3/16/2001 **Location:** Denver, CO	**Health Outcome:** Lung function (FEV1, PEF); recorded symptoms; rescue medication use **Study Design:** Panel study **Statistical Analyses:** Rescue medication use and total symptom score: GEE; Lung function: Mixed effects model **Population:** 1st winter: 16 with a history of more than 10 pack yr of tobacco use, airflow limitation with FEV1 of less than 70% of predicted value, and FEV1/ FVC ratio of less than 60% 2nd winter: 18 with a history of more than 10 pack yr of tobacco use, airflow limitation with FEV1 of less than 70% of predicted value, and FEV1/ FVC ratio of less than 60% **Age Groups Analyzed**: ≥ 40 yr	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 1999-2000: 1.2 (0.555) ppm 2000-2001: 1.1 (0.5) ppm **Range (Min, Max):** 1999-2000: (0.340, 3.790) 2000-2001: (0.360, 2.810) **Copollutant:** NR	The study did not present quantitative results for CO.

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: Slaughter et al. (2003, 086294) **Period of Study:** 12/1994-8/1995 **Location:** Seattle, WA	**Health Outcome:** Asthma severity; medication use **Study Design:** Panel study **Statistical Analyses:** Asthma severity: Ordinal logistic regression; Medication use: Poisson **Population:** 133 mild-to-moderate asthmatic children **Age Groups Analyzed:** 5-13 yr	**Pollutant:** CO **Averaging Time:** 24-h avg **Median unit:** 1.47 ppm IQR (25th, 75th): (0.23, 1.87) **Copollutant:** NR	**Increment:** Increased asthma attack severity: 0.67 ppm Increased rescue inhaler use: 1.0 ppm **Odds Ratio (Lower CI, Upper CI); lag:** Increased asthma attack severity: Without transition: 1.21; 1 With transition: 1.17; 1 Increased rescue inhaler use: Without transition: 1.09 (1.03-1.16); 1 With transition: 1.06 (1.01-1.1); 1
Author: Steerenberg et al. (2001, 017157) **Period of Study:** NR **Location:** Bilthoven and Utrecht, the Netherlands	**Health Outcome:** Lung function (PEF); exhaled nitric oxide; inflammatory nasal markers **Study Design:** Panel study **Statistical Analyses:** Restricted max likelihood linear model **Population:** 126 children **Age Groups Analyzed:** 8-13 yr **Notes:** The study was only conducted for a two mo period: February and March.	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** Utrecht: 0.8 mg/m^3 Bilthoven: 0.5 mg/m^3 **Range (Min, Max):** Utrecht: (0.3, 2.3) Bilthoven: (0.3, 0.9) **Copollutant:** NR	The study did not present quantitative results for CO.
Author: Timonen et al. (2002, 025653) **Period of Study:** 2/1994-4/1994 **Location:** Kuopio, Finland	**Health Outcome:** Exercise induced bronchial responsiveness; Lung function (FVC, FEV1, MMEF, AEFV) **Study Design:** Panel study **Statistical Analyses:** Linear regression **Population:** 33 children with chronic respiratory symptoms **Age Groups Analyzed:** 7-12 yr	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 0.6 mg/m^3 **Range (Min, Max):** (0.1, 2.8) **Copollutant correlation:** PM_{10}: r = 0.52 BS: r = 0.80 PNC0.01-0.03: r = 0.81 PNC0.03-0.1: r = 0.87 PNC0.1-0.3: r = 0.71 PNC0.3-1.0: r = 0.60 PNC1.0-3.2: r = 0.84 PNC3.2-10: r = 0.79 NO_2: r = 0.85	**Increment:** 0.32 mg/m^3 **β Coefficient (SE); lag:** Exercise induced responsiveness ΔFEV_1 (%) -0.081 (0.647); 0 0.03 (0.262); 1 0.087 (0.26); 2 -0.091 (0.275); 3 0.19 (0.599); 0-3 ΔMMEF (%) 0.442 (1.79); 0 0.52 (0.723); 1 0.313 (0.719); 2 -0.616 (0.75); 3 0.096 (1.64); 0-3 ΔAEFV (%) 0.287 (1.19); 0 0.281 (0.482); 1 0.904 (0.474); 2 0.15 (0.483); 3 1.6 (1.05); 0-3 FVC (mL) 0.064 (10.9); 0 -4.79 (4.51); 1 -9.78 (4.24); 2 -13.9 (4.7); 3 -29.4 (10.1); 0-3 FEV_1 (mL) 19.2 (13.2); 0 -9.04 (5.45); 1 -9.15 (5.21); 2 -11.7 (5.77); 3 -17.5 (12.5); 0-3 MMEF (mL/s) 22.2 (36.9); 0 -23 (15.2); 1 -4.63 (14.7); 2 -30.9 (16); 3 -24.9 (34.8); 0-3 AEFV (L2/s) -0.093 (0.088); 0 -0.068 (0.036); 1 -0.06 (0.035); 2 -0.05 (0.039); 3 -0.076 (0.083); 0-3

Study	Design	Concentrations	CO Effect Estimates (95% CI)
Author: von Klot et al. (2002, 034706) **Period of Study:** 9/1996-3/1997 **Location:** Erfurt, Germany	**Health Outcome:** Asthma symptoms; medication use **Study Design:** Panel study **Statistical Analyses:** Logistic regression **Population:** 53 adults with asthma or asthma symptoms **Age Groups Analyzed:** 37-77 yr	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 0.9 mg/m^3 **Range (Min, Max):** (0.3, 3.0) **Copollutant correlation:** NC0.01-0.1: r = 0.66 NC0.1-0.5: r = 0.79 NC0.5-2.5: r = 0.46 MC0.1-0.5: r = 0.66 MC0.01-2.5: r = 0.65 $PM_{2.5-10}$: r = 0.42 PM_{10}: r = 0.69 NO_2: r = 0.82 SO_2: r = 0.32	**Increment:** 0 and 5-day avg lag: 0.6 mg/m^3 14-day avg lag: 0.54 mg/m^3 **Odds Ratio (Lower CI, Upper CI); lag:** Prevalence: Inhaled β2-agonist use 0.98 (0.93-1.03); 0 1.04 (0.97-1.12); 0-4 0.93 (0.86-1.01); 0-13 Prevalence: Inhaled corticosteroid use 1.05 (1-1.11); 0 1.25 (1.17-1.34); 0-4 1.06 (0.97-1.15); 0-13 Prevalence: Wheezing 1.03 (0.97-1.08); 0 1.13 (1.05-1.22); 0-4 1.14 (1.05-1.25); 0-13 Co-pollutant models Inhaled β2-agonist use CO+MC0.01-2.5: 1 (0.91-1.11); 0-4 CO+NC00.01-0.1: 1.01 (0.91-1.11); 0-4 Inhaled corticosteroid use CO+MC0.01-2.5: 0.89 (0.81-0.98); 0-13 CO+NC: 0.01-0. 1: 0.81 (0.72-0.91); 0-13 Wheezing CO+MC0.01-2.5: 1.15 (1.04-1.27); 0-4 CO+NC0.01-0.1: 1.09 (0.98-1.22); 0-4
Author: Yu et al. (2000, 013254) **Period of Study:** 11/1993-8/1995 **Location:** Seattle, Washington	**Health Outcome:** Asthma symptoms (Wheezing, coughing, chest tightness, shortness of breath) **Study Design:** Panel study **Statistical Analyses:** Repeated measures logistic regression models (GEE) **Population:** 133 mild-to-moderate asthmatics **Age Groups Analyzed**: 5-13 yr	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 1.6 ppm **Range (Min, Max)**: (0.65, 4.18) **Copollutant correlation:** $PM_{1.0}$: r = 0.82 PM_{10}: r = 0.86 SO_2: r = 0.31	**Increment**: 1.0 ppm **Odds Ratio (Lower CI, Upper CI); lag:** Marginal GEE 1.22 (1.03-1.45); 0 1.3 (1.11-1.52); 1 1.26 (1.09-1.46); 2 Transition GEE 1.18 (1.02-1.37); 0 1.25 (1.1-1.42); 1 1.18 (1.04-1.33); 2

Table C-5. Studies of short-term CO exposure and respiratory hospital admissions and ED visits.

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Abe et al. (2009, 190536) **Period of Study:** January 1-December 31, 2005 **Location:** Tokyo, Japan	ED Visits **Health Outcome:** Asthma **Study Design:** Time-series **Statistical Analyses:** Bivariate Pearson correlation coefficitnes, ARIMA model **Age Groups Analyzed:** Children: ≤14 yr, Adults: ≤ 15 yr **Sample Description:** Data from daily number of ambulance transports to ED for asthma	**Averaging Time:** NR **Mean (SD) unit:** 11.5ppm **Range (Min, Max):** 3-44ppm **Copollutant:** NR	**Increment:** 0.1ppm ARIMA model for ambulance transports to ED for asthma exacerbation among adults: β coefficient: 0.151, SE: 0.098, t statistic: 1.537, P value: .125 ARIMA model for ambulance transports to ED for asthma exacerbation among children: β coefficient: 0.019, SE: 0.034, t statistic: 0.549, P value: 0.583 Lags examined: 0 On the day with the highest CO the number of transports was 25. The number of transports for adults and CO had significant bivariate correlations. The fitted ARIMA model had no significant associations.

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Anderson et al. (2001, 017033) **Period of Study:** 10/1994-12/1996 **Location:** West Midlands; U.K.	Hospital Admission **Health Outcome (ICD9):** Respiratory diseases asthma (493) COPD (490-492, 494-496) **Study Design:** Time series **Statistical Analyses:** Regression with quasi-likelihood approach and GAM **Age Groups Analyzed:** All ages 0-14 yr 15-64 yr ≥ 65 yr	**Pollutant:** CO **Averaging Time:** Max 8-h avg **Mean (SD) unit:** 0.8 (0.7) ppm **Range (Min, Max):** (0.2, 10) **Copollutant:** correlation PM_{10}: r = 0.55; $PM_{2.5}$: r = 0.54; $PM_{2.5-10}$: r = 0.10; BS: r = 0.77; SO_4^{2-}: r = 0.17; NO_2: r = 0.73; O_3: r = -0.29; SO_2: r = 0.49	**Increment:** 1.0 ppm **% Increase (Lower CI, Upper CI); lag:** Respiratory Diseases Age Group All ages: 0.3% (-1.10 to 1.70); 0-1 0-14: 1.50% (-0.60 to 3.60); 0-1 15-64: -0.70% (-3.60 to 2.30); 0-1 ≥ 65: 0.00% (-2.10 to 2.10); 0-1 Asthma Age Group 0-14: 3.90% (-0.50 to 8.50); 0-1 15-64: -4.90% (-10.60 to 1.10); 0-1 COPD Age Group ≥ 65: 1.00% (-2.50 to 4.60); 0-1
Author: Andersen et al. (2007, 093201) **Period of Study:** 1/1999-12/2004 **Location:** Copenhagen, Denmark	Hospital Admission **Health Outcome (ICD10):** Respiratory diseases: chronic bronchitis (J41-42), emphysema (J43), COPD (J44), asthma (j45), status asthmaticus (j46), pediatric asthma (j45), pediatric asthmaticus (j46) **Study Design:** Time-series **Statistical Analyses:** Poisson GAM **Age Groups Analyzed:** 5-18 yr; ≥ 65 yr	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 0.3 (0.1) ppm IQR (25th, 75th): (0.22, 0.34) **Copollutant; correlation:** PM_{10}: r = 0.45	**Increment:** 0.12 ppm **Relative Risk (Lower CI, Upper CI); lag:** Respiratory Disease Age Group: ≥ 65 CO: 1.024 (0.997-1.053); 0-4 CO, PM_{10}: 1.001 (0.961-1.042); 0-4 Asthma Age Group: 5-18 CO: 1.104 (1.018-1.198); 0-5 CO, PM_{10}: 1.023 (0.911-1.149); 0-5
Author: Atkinson et al. (1999, 007882) **Period of Study:** 1/1992-12/1994 **Location:** London, U.K.	ED Visits **Health Outcome (ICD9):** Respiratory complaints: wheezing, inhaler request, chest infection, chronic obstructive lung disease (COLD), difficulty breathing, cough, other respiratory complaints. e.g., croup, pleurisy, noisy breathing; Asthma (493) **Study Design:** Time-series **Statistical Analyses:** Poisson **Age Groups Analyzed:** All ages 0-14 yr 15-64 yr ≥ 65 yr	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 0.8 (0.4) ppm **Range (Min, Max):** (0.2, 5.6) **Copollutant; correlation:** NO_2 O_3 SO_2 PM_{10} BS	**Increment:** 0.8 ppm **% Increase (Lower CI, Upper CI); lag**: Respiratory complaints Age Group All ages: 0.76% (-0.83, 2.38); 1 0-14: 2.92% (0.60, 5.30); 1 15-64: 2.15% (-0.27, 4.63); 1 ≥ 65: 4.29% (1.15, 7.54); 0 Asthma visits: Single-pollutant model Age Group: All ages: 3.32% (0.56, 6.16); 1 0-14: 4.13% (-0.11, 8.54); 0 15-64: 4.41% (0.46, 8.52); 1 Multi-pollutant model Age Group: 0-14 CO, NO_2: 2.05% (-2.25, 6.54); 0 CO, O_3: 4.48% (0, 9.16); 0 CO, SO_2: 2.34% (-1.94, 6.81); 0 CO, PM_{10}: 2.93% (-1.53, 7.58); 0 CO, BS: 4.19% (-0.04, 8.60); 0

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Bedeschi et al. (2007, 090712) **Period of Study:** 1/2001-3/2002 **Location:** Reggio Emilia, Italy	ED Visits **Health Outcome (ICD9):** Asthma (493); Asthma-like disorders, i.e., asthma, bronchiolitis, dyspnea/ shortness of breath; Other respiratory disorders (i.e., upper and lower respiratory illness including sinusitis, bronchitis, and pneumonia) **Study Design:** Time series **Statistical Analyses:** Poisson GAM, penalized splines **Age Groups Analyzed:** <5 yr	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 1.4 (0.7) mg/m^3 **Range (Min, Max):** (0.4, 4.6) **Copollutant; correlation:** PM_{10}: r = 0.61 TSP: r = 0.61 SO_2: r = 0.71 NO_2: r = 0.77	The study did not provide quantitative results for CO.
Author: Bell et al. (2008, 091268) **Period of Study:** 1/1995-12/2002 **Location:** Taipei, Taiwan	Hospital Admissions **Health Outcome (ICD9):** Pneumonia (486); asthma (493) **Study Design:** Time series **Statistical Analyses:** Poisson **Age Groups Analyzed:** All ages	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SE) unit:** 0.9 ppm **Range (Min, Max):** (0.3, 3.6) **Copollutant:** NR	**Increment:** 0.5 ppm **% Increase (Lower CI, Upper CI); lag** Asthma (avg correlation between monitor pairs = 0.75 (13 monitors)) 3.29% (-0.74 to 7.49); 0 .49% (-4.25 to 3.41); 1 -0.84% (-4.43 to 2.88); 2 0.48% (-4.02 to 3.18); 3 0.74% (-4.62 to 6.4); 0-3 Pneumonia (avg correlation between monitor pairs = 0.75 (13 monitors)) 1.91% (-1.97 to 5.95); 0 0.03% (-3.65 to 3.85); 1 0.36% (-3.2 to 4.04); 2 -1.29% (-4.77 to 2.32); 3 0.21% (-5.03 to 5.73); 0-3 Asthma (avg correlation between monitor pairs = 0.88 (5 monitors)) 1.68% (-1.68 to 5.15); 0 -1.19% (-4.29 to 2.01); 1 -0.83% (-3.83 to 2.26); 2 -0.35% (-3.32 to 2.71); 3 -0.31% (-4.9 to 4.5); 0-3 Pneumonia (avg correlation between monitor pairs = 0.88 (5 monitors)) 1.24% (-2.02 to 4.6); 0 -0.01% (-3.06 to 3.13); 1 0.57% (-2.4 to 3.62); 2 -0.85% (-3.78 to 2.16); 3 0.31% (-4.23 to 5.06); 0-3 Asthma (monitors with ≥ 0.75 between monitor correlations (11 monitors), avg correlation between monitor pairs = 0.81) 2.87% (-0.91 to 6.79); 0 -0.71% (-4.2 to 2.91); 1 -0.73% (-4.08 to 2.73); 2 -0.41% (-3.72 to 3.01); 3 0.51% (-4.6 to 5.89); 0-3 Pneumonia (monitors with ≥ 0.75 between monitor correlations (11 monitors) to avg correlation between monitor pairs = 0.81) 0.98% (-1.68 to 5.76); 0 -0.12% (-3.54 to 3.42); 1 0.37% (-2.95 to 3.8); 2 -1.08% (-4.34 to 2.3); 3 0.3% (-4.71 to 5.57); 0-3

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Bellini et al. (2007, 097787) **Period of Study:** 1996-2002 **Location:** 15 Italian cities	Hospital Admissions **Health Outcome:** Respiratory conditions **Study Design:** Time-series; Meta-analysis **Statistical Analyses:** 1. GLM for city-specific estimates 2. Bayesian random-effects for meta analysis **Age Groups Analyzed:** All ages	**Pollutant:** CO **Averaging Time:** NR **Mean (SD) unit:** NR **Range (Min, Max):** NR **Copollutant: correlation** NR	**Increment:** 1 mg/m^3 **% Increase (Lower CI, Upper CI); Lag** Respiratory conditions All ages: Season: Winter: 0.58%; 0-1 Summer: 3.47%; 0-1 All Season: 1.25%; 0-3 **Note:** Estimates from Biggeri et al. (2004)
Author: Braga et al. (2001, 016275) **Period of Study:** 1/1993-11/1997 **Location:** Sao Paulo, Brazil	Hospital Admissions **Health Outcome (ICD9):** Respiratory (460-519) **Study Design:** Time series **Statistical Analyses:** Poisson GAM, LOESS **Age Groups Analyzed:** ≤ 2 yr 3-5 yr 6-13 yr 14-19 yr 0-19 yr	**Pollutant:** CO **Averaging Time:** Maximum 8-h avg **Mean (SD) unit:** 4.8 (2.3) ppm **Range (Min, Max):** (0.6, 19.1) **Copollutant:** correlation PM_{10}: r = 0.60 O_3: r = -0.07 SO_2: r = 0.47	**Increment:** 3 ppm **% Increase (Lower CI, Upper CI); lag:** Respiratory Age Group: ≤ 2: 5.00% (3.30-6.80); 0-6 3-5: 4.90% (1.40-8.50); 0-6 6-13: 1.00% (-2.50 to4.60); 0-6 14-19: 11.30% (5.90-16.80); 0-6 0-19: 4.90% (3.50-6.40); 0-6
Author: Burnett et al. (1999, 017269) Period of Study: 1/1980-12/1994 **Location:** Toronto, ON, Canada	Hospital Admissions **Health Outcome (ICD9):** Asthma (493); COPD (490-492, 496); respiratory infection (464, 466, 480-487, 494) **Study Design:** Time-series **Statistical Analyses:** Poisson GAM, LOESS **Age Groups Analyzed:** All ages	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 1.18 ppm **IQR (25th, 75th):** (0.9, 1.4) **Copollutant:** correlation $PM_{2.5}$: r = 0.49 $PM_{10-2.5}$: r = 0.20 PM_{10}: r = 0.43 NO_2: r = 0.55 SO_2: r = 0.37 O_3: r = -0.23	**Increment:** 1.18 ppm **% Increase (t-value); lag:** Asthma: 5.35% (3.92); 0 COPD: 2.93% (1.48); 0 Respiratory Infection: 5.00% (4.25); 0 Asthma: Multipollutant model CO, SO_2, O_3: 5.15% CO, $PM_{2.5}$, SO_2, O_3: 4.63% CO, $PM_{10-2.5}$, SO_2, O_3: 5.25% CO, PM_{10}, SO_2, O_3: 4.80% CO, $PM_{10-2.5}$, O_3: 4.00% COPD: Multipollutant model CO, SO_2, O_3: 3.02% CO, $PM_{2.5}$, SO_2, O_3: 2.46% CO, $PM_{10-2.5}$, SO_2, O_3: 3.00% CO, PM_{10}, SO_2, O_3: 2.75% CO, $PM_{10-2.5}$, O_3: 3.00%
Author: Burnett et al. (2001, 093439) **Period of Study:** 1/1980-12/1994 **Location:** Toronto, ON, Canada	Hospital Admissions **Health Outcome (ICD9):** Asthma (493); Acute bronchitis/ bronchiolitis (466); croup (464.4) ; pneumonia (480-486) **Study Design:** Time series **Statistical Analyses:** Poisson GAM **Age Groups Analyzed:** <2 yr	**Pollutant:** CO **Averaging Time:** 1-h avg **Mean (SD) unit:** 1.9 ppm **IQR (25th, 75th):** (1.3, 2.3) **Copollutant:** correlation O_3: r = 0.24	**Increment:** 1.9 ppm **% Increase (Lower CI, Upper CI); lag** Respiratory problems CO: 19.20%; 0-1 CO, O_3: 14.30%; 0-1

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Cakmak et al. (2006, 093272) **Period of Study:** 4/1993-3/2000 **Location:** 10 Canadian cities	Hospital Admissions **Health Outcome (ICD9):** Actue bronchitis/bronchiolitis (466); pneumonia (480-486); chronic/ unspecified bronchitis (490, 491); emphysema (492); asthma (493); bronchiectasis (494); chronic airway obstruction (496) **Study Design:** Time series **Statistical Analyses:** 1. Poisson 2. Restricted Maximum Likelihood Method **Age Groups Analyzed:** All ages	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 0.8 ppm **Range (Min, Max):** (0.0, 6.5) **Copollutant:** correlation SO_2 NO_2 O_3	**Increment:** 0.8 ppm **% Increase (Lower CI, Upper CI); lag:** Respiratory disease CO: 0.60% (0.20, 1); 2.8 CO, SO_2, NO_2, O_3: -0.20% (-0.70- 0.30); 2.8
Author: Cheng et al. (2007, 093034) **Period of Study:** 1996-2004 **Location:** Kaohsiung, Taiwan	Hospital Admissions **Health Outcome (ICD9):** Pneumonia (480-486) **Study Design:** Bidirectional case-crossover **Statistical Analyses:** Conditional logistic regression **Age Groups Analyzed:** All ages	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 0.76 ppm **Range (Min, Max):** (0.14, 1.72) **Copollutant:** correlation PM_{10} SO_2 NO_2 O_3	**Increment:** 0.31 ppm **Odds Ratio (Lower CI, Upper CI); lag:** OR for pneumonia and exposure to various pollutants for all ages in areas ≥ 25°C or <25°C Pollutant and Temperature CO, ≥ 25 ºC: 1.18 (1.14-1.23); 0-2 CO, <25 ºC: 1.47 (1.41-1.53); 0-2 CO, PM_{10}, ≥ 25 ºC: 1.15 (1.11-1.2); 0-2 CO, PM_{10}, <25 ºC: 1.28 (1.21-1.35); 0-2 CO, SO_2, ≥ 25 ºC: 1.22 (1.17-1.27); 0-2 CO, SO_2, <25 ºC: 1.49 (1.42-1.56); 0-2 CO, NO_2, ≥ 25 ºC: 1.2 (1.15-1.27); 0-2 CO, NO_2, <25 ºC: 1.01 (0.95-1.08); 0-2 CO, O_3, ≥ 25 ºC: 1.16 (1.12-1.2); 0-2 CO, O_3, <25 ºC: 1.44 (1.38-1.5); 0-2
Author: Chiu et al. (2009, 190249) **Period of Study:** 1996-2004 **Location:** Taipei, Taiwan	Hospital Admissions **Health Outcome:** pneumonia HA **Study Design:** case-crossover **Statistical Analyses:** Conditional Logistic regression **Age Groups Analyzed:** All ages **Sample Description:** 152,594 HA for 47 hospitals in Taipei city	**Averaging Time:** 24h **Mean (SD) unit:** 1.26 ppm **Range (min, max)**: 0.12, 3.66 **Copollutant:** correlation PM_{10}: r = 0.34 SO_2: r = 0.57 NO_2: r = 0.69 O_3: r = -0.31	Increment: 0.57 ppm (IQR) **OR Estimate [Lower CI, Upper CI] ; lag:** Lags examined: one wk before to one wk after CO: ≥23°C: 1.25 (1.21, 1.29) <23°C: 1.12 (1.09, 1.15) CO + PM_{10}: ≥23°C: 1.23 (1.19, 1.27) <23°C: 1.05 (1.02, 1.09) CO + SO_2: ≥23°C: 1.25 (1.21, 1.30) <23°C: 1.27 (1.22,1.31) CO + NO_2: ≥23°C: 0.97 (0.93, 1.02) <23°C: 1.14 (1.09, 1.20) CO + O_3: ≥23°C: 1.24 (1.20, 1.28) <23°C: 1.21 (1.17, 1.24)

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Cho et al. (2000, 099051) Period of Study: 1/1996-12/1996 **Location:** 3 South Korea cities:	Hospital Admissions **Health Outcome (ICD9):** Bronchial asthma; COPD; bronchitis **Study Design:** Time series **Statistical Analyses:** Poisson GAM, LOESS **Age Groups Analyzed:** All Ages	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** Daejeon: 1.424 (0.611) ppm Ulsan: 0.950 (0.211) ppm Suwon: 1.270 (0.549) ppm **Range (Min, Max):** Daejeon: (.364, 3.504) Ulsan: (.380, 1.675) Suwon: (.250, 3.616) **Copollutant:** correlation Daejeon SO_2: r = 0.280; NO_2: r = 0.041; TSP: r = 0.193; O_3: r = -0.101; O_3 Max: r = -0.069 Ulsan SO_2: r = 0.108; NO_2: r = 0.446; TSP: r = 0.286; O_3: r = -0.195; O_3 Max: r = -0.107 Suwon SO_2: r = 0.556; NO_2: r = 0.291; TSP: r = 0.496; O_3: r = -0.371; O_3 Max: r = -0.365	**Increment:** 1,000 ppm **Relative Risk (Lower CI, Upper CI); lag:** Estimates obtained using dummy variables to apply environmental indicators to the model Daejeon CO: 1.26 (1.08-1.47) TSP, SO_2, NO_2, O_3: 1.21 (1.02-1.44) Ulsan CO: 3.55 (1.65-7.63) TSP, SO_2, NO_2, O_3: 2.51 (1.06-5.93) Suwon CO: 1.24 (0.97-1.59) TSP, SO_2, NO_2, O_3: 1.19 (0.88-1.61) Estimates obtained using actual measured integrated environmental pollution indicator values Daejeon CO: 1.34 (1.14-1.58) Ulsan CO: 1.27 (0.94-1.71) Suwon CO: 3.55 (1.27-9.93)
Author: Delfino et al. (2008, 156390) **Period of Study:** January 1, 2000-December 31, 2003 **Location:** Orange County, California	ED Visits **Health Outcome:** Asthma **Study Design:** Longitudinal, Cohort **Statistical Analyses:** Proportional hazards models in SAS version 9.2 **Age Groups Analyzed:** 0-18 yr **Sample Description:** Various gender, race, insurance status, income, poverty level, residence distance to treating hospital	**Averaging Time:** NR **Mean (SD) unit: Cool season:** 0.114 (0.052), Warm season: 0.103 (0.048) **Range (Min, Max):** Cool season: 0.014 -0.378, Warm season: 0.013-0.482 **Copollutant:** NO_X	**Increment:** 0.056 ppm HR (95% CI): Unadjusted: 1.072 (1.016 – 1.131), Adjusted: 1.073 (1.013 – 1.137), Male: 1.054 (0.978 – 1.137), Female: 1.100 (1.011 – 1.197), 0 yr: 1.158 (1.041 – 1.289), 1-5 yr: 1.021 (0.933 – 1.117), 6-18 yr: 1.076 (0.972 – 1.191), Median or less poverty: 1.054 (0.979 – 1.134), Greater than the median poverty: 1.094 (1.006 – 1.190), Greater than the median income: 1.120 (1.034 – 1.213), Median or less income: 1.041 (0.959 – 1.129), Private insurance: 1.102 (1.006 – 1.206), Government sponsored or self-pay insurance: 1.061 (0.989 – 1.138), Unknown insurance: 0.913 (0.591 – 1.412), White: 1.113 (1.027 – 1.205), Hispanic: 1.081 (0.996 – 1.173), Non-Hispanic nonwhite: 0.804 (0.601 – 1.074) Lags examined: NR The point estimates for CO are stronger in girls than in boy and in infants than in older children. There is little difference in coefficients between adjusted and unadjusted CO models. There were significant increased risks of repeated hospital encounters of 7% to 10% per IQR increase in traffic-related CO exposure.
Author: Farhat et al. (2005, 089461) Period of Study: 8/1996-8/1997 **Location:** Sao Paulo, Brazil	Hospital Visits & ED Visits **Health Outcome (ICD9):** Pneumonia/bronchopneumonia (480-486); asthma (493); bronchiolitis (466) **Study Design:** Time-series **Statistical Analyses:** Poisson GAM, LOESS **Age Groups Analyzed:** All ages	**Pollutant:** CO **Averaging Time:** Max 8-h avg **Mean (SD) unit:** 3.8 (1.6) ppm **Range (Min, Max):** (1.1, 11.4) **Copollutant:** correlation PM_{10}: r = 0.72; SO_2: r = 0.49; NO_2: r = 0.59; O_3: r = -0.8	**Increment:** 1.8 ppm **% Increase (Lower CI, Upper CI); lag:** Lower Respiratory Tract Disease ED Visits CO, PM_{10}: -0.10% (-5.60 to 5.30); 0-2 CO, NO_2: -1.20% (-6.70 to 4.20); 0-2 CO, SO_2: 3.70% (-1.00 to 8.40); 0-2 CO, O_3: 4.80% (0.50-9.10); 0-2 CO, PM_{10}, NO_2, SO_2, O_3:- 0.64% (-6.90 to 5.60); 0-2 Pneumonia/ Bronchopneumonia Hospital Admissions CO, PM_{10}: 4.40% (-7.90 to 16.70); 0-2 CO, NO_2: 4.40% (-88.70 to 17.50); 0-2 CO, SO_2: 7.80% (-2.50 to 18.20); 0-2 CO, O_3: 9.60% (-0.50 to 19.70); 0-2 CO, PM_{10} to NO_2, SO_2, O_3:5.10% (-9.60 to 19.70); 0-2 Asthma/ Bronchiolitis Hospital Admissions CO, PM_{10}: 6.10% (-14.90 to 27.10); 0-2 CO, NO_2: 2.40% (-16.90 to 21.70); 0-2 CO, SO_2: 10.60% (-6.60 to 27.80); 0-2 CO, O_3: 12.40% (-3.60 to 28.40); 0-2 CO, PM_{10} to NO_2, SO_2, O_3: 8.80% (-15.60 to 33.30); 0-2

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Fung et al. (2006, 089789) Period of Study: 6/1995-3/1999 **Location:** Vancouver, Canada	Hospital Admissions **Health Outcome (ICD9):** Respiratory Illness **Study Design:** 1. Dewanji and Moolgavkar 2. Time-series 3. Bidirectional case-crossover **Statistical Analyses:** 1. Dewanji and Moolgavkar 2. Poisson 3. Conditional logistic regression **Age Groups Analyzed:** ≥ 65 yr	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 0.69 0.25) ppm **Range (Min, Max):** (0.28, 2.03) **Copollutant:** correlation CoH: r = 0.85; O_3: r = -0.53; NO_2: r = 0.74; SO_2: r = 0.61; PM_{10}: r = 0.46; $PM_{2.5}$: r = 0.23; $PM_{10-2.5}$: r = 0.51	**Increment:** 0.24 ppm **Relative Risk (Lower CI, Upper CI); lag** Dewanji and Moolgavkar 1.008 (0.997-1.02); 0 1.012 (0.999-1.025); 0-2 1.010 (0.995-1.025); 0-4 1.009 (0.991-1.026); 0-6 Time-series 1.012 (1.000-1.023); 0 1.017 (1.003-1.032); 0-2 1.017 (1.001-1.035); 0-4 1.016 (0.996-1.036); 0-6 Bidirectional case-crossover 1.010 (0.006-1.023); 0 1.012 (0.996-1.027); 0-2 1.012 (0.995-1.03); 0-4 1.010 (0.991 1.031; 0-6
Author: Fusco et al. (2001, 020631) **Period of Study:** 1/1995 10/1997 **Location:** Rome, Italy	Hospital Admissions **Health Outcome (ICD9):** Respiratory conditions (460-519, excluding 470-478); acute respiratory infections plus pneumonia (460-466, 480-486); COPD (490-492, 494-496) asthma (493) **Study Design:** Time-series **Statistical Analyses:** Poisson GAM **Age Groups Analyzed:** All ages 0-14 yr	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 3.6 (1.2) mg/m^3 **IQR (25th, 75th):** (2.8, 4.3) **Copollutant:** correlation All Year SO_2: r = 0.56 NO_2: r = 0.31 O_3: r = -0.57 Cold Season SO_2: r = 0.37 NO_2: r = 0.41 O_3: r = -0.44 Warm Season SO_2: r = 0.44 NO_2: r = 0.59 O_3: r = -0.38	**Increment:** 1.5 mg/m^3 **% Increase (Lower CI, Upper CI); lag:** Age Group: All Ages Respiratory conditions 2.80% (1.30-4.30); 0 1.80% (0.20-3.30); 1 0.20% (-1.30 to 1.80); 2 0.50% (-2.00 to 1.10); 3 0.70% (-0.80 to 2.20); 4 CO, NO_2: 2.30% (0.60-4.00); 0 Acute Respiratory Infections plus pneumonia 2.20% (0.00-4.40); 0 2.10% (-0.10 to 4.40); 0 1.70% (-0.50 to 4.00); 2 -0.90% (-3.00 to 1.30); 3 1.50% (-0.70 to 3.70); 4 CO, NO_2: 0.00% (-2.30 to 2.40); 0 Asthma 5.50% (0.90-10.40); 0 0.80% (-3.80 to 5.70); 1 -1.30% (-5.90 to 3.50); 2 -3.00% (-7.40 to 1.60); 3 0.60% (-4.00 to 5.30); 4 CO, NO_2: 4.80% (0.30-9.50); 0 COPD 4.30% (1.60-7.10); 0 -0.20% (-2.90 to 2.50); 1 -0.20% (-2.90 to 2.60); 2 -0.30% (-3.00 to 2.40); 3 -0.10% (-2.80 to 2.60); 4 CO, NO_2: 4.80% (0.90-7.90); 0 Warm Season Respiratory Conditions: 10.80% (6.70-14.80); 0 Acute respiratory infections plus pneumonia: 8.60% (2.90-14.60); 0 COPD: 13.90% (6.80-21.50); 0 Age Group: 0-14 Respiratory conditions 2.50 (-0.30 to 5.50); 0 0.80 (-2.10 to 3.80); 1; 0.20 (-2.70 to 3.10); 2 -1.00 (-3.70 to 1.90); 3 3.20 (0.40- 6.20); 4 CO, NO_2: 4.10 (-1.20 to 9.80); 1 Acute Respiratory Infections plus Pneumonia 2.50 (-0.80 to 5.80); 0 -0.10 (-3.40 to 3.20); 1 0.90 (-2.30 to 4.30); 2 -2.00 (-5.10 to 1.20); 3 3.20 (0.00-6.60); 4 CO, NO_2: 6.90 (0.80-13.40); 1 Asthma 6.30 (-0.50 to 13.50); 0 8.20 (1.10-15.70); 1; -0.70 (-7.30 to 6.30); 2

Study	Design	Concentrations	Effect Estimates (95% CI)
			3.50 (-3.20 to 10.60); 3; 4.80 (-1.90 to 12.00); 4 CO, NO_2: 3.30 (-4.20 to 11.30); 1
Author: Gouveia and Fletcher (2000, 010436) **Period of Study:** 11/1992-9/1994 **Location:** Sao Paulo, Brazil	Hospital Admissions **Health Outcome (ICD9):** All respiratory diseases Pneumonia (480-486); asthma (493); bronchitis (466, 490, 491) **Study Design:** Time-series **Statistical Analyses:** Poisson **Age Groups Analyzed:** <1 yr; <5 yr	**Pollutant:** CO **Averaging Time:** Max 8-h avg **Mean (SD) unit:** 5.8 (2.4) ppm **Range (Min, Max):** (1.3, 22.8) **Copollutant:** correlation PM_{10}: r = 0.63 SO_2: r = 0.65 NO_2: r = 0.35	**Increment:** 6.9 ppm **Relative Risk (Lower CI, Upper CI); lag:** All respiratory diseases Age Group: <5: 1.017 (0.971-1.065); 0 Pneumonia Age Group: <5: 1.015 (0.961-1.071); 0; <1: 1.035 (0.975-1.099); 2 Asthma Age Group: <5: 1.081 (0.98-1.192); 0
Author: Hajat et al. (1999, 000924) **Period of Study:** 1/1992-12/1994 **Location:** London, U.K.	General Practitioner Visits **Health Outcome (ICD9):** Asthma (493); lower respiratory diseases (464, 466, 476, 480-483, 485-487, 490-492, 494-496, 500, 501, 503-505, 510-515, 518, 519, 786) **Study Design:** Time-series **Statistical Analyses:** Poisson **Age Groups Analyzed:** All ages 0-14 yr 15-64 yr ≥ 65 yr	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** All yr: 0.8 (0.4) ppm Warm Season (April-September): 0.7 (0.3) ppm Cool Season (October-March): 1.0 (0.5) ppm **Range (10th, 90th):** All Year: (0.5, 1.3) Warm Season: (0.4, 1.0) Cool Season: (0.5, 1.6) **Copollutant:** correlation All Year NO_2: r = 0.72; SO_2: r = 0.51; BS: r = 0.85; O_3: r = -0.40; PM_{10}: r = 0.56 Warm Season NO_2: r = 0.70; SO_2: r = 0.32; BS: r = 0.65; O_3: r = -0.12; PM_{10}: r = 0.58 Cool Season NO_2: r = 0.84; SO_2: r = 0.58; BS: r = 0.87	**Increment:** 0.8 & 0.7 ppm **% Increase (Lower CI, Upper CI); Lag** All Year: Asthma – Single Day Lags Increment: 0.8 ppm Age Group 0-14: 4.10% (-0.10 to 8.40); 2 15-64: 0.90% (-2.10 to 4.10); 0 ≥ 65: 7.50% (0.50-14.90); 2 All ages: 1.60% (-1.20 to 4.60); 2 Asthma – Cumulative exposure Increment: 0.7 ppm Age Group 0-14: 6.90% (1.30-12.90); 0-3 15-64: 1.00% (-3.20 to 5.40); 0-2 ≥ 65: 8.20% (0.40-16.60); 0-2 All ages: 1.80% (-1.50 to 5.20); 0-2 Lower Respiratory Diseases – Single Day Lags Increment: 0.8 ppm Age Group 0-14: 4.40 (1.70-7.10); 2 15-64: 1.10 (-0.70 to 3.00); 2 ≥ 65: -2.60 (-4.80 to -0.30); 3 All ages: 2.00 (0.50-3.40); 2 Lower Respiratory Diseases – Cumulative exposure Increment: 0.7 ppm for 0-2 and 0-3; 0.8 for 0-1 Age Group 0-14: 3.00% (-1.00 to 7.20); 0-3 15-64: -0.70% (-2.90 to 1.50); 0-1 ≥ 65: -1.60% (-5.10 to 2.00); 0-3 All ages: 1.80% (0.10-3.60); 0-2 Warm or Cold Seasons: Asthma, Increment: 0.8 ppm Age Group & Season 0-14 & Warm Season: 11.40% (3.30-20.00); 2 0-14 & Cold Season: 2.90% (-3.20 to 9.40); 2 15-64 & Warm Season: 4.80% (-0.60 to 10.60); 0 15-64 & Cold Season: -0.30% (-4.80 to 4.50); 0 ≥ 65 & Warm Season: 15.60% (3.10-29.60); 2 ≥ 65 & Cold Season: 4.20% (-6.00 to 15.60); 2 Lower Respiratory Diseases, Increment: 0.8 ppm Age Group & Season 0-14 & Warm Season: 2.70% (-2.90 to 8.60); 2 0-14 & Cold Season: 6.20% (2.30-10.20); 2 15-64 & Warm Season: 6.20% (2.30-10.20); 2 15-64 & Cold Season: 2.40% (-1.20 to 6.10); 2 ≥ 65 & Warm Season: 1.00% (-1.60 to 3.80); 2 ≥ 65 & Cold Season: -2.20% (-6.50 to 2.40); 3

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Hajat et al. (2002, 030358) **Period of Study:** 1/1992-12/1994 **Location:** London, U.K.	General Practitioner Visits **Health Outcome (ICD9):** Upper respiratory diseases (URD) **Study Design:** Time-series **Statistical Analyses:** Poisson, GAM, LOESS **Age Groups Analyzed:** 0-14 yr 15-64 yr ≥ 65 yr	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** All yr: 0.8 (0.4) ppm Warm Season (April-September): 0.7 (0.3) ppm Cool Season (October-March): 1.0 (0.5) ppm **Range (10th, 90th):** All Year: (0.5, 1.3) Warm Season: (0.4, 1.0) Cool Season: (0.5, 1.6) **Copollutant:** NR	**Increment:** 0.6 ppm, 0.8 ppm, & 1.1 ppm **% Increase (Lower CI, Upper CI); lag:** Warm Season, Increment: 0.6 ppm Age Group 0-14: 2.90% (-0.60 to 6.40); 1 14-64: 7.90% (4.80-11.10); 1 ≥ 65: 4.90% (-1.80 to 12.10); 3 Cold Season, Increment: 1.1 ppm Age Group 0-14: -2.50% (-4.90 to 0.10); 1 14-64: 0.60% (-1.60 to 2.90); 1 ≥ 65: 5.60% (0.90-10.60); 3 All Year, Increment: 0.8 ppm Age Group 0-14: -2.20% (-4.00 to -0.30); 1 14-64: 2.70% (0.10-5.50); 1 ≥ 65: 5.80% (2.40 to 9.30); 3
Author: Hapcioglu et al. (2006, 093263) Period of Study: 1/1997-12/2001 **Location:** Istanbul, Turkey	Hospital Admissions **Health Outcome (ICD9):** COPD (490-492, 494-496) **Study Design:** Cross sectional **Statistical Analyses:** Pearson Correlation Coefficient **Age Groups Analyzed:** All ages	**Pollutant:** CO **Averaging Time:** Monthly **Mean (SD) unit:** NR **Range (Min, Max):** NR **Copollutant:** NR	Correlation Coefficient: Between CO exposure and COPD: 0.57 Between CO exposure and COPD when controlling for temperature: 0.25
Author: Hinwood et al. (2006, 088976) **Period of Study:** 1/1992-12/1998 **Location:** Perth, Australia	Hospital Admissions **Health Outcome (ICD9):** COPD (490.00-496.99 excluding asthma); pneumonia/ influenza (480.00-489.99); Asthma (493) **Study Design:** Case crossover **Statistical Analyses:** Conditional logistic regression **Age Groups Analyzed:** All ages	**Pollutant:** CO **Averaging Time:** Max 8-h avg **Mean (SD) unit:** All Year: 2.3 (1.3) ppm; November-April: 2.2 (1.3) ppm; May-October: 2.4 (1.2) ppm **Range (10th, 90th):** All Year: (0.9, 4.2) November-April: (0.8, 4.2) May-October: (1.1, 4.2) **Copollutant:** correlation All Year: NO_2: r = 0.57 O_3: r = 0.00 November-April: NO_2: r = 0.55 O_3: r = 0.00 May-October: NO_2: r = 0.57 O_3: r = 0.16	**Increment:** 2.3 ppm **Odds Ratio (Lower CI, Upper CI); Lag** Pneumonia 0.99999 (0.9737-1.0268); 0 1.00650 (0.9806-1.0331); 1 1.00351 (0.9779-1.0298); 2 1.00424 (0.9790-1.0301); 3 1.00581 (0.9752-1.0374); 0-1 1.01005 (0.9755-1.0458); 0-2 1.00805 (0.9701-1.0474); 0-3 COPD 0.99915 (0.9693-1.0297); 0 1.00205 (0.9727-1.0323); 1 0.98630 (0.9577-1.0158); 2 0.98970 (0.9619-1.0182); 3 0.99960 (0.9647-1.0357); 0-1 0.99260 (0.9538-1.0329); 0-2 0.99160 (0.9493-1.0357); 0-3
Author: Hwang and Chan (2002, 023222) **Period of Study:** 1998 **Location:** 50 communities in Taiwan	Clinic Visits **Health Outcome (ICD9):** Lower respiratory tract infections (466, 480-486) **Study Design:** Time series **Statistical Analyses:** 1. General linear regression 2. Bayesian hierarchical modeling **Age Groups Analyzed:** All Ages 0-14 yr 15-64 yr ≥ 65 yr	**Pollutant:** CO **Averaging Time:** Max 8-h avg **Mean (SD) unit:** 1.00 (0.30) ppm **Range (Min, Max):** (0.51, 1.71) **Copollutant:** NR	**Increment:** 0.1 ppm **% Increase (Lower CI, Upper CI); Lag** Age Group: All Ages 0.80% (0.60-1.00); 0 0.10% (-0.10 to 0.30); 1 0.10% (-0.10 to 0.30); 2 Age Group: 0-14 0.70% (0.50-1.00); 0 0.10% (-0.20 to 0.30); 1 0.20% (-0.10 to 0.40); 2 Age Group: 15-64 0.90% (0.60-1.10); 0 0.20% (0.00-0.50); 1 0.20% (-0.10 to 0.40); 2 Age Group: ≥ 65 1.10% (0.80-1.50); 0 0.60% (0.30-1.00); 1 0.40% (0.10-0.80); 2

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Ito et al. (2007, 091262) **Period of Study:** 1999-2002 **Location:** New York City, NY	ED Visits **Health Outcome (ICD9):** Asthma (493) **Study Design:** Time series **Statistical Analyses:** Poisson GLM **Age Groups Analyzed:** All ages	**Pollutant:** CO **Averaging Time:** Max 8-h avg **Mean (SD) unit:** All Season: 1.31 (0.43) ppm Warm Months (April-September): 1.22 (0.32) ppm Cold Months (October-March): 1.41 (0.5) ppm **Range (5th, 95th):** All season: (0.77, 2.11) Warm months (April-September): (0.75, 1.82) Cold months (October-March): (0.78, 2.33) **Copollutant:** NR	**Increment:** 1.3 ppm **Relative Risk (Lower CI, Upper CI); Lag** Warm months: 1.15 (1.07-1.25); 0-1
Author: Jayaraman et al. (2008, 180352) **Period of Study:** 2004-2005 **Location:** New Delhi, India	Hospital Admissions **Health Outcome:** respiratory **Study Design:** time series **Statistical Analyses:** Poisson regression (GAM) **Age Groups Analyzed:** All ages Sample Description: daily HA for respiratory unit of Safdarjung hospital	**Averaging Time:** 24-h **Mean (SD) unit:** 2,379.14 (1,289.18) µg/m^3 **Range (min, max):** 588, 8458 **Copollutant:** SO_2: r = 0.217* NO_2: r = 0.204* SPM: r = 0.071 RSPM: r = 0.120 O_3: r = 0.063 *p < 0.05	**Increment:** 10 µg/m^3 **RR Estimate [Lower CI, Upper CI] ; lag:** Lags examined: lag days 0-3 Single Pollutant: 0.9989 (0.985, 2.715), 2 Multi-pollutant: 0.998 (0.993, 1.004), 2 Winter, all ages: 1.027 (1.004, 1.051), 2 Winter, males 50-69: 2.625 (1.048, 1.158)
Author: Karr et al. (2007, 090719) Period of Study: 1995-2000 **Location:** South Coast Air Basin, CA	Hospital Admissions **Health Outcome (ICD9):** Acute bronchiolitis (466.1) **Study Design:** Matched case control **Statistical Analyses:** Conditional logistic regression **Age Groups Analyzed:** Infants: 3 wk to 1 yr	**Pollutant:**CO **Averaging Time:** 24-h avg **Mean (SD) unit:** Chronic: 1,770 ppb Subchronic: 1,720 ppb **Range (Min, Max):** Chronic: (120, 8300) Subchronic: (130, 5070) **Copollutant:** NR	**Increment:** 910 ppb, 960 ppb **Odds Ratio (Lower CI, Upper CI); lag:** Increment: 910 ppb Subchronic broncholitis: 1 (0.97-1.03) Increment: 960 ppb Chronic broncholitis: 1 (0.97-1.03)
Author: Karr et al. (2006, 088751) **Period of Study:** 1995-2000 **Location:** South Coast Air Basin, CA	Hospital Admissions **Health Outcome (ICD9):** Acute bronchiolitis (466.1) **Study Design:** Case crossover **Statistical Analyses:** Conditional logistic regression **Age Groups Analyzed:** Infants: 3 wk to1 yr	**Pollutant:**CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 1-day lag: Index*: 1,730 ppb Referent*: 1,750 ppb 4-day lag: Index*: 1,760 ppb Referent*: 1,790 ppb **Range (Min, Max):** Lag 1: Index*: (4, 9600) Referent*: (4, 9600) Lag 4: Index* (4, 8710) Referent* (4, 9600) **Copollutant:** NR * Index days: days lagged in reference to date of hospitalization of a case. Referent days: are for each case and includes all days that are the same day of wk and in the same mo as the index day for that case for CO.	**Increment:** 1361, 1400 ppb **Odds Ratio (Lower CI, Upper CI); Lag** Increment: 1361 ppb Age Group: Overall: 0.99 (0.96-1.02); 1 25-29 wk: 0.86 (0.68-1.1); 1 29 1/7 – 34 wk: 1 (0.86-1.15); 1 34 1/7 – 37 wk: 0.95 (0.87-1.04); 1 37 1/7 – 44 wk: 1 (0.97-1.03); 1 Increment: 1400 ppb Age Group: Overall: 0.97 (0.94-1); 4 25-29 wk: 0.93 (0.72-1.2); 4 29 1/7 – 34 wk: 0.89 (0.77-1.03); 4 34 1/7 – 37 wk: 0.98 (0.90-1.08); 4 37 1/7 – 44 wk: 0.97 (0.94-1); 4

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Kim et al. (2007, 092837) **Period of Study:** 2002 **Location:** Seoul, Korea	Hospital Admissions **Health Outcome (ICD10):** Asthma (J45 and J46) **Study Design:** Bidirectional case crossover **Statistical Analyses:** Conditional logistic regression **Age Groups Analyzed:** All Ages	**Pollutant:** CO **Averaging Time:** Max 8-h avg **Mean (SD) unit:** Daily Concentration: 8.6 (4.6) ppm Relevant Concentration: 2.8 (2.8) ppm **Range (Min, Max):** Daily Concentration: (0.8, 44.0) Relevant Concentration: (0.0, 30.4) **Copollutant:** NR	**Relative Risk (Lower CI, Upper CI); lag:** Individual Level SEP Quintile 1: 1.06 (1.02-1.09); 1-3 ma Quintile 2: 1.05 (1.02-1.09); 1-3 ma Quintile 3: 1.05 (1.01-1.08); 1-3 ma Quintile 4: 1.07 (1.03-1.11); 1-3 ma Quintile 5: 1.05 (1.00-1.09); 1-3 ma Regional Level SEP Quintile 1: 0.99 (0.92-1.07); 1-3 ma Quintile 2: 1.06 (1.02-1.11); 1-3 ma Quintile 3: 1.04 (1.02-1.07); 1-3 ma Quintile 4: 1.10 (1.06-1.15); 1-3 ma Quintile 5: 1.06 (1.03-1.09); 1-3 ma Overall: 1.06 (1.04-1.07); 1-3 ma Relative Effect Modification for SES Individual Level SEP Quintile 1: 1 Quintile 2: 1 (0.95.1.04); 1-3 ma Quintile 3: 0.99 (0.94-1.03); 1-3 ma Quintile 4: 1.02 (0.97-1.06); 1-3 ma Quintile 5: 0.99 (0.94-1.04); 1-3 ma Regional Level SEP Quintile 1: 1 Quintile 2: 1.05 (0.97-1.14); 1-3 ma Quintile 3: 1.03 (0.96-1.11); 1-3 ma Quintile 4: 1.08 (1-1.16); 1-3 ma Quintile 5: 1.05 (0.97-1.13); 1-3 ma
Author: Kontos et al. (1999, 011326) Period of Study: 1/1987-12/1992 **Location:** Piraeus, Greece	Hospital Admissions **Health Outcome (ICD9):** Respiratory conditions (laryngitis, bronchiolitis, tonsillitis, acute rhinopharyngitis, otitis, bronchopneumonia, pneumonia, asthma) **Study Design:** Time series **Statistical Analyses:** Stochastic dynamical system approach **Age Groups Analyzed:** 0-14 yr	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean Range (SD) unit:** 1987: 4.2 mg/m^3 1992: 3.6 mg/m^3 **Range (Min, Max):** NR **Copollutant:** correlation 1987-1989 Smoke: r = 0.2979; SO_2: r = 0.2166; NO_2: r = 0.1913 1990-1992 Smoke: r = 0.5383; SO_2: r = 0.43283; NO_2: 0.5223	This study did not present quantitative results for CO.
Author: Lee et al. (2002, 034826) **Period of Study:** 12/1997-12/1999 **Location:** Seoul, Korea	Hospital Admissions **Health Outcome (ICD10):** Asthma (J45, J46) **Study Design:** Time series **Statistical Analyses:** Poisson GAM, LOESS **Age Groups Analyzed:** <5 yr	**Pollutant:** CO **Averaging Time:** 1-h max **Mean Range (SD) unit:** 1.8 (0.7) ppm IQR (25th, 75th): (1.2, 2.2) **Copollutant:** correlation PM_{10}: r = 0.598 SO_2: r = 0.812 NO_2: r = 0.785 O_3: r = -0.388	**Increment:** 1.0 ppm **Relative Risk (Lower CI, Upper CI); lag:** RR for asthma and exposure to various pollutants for children under 15 yr old Pollutant: CO: 1.16 (1.10-1.22); 2-3 avg CO, PM_{10}: 1.13 (1.07-1.20); 2-3 avg CO, SO_2: 1.17 (1.08-1.27); 2-3 avg CO, NO_2: 1.04 (0.95-1.14); 2-3 avg CO, O_3: 1.16 (1.11-1.22); 2-3 avg CO, O_3, PM_{10}: 1.148 (1.084-1.217); 2-3 avg CO, O_3, PM_{10}, SO_2: 1.168 (1.075-1.269); 2-3 avg CO, O_3, PM_{10}, SO_2, NO_2: 1.098 (0.994-1.214); 2-3 avg

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Lee et al. (2006, 098248) **Period of Study:** 1/2002-12/2002 **Location:** Seoul, Korea	Hospital Admissions **Health Outcome (ICD10):** Asthma (J45-46) **Study Design:** Time series **Statistical Analyses:** GAM with stringent parameters **Age Groups Analyzed:** <15 yr	**Pollutant:** CO **Averaging Time:** Maximum 2-h avg **Mean (SD) unit:** High SES: 6.08 (2.10) ppb Moderate SES: 6.35 (2.44) ppb Low SES: 6.67 (2.59) ppb **Range (Min, Max):** NR **Copollutant:** correlation NO_2: r = 0.55 SO_2: r = 0.72 PM_{10}: r = 0.28 O_3: r = -0.36	**Increment:** 3.01 ppb, 0.26 ppb, 4.52 ppb, 3.68 ppb **Relative Risk (Lower CI, Upper CI); lag:** Increment: 3.01 ppb Overall: 1.07 (0.96-1.20); 0 Increment: 0.26 ppb High SES: 1.06 (0.96-1.17); 0 Increment: 4.52 ppb Moderate SES: 0.96 (0.84-1.10); 0 Increment: 3.68 ppb Low SES: 1.02 (0.85-1.24); 0
Author: Lee et al. (2007, 090707) **Period of Study:** 1996-2003 **Location:** Kaohsiung, Taiwan	Hospital Admissions **Health Outcome (ICD9):** COPD (490-492, 494, 496) **Study Design:** Bidirectional case crossover **Statistical Analyses:** Conditional logistic regression **Age Groups Analyzed:** All ages	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 0.77 ppm **Range (Min, Max):** (0.23, 1.72) **Copollutant:** PM_{10} SO_2 NO_2 O_3	**Increment:** 0.29 ppm **Odds Ratio (Lower CI, Upper CI); lag:** CO <25°C: 1.398 (1.306-1.496); 0-2 ≥ 25°C: 1.189 (1.123-1.259); 0-2 CO. PM_{10} <25°C: 1.257 (1.152-1.371); 0-2 ≥ 25°C: 1.149 (1.079-1.224); 0-2 CO, SO_2 <25°C: 1.396 (1.295-1.504); 0-2 ≥ 25°C: 1.241 (1.161-1.326); 0-2 CO, NO_2 <25°C: 0.973 (0.877-1.080); 0-2 ≥ 25°C: 1.196 (1.104-1.297); 0-2 CO, O_3 <25°C: 1.378 (1.286-1.477); 0-2 ≥ 25°C: 1.170 (1.105-1.239); 0-2
Author: Lin et al. (1999, 040437) **Period of Study:** 5/1991-4/1993 **Location:** Sao Paulo, Brazil	ED Visits **Health Outcome (ICD9):** Respiratory illness (lower respiratory illness, upper respiratory illness, wheezing) **Study Design:** Time series **Statistical Analyses:** Poisson **Age Groups Analyzed:** <3 yr	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 5 ppm **Range (Min, Max):** (1, 12) **Copollutant:** correlation PM_{10}: r = 0.50 NO_2: r = 0.35 SO_2: r = 0.56 O_3: r = 0.04	Increment: NR **Relative Risk (Lower CI, Upper CI); lag:** Overall Respiratory Illnesses CO: 1.206 (1.066-1.364); 0-5 CO, PM_{10}, O_3, SO_2, NO_2: 0.945 (0.808-1.105); 0-5 Lower Respiratory Illness CO: 1.203 (0.867-1.669); 0-5 CO, PM_{10}, O_3, SO_2, NO_2: 0.971 (0.641-1.472); 0-5 Upper Respiratory Illness CO: 1.237 (1.072-1.428); 0-5 CO, PM_{10}, O_3, SO_2, NO_2: 0.944 (0.785-1.135); 0-5 Wheezing CO: 0.813 (0.606-1.091); 0-5 CO, PM_{10}, NO_2, SO_2, O_3: 0.74 (0.505-1.085); 0-5

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Lin et al. (2003, 042549) **Period of Study:** 1/1981-12/1993 **Location:** Toronto, ON, Canada	Hospital Admissions **Health Outcome (ICD9):** Asthma (493) **Study Design:** Case crossover **Statistical Analyses:** Conditional logistic regression **Age Groups Analyzed:** 6-12 yr	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 1.18 (0.50) ppm **Range (Min, Max):** (0, 6.10) **Copollutant:** correlation SO_2: r = 0.37 NO_2: r = 0.55 O_3: r = -0.16 $PM_{2.5}$: r = 0.45 $PM_{10-2.5}$: r = 0.17 PM_{10}: r = 0.38	**Increment:** 0.5 ppm Odds Ratio (Lower CI, Upper CI); lag: Boys: Adjusting for Daily Weather Variables 1.05 (1-1.11); 1 / 1.07 (1.01-1.14); 2 1.08 (1.01-1.16); 3 / 1.08 (1-1.17); 4 1.07 (0.99-1.16); 5 / 1.07 (0.98-1.17); 6 1.07 (0.98-1.17); 7 Adjusting for PM and Daily Weather Variables 1.05 (0.99-1.11); 1 / 1.08 (1.01-1.16); 2 1.09 (1.01-1.18); 3 / 1.10 (1.02-1.20); 4 1.09 (1.00-1.18); 5 / 1.09 (0.99-1.19); 6 1.09 (0.99-1.20); 7 Girls: Adjusting for Daily Weather Variables 1.00 (0.93-1.06); 1 / 1.01 (0.94-1.10); 2 1.00 (0.91-1.09); 3 / 0.98 (0.89-1.09); 4 1.01 (0.91-1.13); 5 / 1.03 (0.92-1.16); 6 1.04 (0.93-1.17); 7 Adjusting for PM and Daily Weather Variables 1.00 (0.93-1.07); 1 / 1.01 (0.92-1.10); 2 0.99 (0.90-1.09); 3 / 0.97 (0.87-1.08); 4 0.99 (0.89-1.11); 5 / 1.02 (0.90-1.15); 6 1.05 (0.93-1.20); 7
Author: Lin et al. (2004, 055600) **Period of Study:** 1/1987-12/1998 **Location:** Vancouver, BC Canada	Hospital Admissions **Health Outcome (ICD9):** Asthma (493) **Study Design:** Time series **Statistical Analyses:** GAM, LOESS **Age Groups Analyzed:** 6-12 yr	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 0.96 (0.52) ppm **Range (Min, Max):** (0.23, 4.90) **Copollutant:** correlation SO_2: r = 0.67 NO_2: r = 0.73 O_3: r = -0.35	Increment: 0.5 ppm **Relative Risk (Lower CI, Upper CI); lag:** Boys High SES: 1.06 (0.98-1.14); 1 / 1.06 (0.97-1.15); 2 1.07 (0.97-1.17); 3 / 1.03 (0.93-1.14); 4 1.01 (0.91-1.12); 5 / 1.01 (0.91-1.13); 6 1.06 (0.94-1.18); 7 Low SES: 1.06 (0.99-1.14); 1 / 1.03 (0.95-1.12); 2 1.01 (0.93-1.11); 3 / 0.99 (0.90-1.09); 4 0.96 (0.87-1.06); 5 / 0.98 (0.88-1.08); 6 0.98 (0.88-1.09); 7 Girls High SES: 1.05 (0.94-1.16); 1 / 1.02 (0.90-1.15); 2 0.97 (0.85-1.11); 3 / 0.95 (0.83-1.10); 4 0.93 (0.80-1.08); 5 / 0.95 (0.82-1.11); 6 1.01 (0.87-1.19); 7 Low SES: 1.01 (0.92-1.11); 1 / 0.98 (0.89-1.10); 2 0.99 (0.88-1.11); 3 / 1.05 (0.93-1.19); 4 1.07 (0.94-1.21); 5 / 1.07 (0.94-1.23); 6 1.04 (0.91-1.20); 7
Author: Lin et al. (2005, 087828) **Period of Study:** 1998-2001 **Location:** Toronto, Canada	Hospital Admissions **Health Outcome (ICD9):** Respiratory infections (464, 466, and 480-487) **Study Design:** Bidirectional case crossover **Statistical Analyses:** Conditional logistic regression **Age Groups Analyzed:** <5 yr	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 1.16 (0.38) ppm **Range (Min, Max):** (0.38, 2.45) **Copollutant:** correlation $PM_{2.5}$: r = 0.10 $PM_{10-2.5}$: r = 0.06 PM_{10}: r = 0.10 SO_2: r = 0.12 NO_2: r = 0.20 O_3: r = -0.11	**Increment:** 0.44 ppm Odds Ratio (Lower CI, Upper CI); Lag Boys No adjustment: 1.11 (1.01-1.22); 0-3 / 1.10 (1.00-1.22); 0-5 Adjustment for weather variables: 1.13 (1.03-1.24); 0-3 / 1.13 (1.02-1.25); 0-5 Adjustment for weather variables and PM: 1.08 (0.98-1.20); 0-3 / 1.08 (0.97-1.20); 0-5 Girls No adjustment: 0.99 (0.89-1.10); 0-3 / 1.00 (0.89-1.13); 0-5 Adjustment for weather variables: 1.02 (0.92-1.14); 0-3: / 1.05 (0.93-1.18); 0-5 Adjustment for weather variables and PM: 1.01 (0.90-1.13); 0-3 / 1.02 (0.90-1.15); 0-5 Total No adjustment: 1.06 (0.98-1.14); 0-3 / 1.06 (0.98-1.15); 0-5 Adjustment for weather variables: 1.09 (1.01-1.17); 0-3 / 1.10 (1.01-1.19); 0-5 Adjustment for weather variables and PM: 1.05 (0.97-1.14); 0-3 / 1.06 (0.97-1.15); 0-5

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Linn et al. (2000, 002839) **Period of Study:** 1992-1995 **Location:** Los Angeles, CA	Hospital Admissions **Health Outcome (ICD9):** APR-DRG Codes: Pulmonary (75-101); COPD (88) ICD9 Codes: Asthma (493) **Study Design:** Time series **Statistical Analyses:** Poisson **Age Groups Analyzed:** 0-29 yr; ≥ 30 yr	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** Winter 1.7 (0.8) ppm Spring 1.0 (0.3) ppm Summer 1.2 (0.4) ppm Fall 2.1 (0.8) ppm **Range (Min, Max):** Winter: (0.5, 5.3) Spring: (0.4, 2.2) Summer: (0.3,2.7) Fall: (0.6, 4.3) **Copollutant:** correlation Winter NO_2: r = 0.89; PM_{10}: r = 0.78; O_3: r = -0.43 Spring NO_2: r = 0.92; PM_{10}: r = 0.54; O_3: r = 0.29 Summer NO_2: r = 0.94; PM_{10}: r = 0.72; O_3: r = 0.03 Fall NO_2: r = 0.84; PM_{10}: r = 0.58; O_3: r = -0.36	**Increment:** 1.0 ppm **β (SE); lag:** Pulmonary Age Group: ≥ 30 All Year: 0.007 Winter: 0.016 Spring: 0.014 Summer: 0.020 Fall: 0.020 Asthma Age Group 0-29 All Year: 0.036 Asthma Age Group: ≥ 30; All Year: 0.028 Winter: 0.045 Fall: 0.039 COPD Age Group: ≥ 30 All Year: 0.019 Winter: 0.035 Fall: 0.029

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Luginaah et al. (2005, 057327) **Period of Study:** 4/1995-12/2000 **Location:** Windsor, ON, Canada	Hospital Admissions **Health Outcome (ICD9):** Respiratory illness (460-519) **Study Design:** Time series and case crossover **Statistical Analyses:** 1. Time-series: Poisson 2. Case-crossover: conditional logistic regression **Age Groups Analyzed:** All ages 0-14 yr 15-64 yr ≥ 65 yr	**Pollutant:** CO **Averaging Time:** 1-h max **Mean (SD) unit:** 1.3 (1.0) ppm **Range (Min, Max):** (0, 11.82) **Copollutant:** correlation NO_2: r = 0.38 SO_2: r = 0.16 O_3: r = 0.10 CoH: r = 0.31 PM_{10}: r = 0.21	Increment: 1.17 ppm **Relative Risk (Lower CI, Upper CI); Lag** Females and Case-crossover study design Age Group: All ages: 1.037 (0.968-1.111); 1 1.063 (0.976-1.158); 2 1.087 (0.982-1.203); 3 Age Group: 0-14: 1.147 (1.006-1.307); 1 1.186 (1.020-1.379); 2 1.221 (1.022-1.459); 3 Age Group: 15-64: 1.005 (0.884-1.141); 1 1.007 (0.859-1.181); 2 1.032 (0.858-1.240); 3 Age Group: ≥ 65: 1.014 (0.922-1.116); 1 1.024 (0.907-1.156); 2 1.035 (0.893-1.200); 3 Males and Case-crossover study design Age Group: All Ages: 0.950 (0.884-1.020); 1 0.945 (0.862-1.036); 2 0.965 (0.866-1.075); 3 Age Group: 0-14: 1.003 (0.904-1.113); 1 0.997 (0.871-1.141); 2 0.970 (0.824-1.141); 3 Age Group: 15-64: 1.036 (0.870-1.233); 1 1.033 (0.821-1.299); 2 0.991 (0.760-1.293); 3 Age Group: ≥ 65: 0.867 (0.775-0.970); 1 0.865 (0.752-0.994); 2 0.946 (0.807-1.109); 3 Female and Time-series study design Age Group: All Ages: 1.049 (0.993-1.108); 1 1.032 (0.993-1.188); 2 1.051 (0.993-1.112); 3 Age Group: 0-14: 1.077 (0.979-1.184); 1 1.068 (1.001-1.139); 2 1.100 (0.997-1.213); 3 Age Group: 15-64: 1.072 (0.962-1.195); 1 1.025 (0.944-1.112); 2 1.081 (0.963-1.213); 3 Age Group: ≥ 65: 1.029 (0.957-1.118); 1 1.030 (0.928-1.144); 2 1.013 (0.899-1.142); 3 Male and Time-series study design Age Group: All Ages: 0.989 (0.932-1.049); 1 0.986 (0.946-1.029); 2 0.987 (0.929-1.048); 3 Age Group: 0-14: 1.034 (0.949-1.126); 1 0.996 (0.933-1.062); 2 0.968 (0.881-1.064); 3 Age Group: 15-64: 0.994 (0.854-1.157); 1 0.988 (0.884-1.104); 2 0.951 (0.806-1.121); 3 Age Group: ≥ 65: 0.901 (0.817-0.994); 1 0.904 (0.803-1.019); 2 0.963 (0.845-1.098); 3

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Martins et al. (2002, 035059) Period of Study: 5/1996-9/1998 **Location:** Sao Paulo, Brazil	ED Visits **Health Outcome (ICD10):** Chronic lower respiratory disease (CLRD: J40-47) for chronic bronchitis, emphysema, other COPD, asthma, and bronchiectasia **Study Design:** Time series **Statistical Analyses:** Poisson GAM, LOESS **Age Groups Analyzed:** >64 yr	**Pollutant:** CO **Averaging Time:** Max 8-h avg **Mean (SD) unit:** 3.7 (1.7) ppm **Range (Min, Max):** (1.0, 12.6) **Copollutant: correlation** NO_2: r = 0.62; SO_2: r = 0.51; PM_{10}: r = 0.73; O_3: r = 0.07	**Increment:** 1.63 ppm **β (SE); lag:** Chronic Lower Respiratory Diseases Age Group >64: 0.0489 (0.0274); 2
Author: Masjedi et al. (2003, 052100) Period of Study: 9/1997-2/1998 **Location:** Tehran, Iran	ED Visits **Health Outcome (ICD9):** Total acute respiratory conditions; asthma (493); COPD (490-492, 494, 496) **Study Design:** Time series **Statistical Analyses:** Multiple step-wise regression **Age Groups Analyzed:** Adults	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 8.85 ppm **Range (Min, Max):** (2.15, 23.8) **Copollutant:** NR	**Increment:** NR **β (p-value); lag;** Asthma: -0.779 (0.12) COPD: 0.012 (0.71) Acute Respiratory conditions: -0.086 (0.400) Correlation coefficients: Mean 3-day CO levels and asthma: -0.300 (0.149) Mean weekly CO level and asthma: -0.14 (0.2) Mean 10-day CO levels and asthma: -0.05 (0.43)
Author: McGowan et al. (2002, 030325) **Period of Study:** 6/1988- 12/1998 **Location:** Christchurch, New Zealand	Hospital Admissions **Health Outcome (ICD9):** Pneumonia (480-487); acute respiratory infections (460-466); chronic lung diseases (491-492, 494-496); asthma (493) **Study Design:** Time series **Statistical Analyses:** Generalized Additive Model **Age Groups Analyzed:** <15 yr; >64 yr	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 1.16 (1.51) mg/m^3 **Range (Min, Max):** (0, 15.7) **Copollutant:** NR	This study did not provide quantitative results for CO.
Author: Migliaretti et al. (2007, 193772) **Period of Study:** 1/1997-12/1999 **Location:** Turin, Italy	Hospital Admissions **Health Outcome (ICD9):** Respiratory illness (chronic bronchitis, emphysema, and other COPD) (490-496) **Study Design:** Case control **Statistical Analyses:** Multiple logistic regression **Age Groups Analyzed:** ≥ 15 yr 15-64 yr >64 yr	**Pollutant:** CO **Averaging Time:** 8-h median **Median (SD) unit:** 3.36 (1.57) mg/m^3 **Range (Min, Max):** NR **Copollutant:** correlation TSP	**Increment:** 1 mg/m3 **Odds Ratio (Lower CI, Upper CI); lag:** CO Age Group ≥ 15: 1.053 (1.030-1.070) 15-64: 1.040 (0.987-1.085) >64: 1.054 (1.027-1.083) CO , TSP Age Group ≥ 15: 1.058 (1.024-1.096) 15-64: 1.062 (0.993-1.135) >64: 1.054 (1.011-1.099)

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Moolgavkar (2000, 010274) **Period of Study:** 1987-1995 **Location:** 3 U.S. counties: Los Angeles County,CA Cook County, IL Maricopa County, AZ	Hospital Admissions **Health Outcome (ICD9):** COPD plus asthma (490-496) **Study Design:** Time series **Statistical Analyses:** Poisson GAM **Age Groups Analyzed:** All Ages 0-19 yr 20-64 yr ≥ 65 yr	**Pollutant:** CO **Averaging Time:** 24-h median **Median unit:** Cook: 993 ppb LA: 1347 ppb Maricopa: 1240 ppb **Range (Min, Max):** Cook: (224, 3912) LA:(237,5955) Maricopa: (269, 4777) **Copollutant:** correlation Cook County: NO_2: r = 0.63; SO_2: r = 0.35; O_3: r = -0.28 LA County: NO_2: r = 0.80; SO_2: r = 0.78; O_3: r = -0.52 Maricopa County: NO_2: r = 0.66; SO_2: r = 0.53; O_3: r = -0.61	**Increment:** 1.0 ppm **% Increase (t-statistic); lag:** Age Group: ≥ 65 Cook County CO: 2.60 (1.9); 0; / 3.00 (2.2); 1; / 1.30 (1.0); 2; 1.40 (1.1); 3; / 1.10 (0.8); 4; / 2.30 (1.8); 5 Los Angeles County CO: 5.40 (11.3); 0; / 4.90 (10.1); 1; / 5.00 (10.2); 2; 4.90 (10.1); 3; / 4.00 (8.3); 4; / 4.30 (8.6); 5; CO, PM_{10}: 4.30 (3.3); 0; / 5.30 (4.2); 1; / 5.10 (4.0); 2; 6.80 (5.6); 3; / 6.90 (5.4); 4; / 6.30 (4.7); 5; CO, $PM_{2.5}$: 3.00 (1.9); 0; / 3.90 (2.5); 1; / 4.20 (2.6); 2; 6.50 (4.4); 3; / 5.80 (3.8); 4; / 5.10 (3.1); 5 Maricopa County CO: 1.40 (1.0); 0; / 0.80 (0.6); 1; / 1.20 (0.9); 2; 1.20 (0.9); 3; / 1.50 (1.1); 4; / 4.90 (3.8); 5 Age Group: 0-19 Los Angeles County CO: 8.20 (14.4); 0; / 9.00 (15.9); 1; / 9.20 (16.4); 2; 8.50 (15.0); 3; / 7.00 (12.1); 4; / 4.80 (8.1); 5; CO, PM_{10}: 7.50 (14.4); 0; /: 7.40 (5.2); 1; / 6.40 (4.3); 2; 8.00 (5.5); 3; / 6.30 (4.0); 4; / 5.30 (3.5); 5; CO, $PM_{10-2.5}$: 5.70 (3.4); 0; / 7.50 (4.9); 1; / 5.60 (3.3); 2; 5.40 (3.5); 3; / 4.40 (2.7); 4; / 1.80 (1.1); 5 Age Group: 20-64 Los Angeles County CO: 3.70 (8.6); 0; / 3.90 (9.1); 1; / 4.50 (10.6); 2; 3.50 (8.3); 3; / 3.40 (7.9); 4; / 3.50 (7.9); 5; CO, PM_{10}: 5.00 (4.6); 0; / 3.00 (2.7); 1; / 3.10 (2.8); 2; 5.20 (4.7); 3; / 5.90 (5.1); 4; / 4.90 (4.4); 5; CO, $PM_{2.5}$: 3.50 (2.5); 0; / 0.60 (0.4); 1; / 1.10 (0.8); 2; 5.70 (4.1); 3; / 4.70 (3.3); 4; / 3.90 (2.8); 5; CO, $PM_{10-2.5}$: 2.80 (2.2); 0; / 2.50 (2.0); 1;/ 0.60 (0.5); 2; 3.90 (3.2); 3; / 3.40 (2.8); 4; / 4.00 (3.4); 5
Author: Moolgavkar (2003, 042864) **Period of Study:** 1987-1995 **Location:** 2 U.S. counties: Los Angeles County, CA, and Cook County, IL	Hospital Admissions **Health Outcome (ICD9):** COPD plus asthma (490-496) **Study Design:** Time series **Statistical Analyses:** Poisson GAM, Poisson GLM with natural splines **Age Groups Analyzed:** All Ages; ≥ 65 yr	**Pollutant:** CO **Averaging Time:** 24-h median **Median unit:** Cook: 993 ppb LA: 1347 ppb Maricopa: 1240 ppb **Range (Min, Max):** Cook: (224, 3912) LA: (237,5955) **Copollutant:** correlation Cook County: NO_2: r = 0.63; SO_2: r = 0.35; O_3: r = -0.28 Los Angeles County: NO_2: r = 0.80; SO_2: r = 0.78; O_3: r = -0.52	**Increment:** 1 ppm **% Increase (t-statistic); lag:** COPD–Los Angeles County CO: GAM-30 (10-8): 5.48 (17.67); 0; / 5.67 (18.22); 1; / 5.90 (19.01); 2; 5.28 (16.94); 3; / 4.59 (14.50); 4; / 4.10 (12.80); 5 GAM-100 (10-8): 2.37 (8.67); 0; / 2.41 (8.73); 1; / 2.41 (8.76); 2; 1.81 (6.58); 3; / 1.38 (4.94); 4; / 1.07 (3.82); 5 NS-100: 2.28 (5.65); 0; / 2.29 (5.50); 1; / 2.32 (5.33); 2; 1.74 (4.10); 3; / 1.30 (3.16); 4; / 1.00 (2.46); 5 COPD–Cook County CO: GAM-100 (10-8): 2.11 (1.62); 0; / 2.85 (2.16); 1; / 1.14 (0.86); 2; 1.05 (0.79); 3; / 0.43 (0.33); 4; / 0.34 (0.26); 5

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Neidell et al. (2004, 057330) **Period of Study:** 1992-1998 **Location:** California	Hospital Admissions **Health Outcome (ICD9):** Asthma (493) **Study Design:** Time series **Statistical Analyses:** Linear Regression **Age Groups Analyzed:** 0-1 yr 1-3 yr 3-6 yr 6-12 yr 12-18 yr	**Pollutant:** CO **Averaging Time:** 24-h avg Mean (SD) unit: 1.777 (1.037) ppm Range (Min, Max): NR **Copollutant:** correlation O_3 PM_{10} NO_2	**Increment:** NR **β (SE); lag;** Single-pollutant model Age Group 0-1: -0.007 (0.009); 1-3: 0.027 (0.009); 3-6: 0.053 (0.010); 6-12: 0.047 (0.009); 12-18: 0.025 (0.008) Fixed effect controlling for O_3, PM_{10}, and NO_2 Age Group 0-1: -0.01 (0.01); 1-3: 0.024 (0.011); 3-6: 0.049 (0.011); 6-12: 0.023 (0.011); 12-18: 0.021 (0.009) Fixed effect controlling for O_3, PM_{10}, NO_2 and avoidance behavior Age Group 0-1: -0.010 (0.010); 1-3: 0.027 (0.011); 3-6: 0.051 (0.011); 6-12: 0.025 (0.011); 12-18: 0.021 (0.009)
Author: Norris et al. (1999, 040774) **Period of Study:** 9/1995- 12/1996 **Location:** Seattle, WA	ED Visits **Health Outcome (ICD9):** Asthma (493) **Study Design:** Time series **Statistical Analyses:** Semiparametric Poisson GAM **Age Groups Analyzed:** <8 yr	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 1.6 (0.5) ppm **Range (Min, Max):** (0.6, 4.1) **Copollutant: correlation** PM_{10}: r = 0.74 NO_2 (1-h max): r = 0.47 NO_2 (24-h avg.): r = 0.66 SO_2 (1-h max): r = 0.15 SO_2 (24-h avg.): r = 0.32	**Increment:** 0.6 ppm **Relative Risk (Lower CI, Upper CI); Lag** High Utilization: 1.04 (0.93-1.16); 1 Low Utilization: 1.15 (1.05-1.28); 1 All: 1.10 (1.02-1.19); 1
Author: Peel et al. (2005, 056305) **Period of Study:** 1/1993- 8/2000 **Location:** Atlanta, GA	ED Visits **Health Outcome (ICD9):** Asthma (493, 786.09); COPD (491, 492, 496); URI (460-466, 477); pneumonia (480-486) **Study Design:** Time series **Statistical Analyses:** 1. Poisson GEE or asthma, URI, all respiratory 2. Poisson GLM for pneumonia and COPD **Age Groups Analyzed:** Primary Analysis: All Ages Secondary Analysis: 2-18 yr	**Pollutant:** CO **Averaging Time:** 1-h max **Mean (SD) unit:** 1.8 (1.2) ppm **Range (10th, 90th):** (0.5, 3.4) **Copollutant:** NR	**Increment:** 1.0 ppm **Relative Risk (Lower CI, Upper CI); Lag** Health Condition All respiratory illnesses: 1.011 (1.004-1.019); 0-2 URI: 1.012 (1.003-1.021); 0-2 / 1.066 (1.045-1.087); 0-13 Asthma: 1.010 (0.999-1.022); 0-2 1.076 (1.047-1.105); 0-13 Pneumonia: 1.009 (0.996-1.021); 0-2 1.045 (1.011-1.080); 0-13 COPD: 1.026 (1.004-1.048); 0-2 1.032 (0.975-1.092); 0-13 RR for asthma and exposure to CO for children age 2-18: 1.019 (1.004-1.035); 0-2 RR for all respiratory illnesses and CO exposure for all ages AQS (1/1/93- 8/31/00): 1.011 (1.004-1.019); 0-2 AQS (8/1/98- 8/31/00): 1.010 (1.000-1.021); 0-2 ARIES (8/1/98- 8/31/00): 1.018 (1.003-1.033); 0-2

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Sauerzapf et al. (2009, 180082) **Period of Study:** Jan 2006-Feb 2007 **Location:** Norfolk county, England	Hospital Admissions **Health Outcome:** COPD **Study Design:** Case crossover **Statistical Analyses:** Logistic Regression **Age Groups Analyzed:** 18+ yr (90% of patients 60+ yr) **Sample Description:** 1,050 COPD admissions	**Averaging Time:** 24 h **Mean (SD) unit:** Control days: 194.46 (80.93) Case days: 204.73 (119.97) **Range (min, max):** Control days: 105.20, 408.10 Case days: 108.70, 432.20 **Copollutant:** NO, NO_2, NO_X, O_3 * Control days = 7 days prior to admission; Case days = day of admission	**Increment:** 10 µg/m^3 **Lags examined:** 0-8 OR Estimate [Lower CI, Upper CI]; lag: Unadjusted: 1.010 (1.001, 1.019); lag 0-7 Adjusted: 1.015 (1.005, 1.025); lag 0-7 Unadjusted: 1.013 (1.001, 1.025); lag 1-8 Adjusted: 1.018 (1.005, 1.031); lag 1-8
Author: Sheppard et al. (1999, 086921) **Period of Study:** 1987-1994 **Location:** Seattle, WA	Hospital Admissions **Health Outcome (ICD9):** Asthma (493) **Study Design:** Time series **Statistical Analyses:** Poisson **Age Groups Analyzed:** <65 yr	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 1831 ppb **IQR (25th, 75th):** (1277, 2201) **Copollutant:** correlation PM_{10}: r = 0.83; $PM_{2.5}$: r = 0.78; $PM_{10-2.5}$: r = 0.56; O_3: r = -0.18; SO_2: r = 0.24	**Increment:** 924 ppb % **Increase (Lower CI, Upper CI); Lag** CO: 6% (3, 9); 3 CO, $PM_{2.5}$: 5% (1, 8); 3
Author: Slaughter et al. (2005, 073854) **Period of Study:** 1/1995-6/2001 **Location:** Spokane, WA	Hospital Admissions & ED Visits **Health Outcome (ICD9):** Respiratory causes (460-519) Asthma (493); COPD (491, 492, 494, 496) acute respiratory tract infections not including colds and sinusitis (464-466, 490) **Study Design:** Time series **Statistical Analyses:** Poisson GLM, Natural Splines **Age Groups Analyzed:** All ages, Adults	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** NR **Range (5th, 95th):** (1.25, 3.05) **Copollutant:** correlation PM_1: r = 0.63 $PM_{2.5}$: r = 0.62 PM_{10}: r = 0.32 $PM_{10-2.5}$: r = 0.32	**Increment:** 1.0 ppm **Relative Risk (Lower CI, Upper CI); lag:** ED Visits All Respiratory Illnesses Age Group: All Ages: 0.99 (0.96-1.02); 1 / 1.01 (0.98-1.04); 2 1.03 (1.00-1.06); 3 Asthma Age Group: All Ages: 1.00 (0.95-1.06); 1 / 1.01 (0.96-1.07); 2 1.06 (1.00-1.11); 3 COPD Age Group: Adults: 0.92 (0.85-1.00); 1 / 0.99 (0.91-1.08); 2 1.01 (0.93-1.10); 3 Hospital Admissions: All Respiratory Illnesses Age Group: All Ages: 0.99 (0.95-1.02); 1 / 1.00 (0.96-1.04); 2 0.99 (0.96-1.03); 3 Asthma Age Group: All Ages: 1.02 (0.92-1.13); 1 / 1.06 (0.96-1.17); 2 1.00 (0.91-1.11); 3 COPD Age Group: Adults: 0.94 (0.86-1.03); 1 / 1.04 (0.95-1.13); 2 0.97 (0.88-1.06); 3

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Stieb et al. (2000, 011675) **Period of Study:** 7/1992- 3/1996 **Location:** Saint John, Canada	ED Visits **Health Outcome (ICD9):** Asthma; COPD; respiratory infections; all respiratory illnesses **Study Design:** Time series **Statistical Analyses:** Poisson GAM, LOESS **Age Groups Analyzed:** All ages	**Pollutant:** CO **Averaging Time:** 24-h avg 1-h max **Mean (SD) unit:** All yr: 0.5 (0.3) ppm May-September: 0.6 (0.3) ppm All yr: 1.6 (1.1) ppm, May-September: 1.7 (0.9) ppm **Range (Min, Max): NR** **Copollutant: correlation** H_2S: r = -0.10; NO_2: r = 0.68; O_3: r = -0.05; SO_2: r = 0.31; TRS: r = 0.07; PM_{10}: r = 0.28; $PM_{2.5}$: r = 0.27; H+: r = 0.23; SO_4^{2-}: r = 0.27; CoH: r = 0.55	**Increment:** 0.5 & 1.7 ppm **AI% Increase (Lower CI, Upper CI); lag:** Respiratory Illnesses Increment: 0.5 ppm All Year: -3.40; 7 Increment: 1.7 ppm May- September: -5.70
Author: Sun et al. (2006, 090768) **Period of Study:** 1/2004- 12/2004 **Location:** Taiwan	ED Visits **Health Outcome (ICD9):** Asthma (493) **Study Design:** Cross sectional **Statistical Analyses:** Pearson correlation analysis **Age Groups Analyzed:** <16 yr; 16-55 yr	**Pollutant:** CO **Averaging Time:** Monthly **Mean (SD) unit**: NR **Range (Min, Max):** NR **Copollutant:** NR	Incre**ment: NR** **Correlation Coefficient:** Asthma Age Group: <16: 0.653 16-55: 0.425
Author: Tenias et al. (2002, 026077) **Period of Study:** 1/1994- 12/1995 **Location:** Valencia, Spain	ED Visits **Health Outcome (ICD9):** COPD (491, 492, 494, 496) **Study Design:** Time series **Statistical Analyses:** 1. Poisson autoregressive 2. Sensitivity: GAM, LOESS **Age Groups Analyzed:** >14 yr	**Pollutant:** CO **Averaging Time:** 24-h avg 1-h max **Mean (SD) unit:** 24-h avg All yr: 3.1 mg/m^3 Warm Months: 2.5 mg/m^3 Cold Months: 3.7 mg/m^3 1-h avg All yr: 6.7 mg/m^3 Warm Months: 5.4 mg/m^3 Cold Months: 8.0 mg/m^3 **Range (Min, Max):** 24-h avg: (0.9, 7.1) 1-h max: (1.6, 17.2) **Copollutant:** correlation SO_2: r = 0.734; NO_2: r = 0.180; O_3: r = -0.517	Increment: 1 mg/m^3 **Relative Risk (Lower CI, Upper CI); Lag** 24-h avg All Year: 1.074 (0.998- 1156); 1 Cold Months: 1.070 (0.991-1.156); 1 Warm Months: 1.129 (0.960-1.329); 1 1-h max All Year: 1.039 (1.014-1.066); 1 Cold Months: 1.037 (1.010-1.064); 1 Warm Months: 1.058 (0.994-1.127); 1 All Year: sinusoidal terms: 1.039 (1.010-1.066); 1 All Year: humidity and temperature variables: 1.040 (1.014-1.067); 1 All Year: GAM, LOESS: 1.042 (1.019-1.066); 1
Author: Thompson et al. (2001, 073513) **Period of Study:** 1/1993- 12/1995 **Location:** Belfast, Northern Ireland	ED Visits **Health Outcome (ICD9):** Asthma (493) **Study Design:** Time series **Statistical Analyses:** Poisson **Age Groups Analyzed:** Children	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** Warm Season: 0.57 (0.41) ppm Cold Season: 0.74 (0.73) ppm **IQR (25th, 75th):** Warm Season: (0.3, 0.7) Cold Season: (0.4, 0.8) **Copollutant:** correlation SO_2 (log): r = 0.64; PM_{10} (log): r = 0.57; O_3: r = -0.52; NO_X (log): r = 0.74; NO (log): r = 0.71; NO_2: r = 0.69	**Increment:** NR **Relative Risk (Lower CI, Upper CI); lag:** Temperature included in the model: 1.04 (1.00-1.09); 0 / 1.07 (1.02-1.12); 0-1 1.06 (1.00-1.12); 0-2 / 1.07 (1.00-1.14); 0-3 Warm Season: 1.06 (0.98-1.16); NR Cold Season: 1.07 (1.01-1.14); NR Adjusted for benzene level: 0.92 (0.83-.02); 0-1 avg. **Note:** The increment the study uses to calculate effect estimates is a doubling in CO levels, but The study did not provide this value.

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Tolbert et al. (2007, 090316) **Period of Study:** 1/1993- 12/2004 **Location:** Atlanta, GA	ED Visits **Health Outcome (ICD9):** Respiratory disease: asthma (493, 786.07, 786.09); COPD (491, 492, 496); URI (460-465, 460.0, 477); pneumonia (480-496); bronchiolitis (466.1, 466.11, 466.19)) **Study Design:** Time series **Statistical Analyses:** Poisson GLM **Age Groups Analyzed:** All ages	**Pollutant:** CO **Averaging Time:** 1-h max **Mean (SD) unit:** 1.6 ppm **Range (Min, Max):** (0.1, 7.7) **Copollutant: correlation** PM_{10}: r = 0.51; O_3: r = 0.27; NO_2: r = 0.70; SO_2: r = 0.28; Coarse PM: r = 0.38; $PM_{2.5}$: r = 0.47; SO_4: r = 0.14;EC: r = 0.66; OC: r = 0.59; TC: r = 0.63; OHC: r = 0.29	**Increment:** 1.22 ppm **Relative Risk (Lower CI, Upper CI); lag:** **Respiratory Diseases:** 1.016 (1.009-1.022); 3 **Note:** The study only provides results of the multi-pollutant models in figures, not quantitatively.
Author: Trapasso and Keith (1999, 180127) **Period of Study:** 1/1994- 12/1994 **Location:** Bowling Green, KY	Hospital Admissions **Health Outcome (ICD9):** Asthma (493) **Study Design:** Time series **Statistical Analyses:** Spearman Rank Correlation Coefficient **Age Groups Analyzed:** All ages	**Pollutant: CO** **Averaging Time:** NR **Mean (SD) unit:** NR **Range (Min, Max):** NR **Copollutant:** NR	**Increment:** NR **Correlation Coefficient (lag)** CO Mean: r = 0.19;0 CO Mean: r = 0.27; 1 CO Mean: r = 0.21; 2 CO Max: r = 0.26; 0 CO Max: r = 0.36; 1 CO Max: r = 0.24; 2
Author: Tsai et al. (2006, 089768) **Period of Study:** 1996-2003 **Location:** Kaohsiung, Taiwan	Hospital Admissions **Health Outcome (ICD9):** Asthma (493) **Study Design:** Case crossover **Statistical Analyses:** Conditional logistic regression **Age Groups Analyzed:** All ages	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 0.77 ppm **Range (Min, Max):** (0.23, 1.72) **Copollutant:** PM_{10} SO_2 NO_2 O_3	**Increment:** 0.29 ppm **Odds Ratio (Lower CI, Upper CI); lag** OR for getting asthma and exposure to various pollutants for all ages at either <25°C or ≥ 25°C CO <25°C: 1.414 (1.300-1.537); 0-2 ≥ 25°C: 1.222 (1.138-1.312); 0-2 CO, PM_{10} <25°C: 1.251 (1.125-1.393); 0-2 ≥ 25°C: 1.178 (1.088-1.274); 0-2 CO, SO_2 <25°C: 1.207 (1.076-1.354); 0-2 ≥ 25°C: 1.290 (1.188-1.400); 0-2 CO, NO_2 <25°C: 0.916 (0.807-1.039); 0-2 ≥ 25°C: 1.249 (1.127-1.384); 0-2 CO, O_3 <25°C: 1.396 (1.282-1.520); 0-2 ≥ 25°C: 1.195 (1.113-1.284); 0-2
Author: Vigotti et al. (2007, 090711) **Period of Study:** 1/2000- 12/2000 **Location:** Pisa, Italy	ED Visits **Health Outcome (ICD9):** Respiratory disease: asthma (493); dry cough (468); acute bronchitis (466) **Study Design:** Time series **Statistical Analyses:** Poisson GAM, LOESS **Age Groups Analyzed:** <10 yr; >65 yr	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 1.5 (0.7) ug/m^3 **Range (Min, Max):** (0.3, 3.5) **Copollutant:** correlation NO_2: r = 0.62 PM_{10}: r = 0.70	**Increment:** 1mg/m^3 **% Increase (Lower CI, Upper CI); lag** Age Group <10: 18.60% (-6.90 to 51.10); 1 >65: 26.50% (3.40-54.80); 4

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Villeneuve et al. (2006, 091179) **Period of Study:** 1995-2000 **Location:** Toronto, ON, Canada	Physician Visits **Health Outcome (ICD9):** Allergic rhinitis (177) **Study Design:** Time series **Statistical Analyses:** Poisson GLM **Age Groups Analyzed:** >65 yr	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 1.1 (0.4) ppm **Range (Min, Max):** (0.0, 2.2) **Copollutant:** $PM_{2.5}$ PM_{10} $PM_{10-2.5}$ SO_2 NO_2 O_3	Increment: 0.4 ppm **Odds Ratio (Lower CI, Upper CI); Lag** The study did not present quantitative results for CO.
Author: Xirasagar et al. (2006, 093267) **Period of Study:** 1998- 2001 **Location:** Taiwan	Hospital Admissions **Health Outcome (ICD9):** Asthma (493) **Study Design:** Cross sectional **Statistical Analyses:** Spearman Rank Correlations **Age Groups Analyzed:** 0-14 yr; <2 yr; 2-5 yr; >5 yr	**Pollutant:** CO **Averaging Time:** Monthly **Mean (SD) unit:** NR **Range (Min, Max):** NR **Copollutant:** NR	**Increment:** NR **Correlation Coefficient (Lag)** Age Group: <2: r = -0.208 2-5: r = -0.281 >5: r = -0.134
Author: Yang et al. (2007, 092848) **Period of Study:** 1996-2003 **Location:** Taipei, Taiwan	Hospital Admissions **Health Outcome (ICD9):** Asthma (493) **Study Design:** Case crossover **Statistical Analyses:** Conditional logistic regression **Age Groups Analyzed:** All ages	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 1.33 ppm **Range (Min, Max):** (0.32, 3.62) **Copollutant:** PM_{10} SO_2 NO_2 O_3	**Increment:** 0.53 ppm **Odds Ratio (Lower CI, Upper CI); Lag** CO <25°C: 1.076 (1.019-1.136); 0-2 ≥ 25°C: 1.277 (1.179-1.383); 0-2 CO, PM_{10} <25°C: 1.050 (0.983-1.122); 0-2 ≥ 25°C: 1.332 (1.216-1.459); 0-2 CO, SO_2 <25°C: 1.131 (1.059-1.207); 0-2 ≥ 25°C: 1.278 (1.174-1.392); 0-2 CO, NO_2 <25°C: 0.915 (0.839-0.997); 0-2 ≥ 25°C: 1.177 (1.049-1.320); 0-2 CO, O_3 <25°C: 1.169 (1.102-1.240); 0-2 ≥ 25°C: 1.275 (1.177-1.382); 0-2
Author: Yang et al. (2007, 092847) **Period of Study:** 1996-2003 **Location:** Taipei, Taiwan	Hospital Admissions **Health Outcome (ICD9):** COPD: (490-492, 494, 496) **Study Design:** Case crossover **Statistical Analyses:** Conditional logistic regression **Age Groups Analyzed:** All ages	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 1.33 ppm **Range (Min, Max):** (0.32, 3.66) ppm **Copollutant:** PM_{10} SO_2 NO_2 O_3	**Increment:** 0.53 ppm **Odds Ratio (Lower CI, Upper CI); Lag** CO <20°C: 0.975 (0.921,1.033); 0-2 ≥ 20°C: 1.227 (1.178-1.277); 0-2 CO, PM_{10} <20°C: 0.925 (0.863-0.992); 0-2 ≥ 20°C: 1.177 (1.123-1.235); 0-2 CO, SO_2 <20°C: 0.895 (0.832-0.962); 0-2 ≥ 20°C: 1.274 (1.219-1.331); 0-2 CO, NO_2 <20°C: 1.000 (0.910-1.099); 0-2 ≥ 20°C: 1.061 (0.998-1.129); 0-2 CO, O_3 <20°C: 0.935 (0.875-0.999); 0-2 ≥ 20°C: 1.234 (1.185-1.285); 0-2

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Yang et al. (2005, 090184) **Period of Study:** 1/1994- 12/1998 **Location:** Vancouver, Canada	Hospital Admissions **Health Outcome (ICD9):** COPD (490-492, 494, 496) **Study Design:** Time series **Statistical Analyses:** Poisson **Age Groups Analyzed:** ≥ 65 yr	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** .71 (0.28) ppm **Range (Min, Max):** (0.30, 2.48) **Copollutant:** correlation O_3: r = -0.56 NO_2: r = 0.73 SO_2: r = 0.67 PM_{10}: r = 0.50	**Increment:** 0.3 ppm **Relative Risk (Lower CI, Upper CI); lag** CO 1.03 (1.00-1.06); 0 / 1.04 (1.01-1.08); 0-1 1.05 (1.01-1.09); 0-2 / 1.05 (1.00-1.10); 0-3 1.06 (1.01-1.11); 0-4 / 1.07 (1.02-1.12); 0-5 1.08 (1.02-1.13); 0-6 MultiPollutant: CO, O_3: 1.11 (1.04-1.18); 0-6 CO, NO_2: 1.04 (0.95-1.14); 0-6 CO, SO_2: 1.11 (1.01-1.22); 0-6 CO, PM_{10}: 1.02 (0.93-1.12); 0-6 CO, PM_{10}, O_3, NO_2, SO_2: 1.08 (0.96-1.22); 0-6 CO, O_3, NO_2, SO_2: 1.10 (0.98-1.23); 0-6
Author: Yang et al. (2003, 055621) **Period of Study:** 1/1986- 12/1998 **Location:** Vancouver, BC, Canada	Hospital Admissions **Health Outcome (ICD9):** Respiratory diseases (460-519) **Study Design:** Case crossover **Statistical Analyses:** Conditional logistic regression **Age Groups Analyzed:** <3 yr; ≥ 65 yr	**Pollutant**: CO **Averaging Time:** 24-h avg **Mean (SD) unit**: 0.98 (0.54) ppm **IQR (25th, 75th):** (0.62, 1.16) **Copollutant: correlation** O_3: r = -0.52 CoH NO_2 SO_2	**Increment:** 0.54 ppm **Odds Ratio (Lower CI, Upper CI); lag** OR for respiratory diseases and exposure to various pollutants for people <3 and ≥ 65 Age Group: <3 CO alone: 1.04 (1.01-1.07); 1 CO, O_3: 1.04 (1.01-1.07); 1 CO, O_3, CoH, NO_2, SO_2: 1.02 (0.96-1.08); 1 Age Group: ≥ 65 CO alone: 1.02 (1.00-1.04); 1 CO, O_3: 1.02 (1.00-1.04); 1 CO, O_3, CoH, NO_2, SO_2: 0.96 (0.93-1.00); 1
Author: Yang et al. (2004, 087488) **Period of Study:** 6/1/1995-3/31/1999 **Location:** Vancouver, Canada	Hospital Admissions **Health Outcome (ICD9):** Respiratory diseases (460-519); pneumonia (480-486); asthma (493) **Study Design:** Case control **Statistical Analyses:** Pearson's correlation coefficient **Age Groups Analyzed:** <3 yr	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 0.70 (0.30) ppm **IQR (25th, 75th):** (0.50, 0.80) **Copollutant:** correlation PM_{10}: r = 0.46; $PM_{2.5}$: r = 0.24; $PM_{10-2.5}$: r = 0.33; O_3: r = -0.53; NO_2: r = 0.74; SO_2: r = 0.61	This study did not present quantitative results for CO.
Author: Zanobetti and Schwartz (2006, 090195) **Period of Study:** 1995-1999 **Location:** Boston, MA	Hospital Admissions **Health Outcome (ICD9):** Pneumonia (480-487) **Study Design:** Case crossover **Statistical Analyses:** Conditional logistic regression **Age Groups Analyzed:** All ages	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** NR **IQR (25th, 75th):** (0.39, 0.60) **Copollutant:** correlation $PM_{2.5}$: r = 0.52; BC: r = 0.82; NO_2: r = 0.67; O_3: r = -0.30	**Increment:** 0.475 ppm **% Increase (Lower CI, Upper CI); lag:** 5.45 (1.10, 9.51); 0 5.12 (0.83, 9.16); 0-1

Table C-6. Studies of long-term CO exposure and respiratory morbidity.

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Goss et al. (2004, 055624) **Period of Study:** 1999-2000 **Location:** U.S.	**Health Outcome:** Lung function (FEV_1, cystic fibrosis pulmonary exacerbation) **Study Design:** Cohort **Statistical Analyses:** Logistic regression **Population:** 11,484 cystic fibrosis patients **Age Groups Analyzed:** >6 yr	**Pollutant:** CO **Averaging Time:** Annual avg **Mean (SD) unit:** 0.692 (0.295) ppm **IQR (25th, 75th):** (0.48, 0.83) **Copollutant:** NR	**Increment:** 1.0 ppm **Odds Ratio (Lower CI, Upper CI); lag:** Two or more pulmonary exacerbations during 2000 1.02 (0.85-1.22)
Author: Guo et al. (1999, 010937) **Period of Study:** 10/1995-5/1996 **Location:** Taiwan	**Health Outcome:** Asthma **Study Design:** Cohort **Statistical Analyses:** Logistic regression **Population:** 331,686 nonsmoking children **Age Groups Analyzed:** Middle-school children (mean age = 13.8 yr)	**Pollutant:** CO **Averaging Time:** Annual avg **Mean (SD) unit:** 853 (277) ppb **Range (Min, Max):** (381, 1610) **Copollutant:** NR	**Increment:** 326 ppb **% Increase (Lower CI, Upper CI); lag:** Boys Physician-diagnosed asthma: 1.17% (0.63-1.72) Questionnaire-diagnosed asthma: 1.10% (0.45-1.75) Girls Physician-diagnosed asthma: 0.84% (0.45-1.22) Questionnaire-diagnosed asthma: 1% (0.44-1.56)

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Hirsch et al. (1999, 003537) **Period of Study:** Population: 9/1995-6/1996 Air: 4/1994-4/1995 **Location:** Dresden, Germany	**Health Outcome:** Asthma symptoms in the past 12 mo (wheeze, morning cough); Doctor's diagnosis (asthma, bronchitis); Lung function (bronchial hyperresponsiveness (BHR), FEV_1 <85% pred., $FEF_{25-75\%}$ <70% pred.) **Study Design:** Cross sectional **Statistical Analyses:** Multiple logistic regression **Population:** 5-7: 2,796; 9-11: 2,625 **Age Groups Analyzed:** 5-7 and 9-11 yr	**Pollutant:** CO **Averaging Time:** Annual avg **Mean (SD) unit:** 0.69 mg/m^3 **Range (Min, Max):** (0.32, 1.54) **Copollutant:** NR	**Increment:** 0.2 $\mu g/m^3$ **Prevalence Odds Ratio (Lower CI, Upper CI); lag:** Symptoms in the past 12 mo: Wheeze Home Exposure Age Groups: 5-7; 9-11: 1.05 (0.93-1.18) Home/School Exposure Age Groups: 9-11: 1.02 (0.85-1.22) Morning Cough Home Exposure Age Groups: 5-7; 9-11: 1.12 (1.01-1.23) Age Group: 9-11: 1.13 (0.98-1.3) Doctor's diagnosis: Asthma Home Exposure Age Groups: 5-7; 9-11: 1.07 (0.94-1.21) Age Groups: 9-11: 1.16 (0.97-1.38) Doctor's diagnosis: Bronchitis Age Groups: 5-7; 9-11: 1.19 (1.11-1.27) Age Group: 9-11: 1.24 (1.12-1.38) Lung function: BHR Age Groups: 5-7; 9-11: 0.79 (0.63-0.99) Age Group: 9-11: 0.77 (0.6-0.99) Lung function: FEV1 <85% pred. Age Groups: 5-7; 9-11: 1.09 (0.81-1.47) Age Group: 9-11: 1.01 (0.73-1.41) Lung function: FEV25-75% <70% pred. Age Groups: 5-7; 9-11: 1.15 (0.94-1.39) Age Group: 9-11: 1.07 (0.86-1.34) Symptoms in the past 12 mo: Wheeze Age Groups: 5-7; 9-11 Atopic children: 1 (0.81-1.24) Nonatopic children: 1.05 (0.83-1.31) Morning cough Age Groups: 5-7; 9-11 Atopic children: 1.03 (0.82-1.29) Nonatopic children: 1.22 (1.05-1.41) Doctor's diagnosis: Asthma Atopic children: 1.05 (0.83-1.32) Nonatopic children: 1.29 (1.05-1.59) Doctor's diagnosis: Bronchitis Age Groups: 5-7; 9-11 Atopic children: 1 (0.86-1.16) Nonatopic children: 1.21 (1.1-1.33) Notes: Atopic Children were defined as those children with specific IgE to aeroallergens >0.7 kU-L-1; Nonatopic Children were defined as those children with specific IgE to aeroallergens ≤ 0.7 kU-L-1.
Author: Hwang et al. (2006, 088971) **Period of Study:** 2001 **Location:** Taiwan	**Health Outcome:** Allergic rhinitis **Study Design:** Cross sectional **Statistical Analyses:** Two-stage hierarchical model (logistic and linear regression) **Population:** 32,143 Taiwanese school children **Age Groups Analyzed:** 6-15 yr	**Pollutant:** CO **Averaging Time:** Annual avg **Mean (SD) unit**: 664 (153) ppb **Range (Min, Max):** (416, 964) **Copollutant:** correlation NO_X: r = 0.88 O_3: r = -0.37 PM_{10}: r = 0.27 SO_2: r = 0.40	Increment: 100 ppb **Adjusted Odds Ratio (Lower CI, Upper CI); lag:** Physician-diagnosed allergic rhinitis 1.05 (1.04-1.07) CO, SO_2: 1.04 (1.02-1.06) CO, PM_{10}: 1.05 (1.03-1.07) CO, O_3: 1.07 (1.05-1.09) Male: 1.06 (1.03-1.08); Female: 1.05 (1.02-1.08) Parental atopy: Yes: 1.05 (1.02-1.08) Parental atopy: No: 1.06 (1.03-1.08) Parental Education: <6: 1 (0.91-1.09) Parental Education: 6-8: 1.07 (1.02-.12) Parental Education: 9-11: 1.05 (1.02-1.08) Parental Education: ≥ 12: 1.06 (1.03-1.09) ETS: Yes: 1.06 (1.03-1.08); ETS: No: 1.05 (1.02-1.08) Visible Mold: Yes: 1.07 (1.03-1.11) Visible Mold: No: 1.05 (1.03-1.07)

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Hwang et al. (2005, 089454) **Period of Study:** 2001 **Location:** Taiwan	**Health Outcome:** Asthma **Study Design:** Cross sectional **Statistical Analyses:** Two-stage hierarchical model (logistic and linear regression) **Population:** 32,672 Taiwanese school children **Age Groups Analyzed:** 6-15 yr	**Pollutant:** CO **Averaging Time:** Annual avg **Mean (SD) unit:** 664 (153) ppb **Range (Min, Max):** (416, 964) **Copollutant:** correlation NO_X: r = 0.88 O_3: r = -0.37 PM_{10}: r = 0.27 SO_2: r = 0.40	**Increment:** 100 ppb **Adjusted Odds Ratio (Lower CI, Upper CI); lag:** Physician-diagnosed asthma: 1.045 (1.017-1.074) CO, SO_2: 1.066 (1.034-1.099) CO, PM_{10}: 1.079 (1.047-1.112) CO, O_3: 1.063 (1.1-1.474) CO, SO_2, O_3: 1.111 (1.074-1.15) CO, PM_{10}, O_3: 1.119 (1.084-1.155) Male: 1.49 (1.37-1.63); Female: 1 Parental atopy: Yes: 1 Parental atopy: No: 2.72 (2.5-2.97) Parental Education: <6: 1 Parental Education: 6-8: 1.17 (0.9-1.52) Parental Education: 9-11: 1.61 (1.26-2.05) Parental Education: ≥ 12: 2.43 (1.9-3.09) ETS: Yes: 0.85 (0.78-0.92); ETS: No: 1 Visible Mold: Yes: 1.27 (1.16-1.4); Visible Mold: No: 1 Maternal smoking during pregnancy: Yes: 1.18 (0.89-1.56) Maternal smoking during pregnancy: No: 1 Cockroaches noted monthly: Yes: 1.15 (1.03-1.29) Cockroaches noted monthly: No: 1 Water damage: Yes: 0.96 (0.81-1.12) Water damage: No: 1
Author: Lee et al. (2003, 049201) **Period of Study:** 10/1995-5/1996 **Location:** Taiwan	**Health Outcome:** Allergic rhinitis **Study Design:** Cohort **Statistical Analyses:** Multiple logistic regression **Population:** 331,686 nonsmoking children **Age Groups Analyzed:** 12-14 yr	**Pollutant:** CO **Averaging Time:** Annual avg **Mean (SD) unit:** 853 (277) ppb **Range (Min, Max):** (381, 1610) **Copollutant:** NR	The study did not present quantitative results for CO.
Author: Meng et al. (2007, 093275) **Period of Study:** 11/2000-9/2001 **Location:** Los Angeles County and San Diego County, California	**Health Outcome:** Asthma **Study Design:** Cohort **Statistical Analyses:** Logistic regression **Population:** 1,609 physician-diagnosed asthmatics **Age Groups Analyzed:** ≥ 18 yr	**Pollutant:** CO **Averaging Time:** Annual avg **Mean (SD) unit:** NR **Range (Min, Max):** NR **Copollutant:** correlation Traffic: r = -0.04; O_3: r = -0.55; PM_{10}: r = 0.42; $PM_{2.5}$: r = 0.52; NO_2: r = 0.55	The study did not present quantitative results for CO.

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Mortimer et al. (2008, 122163) **Period of Study:** 1989-2000 **Location:** San Joaquin Valley, CA	**Health Outcome:** Lung function (FVC, FEV_1, PEF, FEF25-75, FEV_1/FVC, FEF25-75/FVC, FEF25, FEF75) **Study Design:** Cohort **Statistical Analyses:** 1. DSA algorithm 2. GEE **Population:** 232 asthmatic children **Age Groups Analyzed:** 6-11 yr	**Pollutant:** CO **Averaging Time:** 8-h max monthly mean **Mean (SD) unit:** NR **Range (Min, Max):** NR **Copollutant;** correlation: Lifetime NO_2 (24-h avg): r = 0.68 O_3 (8-h max): r = -0.40 PM_{10} (24-h avg): r = 0.05 Prenatal CO (8-h max): r = 0.52 NO_2 (24-h avg): r = 0.37 O_3 (8-h max): r = -0.16 PM_{10} (24-h avg): r = -0.05	**Increment:** NR Effect Size per IQR Increase in Pollutant (SE): FEF25-75: 24-h avg CO exposure during 1st trimester 0.90% (0.0113) FEV_1/FVC Daily max CO exposure during ages 0 to 3 -2.50% (0.0016) FEF25-75/FVC 24-h avg CO exposure during ages 0 to 6 and diagnosed with asthma <2 yr old -4.80% (0.0446) FEF25 24-h avg CO exposure during ages 0 to 6 and diagnosed with asthma <2 yr old plus 24-h avg PM_{10} exposure during 2nd trimester and mother smoked when pregnant -6.70% (0.015) Coefficient (SE): FVC 24-h avg CO exposure during 2nd trimester -0.0878 (0.0415) FEF25-75 Lifetime 24-h avg CO exposure -0.94454 (0.3975) FEF25-75/FVC -0.1090 (0.0303) FEV_1/FVC Prenatal 8-h max CO exposure: 0.1711 (0.0653) Lifetime 1-h max CO exposure: -0.3242 (0.0919) 24-h avg CO exposure during ages 0-3 and diagnosed with asthma <2 yr old: -0.1814 (0.0599) FEF25 24-h avg CO exposure during ages 0-6 and diagnosed with asthma <2 yr old: -1.0460 (0.1953) FEF75 Lifetime 8-h max CO exposure: -0.4214 (0.1423)
Author: Singh et al. (2003, 052686) **Period of Study:** NR **Location:** Jaipur, India	**Health Outcome:** Lung function **Study Design:** Panel study **Statistical Analyses:** Parametric statistical methods **Population:** Campus panel: 142 Commuter panel: 158 **Age Groups Analyzed:** ~20 yr	**Pollutant:** CO **Averaging Time:** Annual avg **Mean (SD) unit**: Roadside: 3,175 $\mu g/m^3$ Campus: 2,150 $\mu g/m^3$ **Range (Min, Max):** NR **Copollutant:** NR	The study did not present quantitative results for CO.

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Sole et al. (2007, 090706) **Period of Study:** **Location:** Sao Paulo West, Sao Paulo South, Santo Andre, Curitba, & Porto Alegre, Brazil	**Health Outcome:** Symptoms of asthma, rhinitis, and eczema **Study Design:** Panel **Statistical Analyses:** Logistic Regression **Age Groups Analyzed:** 13-14 yr	**Averaging Time:** Annual **Mean (SD) unit:** Sao Paulo West: 7.70 ppm Sao Paulo South: 7.50 ppm Santo Andre: 9.80 ppm Curitba: 7.90 ppm Porto Alegre: 1.51 ppm **Range (min, max):** NR **Copollutant:** NO_2, SO_2, O_3	**Increment:** Risk in relation to center w/ lowest annual mean (Porto Alegre = ref) **OR Estimate [Lower CI, Upper CI]:** **Lags examined:** NR **Current Wheezing:** Sao Paulo West: 1.26 (1.11, 1.42) Sao Paulo South: 1.03 (0.91, 1.18) Santo Andre: 1.36 (1.20, 1.56) Curitba: 1.05 (0.93, 1.19) **Severe Asthma:** Sao Paulo West: 1.20 (0.95, 1.50) Sao Paulo South: 0.59 (0.45, 0.78) Santo Andre: 0.62 (0.48, 0.81) Curitba: 0.64 (0.50, 0.82) **Nighttime Coughing:** Sao Paulo West: 1.06 (0.95, 1.17) Sao Paulo South: 0.93 (0.84, 1.03) Santo Andre: 0.91 (0.82, 1.02) Curitba: 0.99 (0.89, 1.10) **Rhinoconjunctivitis:** Sao Paulo West: 1.31 (1.15, 1.15) Sao Paulo South: 0.73 (0.64, 0.85) Santo Andre: 0.85 (0.74, 0.97) Curitba: 1.10 (0.96, 1.25) **Severe Rhinits:** Sao Paulo West: 1.01 (0.91, 1.49) Sao Paulo South: 0.68 (0.59, 0.77) Santo Andre: 0.73 (0.64, 0.83) Curitba: 1.03 (0.91, 1.16) **Eczema:** Sao Paulo West: 1.45 (1.20, 1.74) Sao Paulo South: 1.03 (0.85, 1.25) Santo Andre: 1.03 (0.85, 1.25) Curitba: 0.90 (0.75, 1.10) **Flexural Eczema:** Sao Paulo West: 1.42 (1.15, 1.76) Sao Paulo South: 0.71 (0.56, 0.91) Santo Andre: 0.68 (0.53, 0.87) Curitba: 0.73 (0.57, 0.92) **Severe Eczema:** Sao Paulo West: 1.08 (0.86, 1.35) Sao Paulo South: 0.42 (0.31, 0.56) Santo Andre: 0.38 (0.28, 0.51) Curitba: 0.30 (0.22, 0.41)
Author: Wang et al. (1999, 008105) **Period of Study:** 10/1995-6/1996 **Location:** Kaohsiung and Pintong, Taiwan	**Health Outcome:** Asthma **Study Design:** Cross sectional **Statistical Analyses:** Multiple logistic regression **Population:** 165,173 high school students **Age Groups Analyzed:** 11-16 yr	**Pollutant:** CO **Averaging Time:** Annual median **Median (SD) unit:** 0.80 ppm **Range (Min, Max):** NR **Copollutant:** NR	**Increment:** NR **Adjusted Odds Ratio (Lower CI, Upper CI); lag:** CO Concentrations: <0.80 ppm: 1.0 CO Concentrations ≥ 0.80 ppm: 1.23 (1.19-1.28) Multivariate analysis with variables for exercise, smoking, alcohol, incense use, ETS: 1.15 (1.1-1.2)
Author: Wilhelm et al. (2008, 191912) **Period of Study:** 2000-2001 **Location:** Los Angeles County or San Diego County, California	**Health Outcome:** Asthma symptoms/ED visit/HA **Study Design:** Panel **Statistical Analyses:** Logistic regression **Age Groups Analyzed:** 0-17 yr **Sample Description:** 612 children who reported a physician diagnosis of asthma at some point in their lives	**Averaging Time:** annual **Mean (SD) unit:** 1.0 ppm **Range (min, max):** 0.34, 1.8 **Copollutant:** correlation O_3: r= -0.67 PM_{10}: r= 0.41 $PM_{2.5}$: r= 0.60 NO_2: r= 0.57 traffic density: r= 0.02	**Increment:** NR **OR Estimate [Lower CI, Upper CI] ; lag:** **Lags examined:** NR No associations observed between asthma symptom outcome measures (no results shown)

Table C-7. Studies of short-term CO exposure and mortality.

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Anderson et al. (2001, 017033) **Period of Study:** 10/1994-12/1996 **Location:** West Midlands, United Kingdom	**Health Outcome (ICD9):** Mortality: All-cause (nonaccidental) (<800); cardiovascular (390-459); respiratory (460-519) **Study Design:** Time series **Statistical Analyses:** Poisson GAM **Age Groups Analyzed:** All ages	**Pollutant:** CO **Averaging Time:** Max 8-h ma **Mean (SD) unit:** 0.8 (0.7) ppm **Range (Min, Max):** (0.2, 10.0) **Copollutant** correlation: PM_{10}: r = 0.55; $PM_{2.5}$: r = 0.54; $PM_{10-2.5}$: r = 0.10; BS: r = 0.77; SO_4^{2-}: r = 0.17; NO_2: r = 0.73; O_3: r = -0.29; SO_2: r = 0.49	**Increment:** 1.0 ppm **% Increase (Lower CI, Upper CI); lag:** All-cause 0.8% (-0.6 to 2.2); 0-1 Cardiovascular 2.5% (0.4-4.6); 0-1 Respiratory 1.2% (-2.1 to 4.6); 0-1
Author: Bellini et al. (2007, 097787) **Period of Study:** 1996-2002 **Location:** 15 Italian cities	**Health Outcome (ICD9):** Mortality: All-cause (nonaccidental) (<800); cardiovascular (390-459); respiratory (460-519) **Study Design:** Meta-analysis Statistical Analyses: Poisson GLM **Age Groups Analyzed:** All ages	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** NR **Range (Min, Max):** NR **Copollutant:** SO_2 NO_2 O_3 PM_{10}	**Increment:** 1 mg/m^3 **% Increase (Lower CI, Upper CI); lag:** All-cause 1.19% (0.61-1.72); 0-1 Respiratory 0.66% (-1.46 to 2.88); 0-1 Cardiovascular 0.93% (-0.10 to 1.77); 0-1
Author: Berglind et al. (2009, 190068) **Period of Study:** 1992-2002 **Location:** Augsburg, Germany; Barcelona, Spain; Helsinki, Finland; Rome, Italy; Stockholm, Sweden	**Health Outcome:** Mortality **Study Design:** Cohort **Statistical Analyses:** Poisson regression analysis **Age Groups Analyzed:** ≥ 35 yr **Sample Description:** First-time MI patients	**Averaging Time:** 24 h **Mean (SD) unit:** Median calculated from daily 24-h means: Augsburg: 0.85 Barcelona: 0.75 Helsinki: 0.36 Rome: 1.66 Stockholm: 0.38 Range (IQR): Augsburg: 0.43 Barcelona: 0.75 Helsinki: 0.36 Rome: 1.11 Stockholm: 0.38 **Copollutant:** NR	**Increment:** 0.2 mg/m^3 % Change in Daily Nontrauma Deaths [Lower CI, Upper CI]: Mean of Lag 0 and 1: 2.61 (-0.26-5.56) Mean of Lag 0-4: 3.82 (1.00-6.72) Mean of Lag 0-14: 4.92 (2.11-7.81) Lags examined: 0, 1, 4, 14 CO had a trend towards or positive associations with all cities for 2-day mean effects on daily mortality. CO was associated with risk for the 5-day avg. The strongest association was observed for the 15-day avg.

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Biggeri et al. (2005, 087395) **Period of Study:** 1990-1999 **Location:** 8 Italian Cities (Turin, Milan, Verona, Bologna, Ravenna, Florence, Rome, and Palermo)	**Health Outcome (ICD9):** Mortality: All-cause (nonaccidental) (<800); cardiovascular (390-459); respiratory (460-519); cardio-respiratory **Study Design:** Meta-analysis **Statistical Analyses:** Poisson GLM, cubic splines **Age Groups Analyzed:** All ages	**Pollutant:** CO **Averaging Time:** Max 8-h ma **Mean (SD) unit:** Turin, 1991-1994: 5.8 mg/m^3 Turin, 1995-1998: 4.0 mg/m^3 Milan, 1990-1994: 5.9 mg/m^3 Milan, 1995-1997: 4.0 mg/m^3 Verona, 1995-1999: 2.5 mg/m^3 Ravenna, 1991-1995: 1.8 mg/m^3 Bologna, 1996-1998: 2.4 mg/m^3 Florence, 1996-1998: 2.7 mg/m^3 Rome, 1992-1994: 6.5 mg/m^3 Rome, 1995-1997: 5.4 mg/m^3 Palermo, 1997- 1999: 2.1 mg/m^3 **Range (Min, Max):** Turin, 1991-1994: (NR, 24.7) Turin, 1995-1998: (NR, 19.8) Milan, 1990-1994: (NR, 26.5) Milan, 1995-1997: (NR, 12.3) Verona, 1995-1999: (NR, 10.2) Ravenna, 1991-1995: (NR, 7.0) Bologna, 1996-1998: (NR, 11.1) Florence, 1996-1998: (NR, 8.7) Rome, 1992-1994: (NR, 22.3) Rome, 1995-1997: (NR, 18.5) Palermo, 1997- 1999: (NR, 8.0) **Copollutant:** NR	**Increment:** 1.0 mg/m^3 **% Increase (Lower CI, Upper CI); lag:** Non-accidental Fixed: 0.93 (0.50-1.36); 0-1 Random: 0.93 (0.50-1.36); 0-1 Cardiovascular Fixed: 1.29 (0.62-1.96); 0-1 Random: 1.29 (0.62-1.96); 0-1 Respiratory Fixed: 2.44 (0.74-4.17); 0-1 Random: 2.47 (0.14-4.85); 0-1
Author: Botter et al. (2002, 011922) **Period of Study:** 1991-1993 **Location:** São Paulo, Brazil	**Health Outcome (ICD9):** Mortality **Study Design:** Longitudinal study Statistical Analyses: State space model **Age Groups Analyzed:** ≥ 65 yr	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** NR **Range (Min, Max):** NR **Copollutant:** TSP; NO_2; O_3; SO_2	**Increment:** NR **β (SE):** Model 1: 0.0053 (0.0036) Model 2: 0.0046 (0.0028) Model 3: 0.0040 (0.0028) Model 4: 0.0032 (0.0028)
Author: Bremner et al. (1999, 007601) **Period of Study:** 1/1992–12/1994 **Location:** London, U.K.	**Health Outcome (ICD9):** Mortality: All-cause (nonaccidental) (<800); cardiovascular (390-459); respiratory (460-519) **Study Design:** Time series **Statistical Analyses:** Poisson, cubic splines **Age Groups Analyzed:** All ages 0-64 yr ≥ 65 yr 65-74 yr ≥ 75 yr	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit**: 0.8 (0.4) ppm **Range (Min, Max):** (0.2, 5.6) **Copollutant:** NO_2; O_3; SO_2; PM_{10}; BS	**Increment:** 0.8 ppm **% Increase (Lower CI, Upper CI); lag:** All-cause Age Group: All ages: 0.9% (-0.2 to 2.0); 1 0-64: 1.2% (-1.0 to 3.5); 1 ≥ 65: 0.8% (-0.4 to 1.9); 2 65-74: 0.8% (-1.2 to 2.8); 3 ≥ 75: 0.9% (-0.4 to 2.2); 2 Respiratory Age Group: All ages: 2.0% (-0.3 to 4.5); 3 0-64: 7.8% (0.2-15.9); 3 ≥ 65: 0.7% (-1.7 to 3.2); 3 65-74: 7.5% (2.1-13.2); 3 ≥ 75: 2.3% (-0.5 to 5.3); 0 Multipollutant: CO, SO_2: 1.90% (0.18-3.64); 3 CO, PM_{10}: 1.25% (0.04-2.47); 3 CO, BS: 2.41% (-0.65 to 5.57); 3 Cardiovascular Age Group: All ages: 1.4% (-0.1 to 3.0); 1 0-64: 2.1% (-1.7 to 6.0); 2 ≥ 65: 1.1% (-0.4 to 2.8); 2 65-74: 2.4% (-0.6 to 5.5); 2 ≥ 75: 1.9% (0.0-3.9); 2 Multipollutant: CO, NO_2: 2.55% (0.40-4.75); 1 CO, O_3: 3.98% (0.85-7.21); 1 CO, PM_{10}: 0.62% (-0.59 to 1.85); 1 CO, BS: 1.29% (-1.53 to 4.19); 1

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Burnett et al. (2000, 010273) **Period of Study:** 1986-1996 **Location:** 8 Canadian cities	**Health Outcome (ICD9):** Mortality: All-cause (nonaccidental) (<800) **Study Design:** Time series **Statistical Analyses:** 1. Single-pollutant models: Poisson GAM, LOESS 2. Multi-pollutant models: Principal component regression analysis **Age Groups Analyzed:** All ages	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 0.9 ppm **Range (Max):** 7.2 ppm **Copollutant:** correlation O_3: r = -0.05 SO_2: r = 0.42 $PM_{2.5}$: r = 0.44 $PM_{10-2.5}$: r = 0.29 PM_{10}: r = 0.45	**Increment:** 0.9 ppm **% Increase (t-value); lag:** Temporally filtered daily nonaccidental mortality (days in which PM_{10} data available) CO: 0.4 (0.4); 0; 2.0 (2.3); 1 CO, $PM_{2.5}$: -0.7 (-0.7); 0; 1.1 (1.1); 1 CO, $PM_{10-2.5}$: 0.1 (0.2); 0; 1.8 (2.1); 1 CO, PM_{10}: -0.5 (-0.6); 0; 1.2 (1.3); 1 Daily filtered non-accidental mortality Single-pollutant model: 2.1 (2.1) Multi-pollutant models: Model 1: CO, $PM_{2.5}$, $PM_{10-2.5}$, O_3, NO_2, SO_2: 0.7 (1.9) Model 2: CO, SO_4, Ni, Fe, Zn, O_3, NO_2: 0.7 (1.7)
Author: Burnett et al. (2004, 086247) **Period of Study:** 1981-1999 **Location:** 12 Canadian cities	**Health Outcome (ICD9):** Mortality: All-cause (nonaccidental) (<800) **Study Design:** Time series **Statistical Analyses:** 1. Poisson, natural splines 2. Random effects regression model **Age Groups Analyzed:** All ages	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 1.02 ppm **Range (Min, Max):** NR **Copollutant:** NO_2; O_3; SO_2; $PM_{2.5}$; $PM_{10-2.5}$	**Increment:** 1.02 ppm **% Increase (t-value); lag:** 0.68% (3.12); 1 CO, NO_2: 0.07% (0.30); 1
Author: Cakmak et al. (2007, 091170) **Period of Study:** 1/1997-12/2003 **Location:** Chile-7 cities	**Health Outcome (ICD9):** Mortality: All-cause (nonaccidental) (<800); CVDs (390-459); respiratory diseases (460-519) **Study Design:** Time series **Statistical Analyses:** Poisson; Random effects regression model **Age Groups Analyzed:** All ages ≤ 64 yr 65-74 yr 75-84 yr ≥ 85 yr	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 1.29 ppm **Range (Min, Max):** NR **Copollutant** correlation: O_3: r = -0.55 to -0.01 SO_2: r = 0.31 to 0.67 PM_{10}: r = 0.49 to 0.82 **Note:** Correlations are between pollutants for seven monitoring stations.	**Increment:** 1.29 ppm **% Increase (t-value); lag:** Nonaccidental: 5.88% (6.42); 1; 9.39% (6.89); 0-5 CO+PM_{10}+O_3+SO_2: 6.13% (4.34); 1 Age Group: ≤ 64 4.10% (2.52); 1; / 4.76% (2.19); 0-5 Age Group: 65-74 6.24% (3.17); 1; / 8.12% (3.88); 0-5 Age Group: 75-84 8.64% (4.82); 1; / 13.12% (5.12); 0-5 Age Group: ≥ 85 8.58% (4.45); 1; / 13.20% (4.82); 0-5 April-September 7.09% (4.02); 1; / 9.65% (4.50); 0-5 October-March 5.45% (1.14); 1; / 7.80% (1.89); 0-5 Cardiac 7.79% (4.56); 1; / 11.22% (4.8); 0-5 Respiratory 12.93% (5.78); 1; / 21.31% (6.34); 0-5
Author: Chock et al. (2000, 010407) **Period of Study:** 1989-1991 **Location:** Pittsburgh, PA	**Health Outcome (ICD9):** Mortality: Respiratory (480-486, 490-496, 507); cardiovascular (390-448); influenza (487) **Study Design:** Time series **Statistical Analyses:** Poisson GAM; Cubic B-spline basis functions **Age Groups Analyzed:** All ages <75 yr >75 yr	**Pollutant:** CO **Averaging Time:** 1-h avg **Mean (SD) unit:** NR **Range (Min, Max):** NR **Copollutant:** PM_{10}; $PM_{2.5}$; O_3; SO_2; NO_2	**Increment:** NR **β (SE); lag:** Age Group: <75 CO alone: 0.0080 (1.56); 0 PM_{10}, CO: 0.0030 (0.48); 0 PM_{10}, NO_2, CO: 0.0079 (1.14); 0 PM_{10}, O_3, SO_2, NO_2, CO: 0.072 (1.02); 0 CO -0.00738 (-1.42); -3; / 0.00133 (0.23); -2; -0.00219 (-0.38); -1; / 0.00809 (1.48); 0; -0.00129 (-0.22); 1; / 0.00512 (0.90); 2; -0.00974 (-1.87); 3 CO, PM_{10}, O_3, SO_2, NO_2 -0.01103 (-1.48); -3; / -0.00097 (-0.13); -2; 0.00514 (0.67); -1; / 0.00853 (1.15); 0; -0.00404 (-0.52); 1; / -0.00296 (-0.39); 2; -0.00346 (-0.46); 3 Season CO Winter: 0.00539 (0.78); 0 Spring: 0.01655 (1.90); 0 Summer: 0.00155 (0.14); 0 Fall: 0.00797 (1.14); 0

Study	Design	Concentrations	Effect Estimates (95% CI)
			CO, PM_{10} Winter: -0.00563 (-0.50); 0 Spring: 0.01233 (0.99); 0 Summer: -0.00712 (-0.48); 0 Fall: 0.00661 (0.73); 0 CO, PM_{10}, O_3, SO_2, NO_2 Winter: -0.01326 (-0.95); 0 Spring: 0.02501 (1.54); 0 Summer: 0.01874 (0.92); 0 Fall: 0.01011 (0.88); 0 Age Group:>75 CO Alone: -0.0035 (-0.67); 0 CO, PM_{10}: -0.0104 (-1.67); 0 CO, PM_{10}, NO_2: -0.0128 (-1.80); 0 CO, PM_{10}, O_3, SO_2, NO_2: -0.0144 (-1.99); 0 CO -0.00025 (-0.05); -3; / -0.00242 (-0.42); -2; -0.00238 (-0.41); -1; / -0.00302 (-0.54); 0; -0.00116 (-0.20); 1; / -0.00508 (-0.88); 2; -0.00251 (-0.48); 3 CO, PM_{10}, O_3, SO_2, NO_2 -0.00123 (-0.17); -3; / -0.00876 (-1.13); -2; -0.00682 (-0.88); -1; / -0.01248 (-1.66); 0; -0.00672 (-0.86); 1; / -0.00181 (-0.23); 2; -0.00515 (-0.69); 3 Season CO Winter: -0.00304 (-0.43); 0 Spring: 0.00482 (0.54); 0 Summer: 0.01178 (1.07); 0 Fall: -0.01011 (-1.43); 0 CO, PM_{10} Winter: -0.02303 (-2.03); 0 Spring: -0.00517 (-0.40); 0 Summer: 0.00735 (0.50); 0 Fall: -0.01042 (-1.14); 0 CO, PM_{10}, O_3, SO_2, NO_2 Winter: -0.03370 (-2.41); 0 Spring: -0.00652 (-0.39); 0 Summer: 0.01258 (0.61); 0 Fall: -0.01250 (-1.07); 0

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Cifuentes et al. (2000, 010351) **Period of Study:** 1988-1996 **Location:** Santiago, Chile	**Health Outcome (ICD9):** Mortality: All causes (nonaccidental) (<800) **Study Design:** Time series **Statistical Analyses:** Poisson GAM, GAM with filtered variables & GLM **Age Groups Analyzed:** All ages	**Pollutant:** CO **Averaging Time:** 1-h avg **Mean (SD) unit:** 2.5 ppb **Range (5th, 95th):** (0.6, 6.2) **Copollutant** correlation: $PM_{2.5}$: r = 0.80 $PM_{10-2.5}$: r = 0.47 SO_2: r = 0.62 NO_2: r = 0.65 O_3: r = -0.01	**Increment:** All yr: 2.5 ppm Winter: 3.6 ppm Summer: 1.3 ppm **Relative Risk (t-ratio); Lag** All Year CO: 1.041 (7.2); 0-1 CO, $PM_{2.5}$: 1.025 (3.5); 0-1 CO, $PM_{10-2.5}$: 1.035 (4.9); 0-1 CO, SO_2: 1.038 (6.0); 0-1 CO, NO_2: 1.026 (3.9); 0-1 CO, O_3: 1.036 (4.8); 0-1 Winter CO: 1.052 (5.9); 0-1 CO, $PM_{2.5}$: 1.025 (2.1); 0-1 CO, $PM_{10-2.5}$: 1.049 (4.3); 0-1 CO, SO_2: 1.049 (5.0); 0-1 CO, NO_2: 1.027 (2.6); 0-1 CO, O_3: 1.051 (4.4); 0-1 Summer CO: 1.053 (6.0); 0-1 CO, $PM_{2.5}$: 1.053 (5.3); 0-1 CO, $PM_{10-2.5}$: 1.053 (5.3); 0-1 CO, SO_2: 1.050 (5.2); 0-1 CO, NO_2: 1.047 (5.2); 0-1 CO, O_3: 1.042 (3.6); 0-1 All Year GAM model CO: 1.041 (7.2); 0-1 CO, $PM_{2.5}$, $PM_{10-2.5}$, SO_2, NO_2, O_3: 1.032 (4.6); 0-1 GAM Filtered Variables CO: 1.030 (4.3); 0-1 CO, $PM_{2.5}$, $PM_{10-2.5}$, SO_2, NO_2, O_3: 1.022 (2.4); 0-1 GLM CO: 1.023 (2.4); 0-1 CO, $PM_{2.5}$, $PM_{10-2.5}$, SO_2, NO_2, O_3: 1.013 (1.1); 0-1
Author: Conceicao et al. (2001, 016628) **Period of Study:** 1994-1997 **Location:** Sao Paulo, Brazil	**Health Outcome (ICD9):** Mortality: Respiratory diseases (460-519) **Study Design:** Time series **Statistical Analyses:** Poisson GAM **Age Groups Analyzed:** <5 yr	**Pollutant:** CO **Averaging Time:** Max 8-h ma **Mean (SD) unit:** Total: 4.4 (2.2) ppm 1994: 5.1 (2.4) ppm 1995: 5.1 (2.4) ppm 1996: 3.9 (2.0) ppm 1997: 3.7 (1.6) ppm **Range (Min, Max):** NR **Copollutant:** PM_{10}; SO_2; O_3	**Increment:** NR **β (SE); lag:** CO: 0.0306 (0.0076); 2 CO, SO_2, PM_{10}, O_3: 0.0259 (0.0116); 2 Model 1: Pollutant concentration: 0.0827 (0.0077); 2 Model 2: 1+loess(time): 0.0285 (0.0074); 2 Model 3: 2+loess(temperature)+humidity: 0.0309 (0.0076); 2 Model 4: 3+nonrespiratory counts: 0.0306 (0.0076); 2 Model 5: 4+autoregressive parameters: 0.0292 (0.0118); 2
Author: De Leon et al. (2003, 055688) **Period of Study:** 1/1985-12/1994 **Location:** New York, NY	**Health Outcome (ICD9):** Mortality: Circulatory (390-459); cancer (140-239) **Study Design:** Time series **Statistical Analyses:** Poisson GAM **Age Groups Analyzed:** All ages <75 yr >75 yr	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 2.45 ppm **IQR (25th, 75th):** (1.80, 2.97) **Copollutant:** PM_{10}; O_3; SO_2; NO_2	The study did not present quantitative results for CO.

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Dominici et al. (2003, 056116) **Period of Study:** 1987-1994 **Location:** 90 U.S. cities (NMMAPS)	**Health Outcome (ICD9):** Mortality: All-cause (nonaccidental); cardiovascular; respiratory **Study Design:** Time series **Statistical Analyses:** 1. GAM with S-PLUS default convergence criteria 2. GAM with more stringent convergence criteria 3. Poisson GLM with natural cubic splines **Age Groups Analyzed:** All ages	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** NR **Range (Min, Max):** NR **Copollutant:** O_3; NO_2; SO_2; CO	**Increment:** 1 ppm **% Increase (Lower CI, Upper CI); Lag** CO 0.08% (-0.18 to 0.34); 0 0.46% (0.18-0.73); 1 0.16% (-0.12 to 0.45); 2
Author: Fairley et al. (1999, 000896) **Period of Study:** 1989-1996 **Location:** Santa Clara, CA	**Health Outcome (ICD9):** Mortality: Respiratory; cardiovascular **Study Design:** Time series **Statistical Analyses:** Poisson GAM **Age Groups Analyzed:** All ages	**Pollutant:** CO **Averaging Time:** 24-h avg; Max 8-h avg **Median (SD) unit:** 24-h avg: 1.4 (1.0) ppm Max 8-h avg: 2.1 (1.6) ppm **Range (Min, Max):** 24-h avg: (0.0, 7.6) Max 8-h avg: (0.2, 2.5) **Copollutant:** correlation PM_{10}: r = 0.609; $PM_{2.5}$: r = 0.435; $PM_{10-2.5}$: r = 0.326; COH: r = 0.736; NO_3: r = 0.270; SO_4: r = 0.146; O_3: r = -0.215	**Increment:** 2.2 ppm **Relative Risk (Lower CI, Upper CI); lag:** 1980-1986 CO: 1.04; 0; CO: 1.05; 1; CO, COH: 1.00; 1; CO, NO_3: 1.03; CO, NO_3, O_3, COH: 1.00 1989-1996 CO: 1.02; 0; CO: 1.04; 1; CO, $PM_{2.5}$: 0.98; CO, NO_3: 1.01; CO, NO_2, O_3, NO_3: 1.06 Respiratory mortality: CO: 1.08; 1 Cardiovascular mortality: CO: 1.04; 1
Author: Fischer et al. (2003, 043739) **Period of Study:** 1986-1994 **Location:** The Netherlands	**Health Outcome (ICD9):** Mortality: Nonaccidental (<800); pneumonia (480-486); COPD (490-496); cardiovascular (390-448) **Study Design:** Time series **Statistical Analyses:** Poisson GAM, LOESS **Age Groups Analyzed:** <45 yr 45-64 yr 65-74 yr ≥ 75 yr	**Pollutant:** CO **Averaging Time:** 24-h avg **Median (SD) unit:** 406 µg/m^3 **Range (Min, Max):** (174, 2620) **Copollutant:** PM_{10}; BS; O_3; NO_2; SO_2	**Increment:** 1,200 µg/m^3 **Relative Risk (Lower CI, Upper CI); lag:** Cardiovascular Age Group: <45: 0.965 (0.750-1.240); 0-6 45-64: 1.029 (0.941-1.125); 0-6 65-74: 1.038 (0.972-1.108); 0-6 ≥ 75: 1.024 (0.984-1.065); 0-6 COPD Age Group: <45: 1.710 (0.852-3.435); 0-6 45-64: 1.181 (0.850-1.640); 0-6 65-74: 1.377 (1.147-1.654); 0-6 ≥ 75: 1.072 (0.963-1.193); 0-6 Pneumonia Age Group: <45: 0.927 (0.463-1.856); 0-6 45-64: 2.691 (1.509-4.800); 0-6 65-74: 1.118 (0.743-1.683); 0-6 ≥ 75: 1.230 (1.090-1.389); 0-6
Author: Forastiere et al. (2005, 086323) **Period of Study:** 1998-2000 **Location:** Rome, Italy	**Health Outcome (ICD9):** Mortality: IHD (410-414) **Study Design:** Time-stratified case crossover **Statistical Analyses:** Conditional logistic regression **Age Groups Analyzed:** >35 yr	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 2.4 (1.0) mg/m^3 **IQR (25th, 75th):** (1.7, 2.9) **Copollutant correlation:** PNC: r = 0.89; PM_{10}: r = 0.34; NO_2: r = 0.54; SO_2: r = 0.52; O_3: r = 0.01	**Increment: 1.2 mg/m3** **% Increase (Lower CI, Upper CI); lag:** 6.5% (1.0-12.3); 0 4.7% (-0.9 to 10.7); 1 2.6% (-3.0 to 8.5); 2 -0.1% (-5.5 to 5.5); 3 7.0% (0.8-13.7); 0-1

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Forastiere et al. (2007, 090720) **Period of Study:** 1998-2001 **Location:** Rome, Italy	**Health Outcome (ICD9):** Mortality: Malignant neoplasms (140-208); diabetes mellitus (250); hypertensive (401-405); previous AMI (410, 412); IHD (410-414); conduction disorders of the heart (426); dysrhythmia (427); heart failure (428); cerebrovascular (430-438); peripherical artery disease (440-448); COPD (490-496) **Study Design:** Time-stratified case crossover **Statistical Analyses:** Conditional logistic regression **Age Groups Analyzed:** >35 yr	**Pollutant:** CO **Averaging Time:** 24-h avg Mean **(SD) unit:** NR **IQR (25th, 75th):** NR **Copollutant:** PM_{10}; $PM_{2.5}$; NO_X; Benzene	This study did not present quantitative results for CO.
Author: Goldberg et al. (2001, 016548) **Period of Study:** 1984-1993 **Location:** Montreal, Quebec, Canada	**Health Outcome (ICD9):** Mortality: Upper respiratory diseases (472-478); acute upper respiratory diseases (460-465); acute lower respiratory (466, 480-487, 512, 513, 518, 519) **Study Design:** Time series **Statistical Analyses:** Poisson GAM; LOESS **Age Groups Analyzed:** <65 yr; ≥ 65 yr	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 0.8 (0.5) ppm **Range (Min, Max):** (0.1, 5.1) **Copollutant:** TSP; PM_{10}; $PM_{2.5}$; Sulfates; COH; SO_2; NO_2; NO; O_3	The study did not present quantitative results for CO.
Author: Goldberg et al. (2003, 035202) **Period of Study:** 1984-1993 **Location:** Montreal, Quebec, Canada	**Health Outcome (ICD9):** Mortality: CHF (428) **Study Design:** Time-series **Statistical Analyses:** Poisson GLM, natural splines **Age Groups Analyzed:** ≥ 65 yr	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 0.8 (0.5) ppm **Range (Min, Max):** (0.1, 5.1) **Copollutant:** $PM_{2.5}$; Sulfate; SO_2; NO_2; O_3	**Increment:** 0.50 ppm **% Increase (Lower CI, Upper CI); lag:** Daily mortality from CHF -0.99% (-6.31 to 4.63); 0 0.12% (-5.29 to 5.84); 1 -1.38% (-8.81 to 6.66); 0-2 Daily mortality among persons classified as having CHF before death 2.10% (-0.24 to 4.49); 0 2.28% (-0.09 to 4.72); 1 2.86% (-0.46 to 6.29); 0-2
Author: Goldberg et al. (2006, 088641) **Period of Study:** 1984-1993 **Location:** Montreal, Quebec, Canada	**Health Outcome (ICD9):** Mortality: Diabetes (250) **Study Design:** Time series **Statistical Analyses:** Poisson, natural splines **Age Groups Analyzed:** ≥ 65 yr	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 0.8 (0.5) ppm **Range (Min, Max):** (0.1, 5.1) **Copollutant:** $PM_{2.5}$; Sulfate; SO_2; NO_2; O_3	**Increment:** 0.50 ppm **% Increase (Lower CI, Upper CI); lag:** Daily mortality from diabetes 2.64% (-2.56 to 8.12); 0 6.54% (1.31-12.03); 1 8.08% (1.03-15.62); 0-2 Daily mortality among persons classified as having diabetes before death 1.15% (-1.69 to 4.07) ; 0 1.30% (-1.58 to 4.27) ; 1 2.63% (-1.42 to 6.85) ; 0-2
Author: Gouveia et al. (2000, 012132) **Period of Study:** 1991-1993 **Location:** Sao Paulo, Brazil	**Health Outcome (ICD9):** Mortality: Respiratory; cardiovascular; all other causes **Study Design:** Time series **Statistical Analyses:** Poisson **Age Groups Analyzed:** All ages >65 yr <5 yr	**Pollutant:** CO **Averaging Time:** Maximum 8-h moving avg Mean **(SD) unit:** 5.8 (2.1) ppm **Range (Min, Max):** (1.3, 16.2) **Copollutant:** PM_{10}; SO_2; NO_2; O_3	**Increment:** 5.1 ppm **Relative Risk (Lower CI, Upper CI); lag:** Age Group: All ages: All-causes 1.012 (0.994-1.031); 0 Age Group: >65 All-causes: 1.020 (0.996-1.046); 0 Respiratory: 0.981 (0.927-1.037); 2 CVD: 1.041 (1.007-1.076); 0 Age Group: <5 Respiratory: 1.086 (0.950-1.238); 0 Pneumonia: 1.141 (0.962-1.321); 2

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Gwynn et al. (2000, 074109) **Period of Study:** 5/1988-10/1990 **Location:** Buffalo, NY	**Health Outcome (ICD9):** Mortality: Respiratory (466, 480-486); Circulatory (401-405, 410-414, 415-417); All non-accidental causes (<800) **Study Design:** Time-series **Statistical Analyses:** Poisson GLM **Age Groups Analyzed:** All ages	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** NR **Range (Min, Max):** NR **Copollutant correlation:** H+: r =0.15; SO_4^{2-}: r = 0.24; O_3: r = -0.23; SO_2: r = 0.11; NO_2: r = 0.65	**Increment:** NR β (SE); lag: Respiratory mortality: 0.032466 (0.053802); 0 Circulatory mortality: 0.039216 (0.026544); 3 Total mortality: 0.040214 (0.015205); 3
Author: Hoek et al. (2001, 016550) **Period of Study:** 1986-1994 **Location:** The Netherlands	**Health Outcome (ICD9):** Mortality: Heart failure (428); arrhythmia (427); cerebrovascular (430-436); thrombocytic (433, 434, 444, 452, 453); cardiovascular (390-448) **Study Design:** Time series **Statistical Analyses:** Poisson GAM **Age Groups Analyzed:** All ages	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** NR **Range (Min, Max):** NR **Copollutant:** O_3; BS; PM_{10}; SO_2; NO_2	**Increment:** 120 µg/m^3 **Relative Risk (Lower CI, Upper CI); Lag** Total CVD mortality: 1.026 (0.993-1.060); 0-6 MI and other IHD mortality: 1.050 (1.004-1.099); 0-6 Arrhythmia: 1.062 (0.937-1.203); 0-6 Heart failure mortality: 1.109 (1.012-1.216); 0-6 Cerebrovascular mortality: 1.066 (1.029-1.104); 0-6 Embolism, thrombosis: 1.065 (0.926-1.224); 0-6
Author: Hoek et al. (2000, 010350) **Period of Study:** 1986-1994 **Location:** The Netherlands	**Health Outcome (ICD9):** Mortality: Pneumonia (480-486); COPD (490-496); CVDs (CVD) (390-448) **Study Design:** Time series **Statistical Analyses:** Poisson GAM, LOESS **Age Groups Analyzed:** All ages	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** Netherlands: 457 µg/m^3 Four Major Cities: 589 µg/m^3 **Range (Min, Max):** Netherlands: (174, 2620) Four Major Cities: (202, 4621) **Copollutant correlation:** PM_{10}: r = 0.64; BS: r = 0.89; O_3: r = -0.48; NO_2: r = 0.89; SO_2: r = 0.65; SO_4^{2-}: r = 0.55; NO_3-: r = 0.58	**Increment:** Single-day lag (1): 1,500 µg/m^3 Weekly avg (0-6): 1200 µg/m^3 **Relative Risk (Lower CI, Upper CI); Lag** CO Four Major Cities: 1.022 (0.995-1.050); 1 Four Major Cities: 1.044 (1.008-1.082); 0-6 Netherlands w/o Major Cities: 1.040 (1.020-1.060); 1 Netherlands w/o Major Cities: 1.051 (1.026-1.076); 0-6 avg Entire Netherlands: 1.035 (1.018-1.052); 1 Entire Netherlands: 1.046 (1.025-1.068); 0-6 CVD: 1.044 (1.012-1.077); 0-6 COPD: 1.194 (1.099-1.298); 0-6 Pneumonia: 1.276 (1.143-1.426); 0-6 Winter: 1.038 (1.013-1.063); 0-6 Summer: 1.199 (1.108-1.296); 0-6 Multi-pollutant model CO, PM_{10} Total mortality: 0.969 (0.914-1.028); 0-6 CVD: 1.005 (0.918-1.101); 0-6 BS, CO Total mortality: 0.980 (0.933-1.030); 0-6 CVD: 0.927 (0.860-0.999); 0-6 CO, SO_4^{2-} Total mortality: 0.990 (0.951-1.030); 0-6 CVD: 0.999 (0.939-1.063); 0-6
Author: Honda et al. (2003, 193774) **Period of Study:** 1976-1990 **Location:** Tokyo, Japan	**Health Outcome (ICD9):** Mortality: Total (nonaccidental) (<800) **Study Design:** Time series **Statistical Analyses:** Poisson **Age Groups Analyzed:** ≥ 65 yr	**Pollutant:** CO **Averaging Time:** 24-h avg **Median (SD) unit:** 1.6 ppm **Range (Min, Max):** (0, 6.8) **Copollutant correlation:** NO: r = 0.403; NO_2: r = 0.415; Oxidant: r = 0.396; SO_2: r = 0.675	**Increment:** NR **Rate Ratio (Lower CI, Upper CI); lag:** CO concentration <1.1 ppm: 1.00 (reference category) 1.1-1.6 ppm: 1.017 (1.009, 1.026) 1.6-2.2 ppm: 1.031 (1.020, 1.041) >2.2 ppm: 1.051 (1.039, 1.063)

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Hong et al. (2002, 035060) **Period of Study:** 1/1991-12/1997 **Location:** Seoul, Korea	**Health Outcome (ICD9):** Mortality: Hemorrhagic and ischemic stroke (431-434) **Study Design:** Time series Statistical Analyses: Poisson GAM, LOESS **Age Groups Analyzed:** All ages	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 1.44 (0.70) ppm **Range (Min, Max):** (0.430, 5.14) **Copollutant:** TSP; SO_2; NO_2; O_3	**Increment:** 0.76 ppm **Relative Risk (Lower CI, Upper CI); lag:** 1.06 (1.02, 1.09); 1 Multipollutant: CO, TSP: 1.07 (1.03, 1.11); 1 CO, NO_2: 1.06 (1.00, 1.11); 1 CO, SO_2: 1.05 (1.01, 1.10); 1 CO, O_3: 1.09 (1.05, 1.13); 1
Author: Hong et al. (1999, 011195) **Period of Study:** 1/1995-12/1995 **Location:** Inchon, Korea	**Health Outcome (ICD9):** Mortality: Cardiovascular (400-440); respiratory (460-519); nonaccidental causes (<800) **Study Design:** Time series **Statistical Analyses:** Poisson GAM, LOESS **Age Groups Analyzed:** All ages	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 1.7 (0.8) ppm **Range (Min, Max):** (0.3, 5.1) **Copollutant:** SO_2; NO_2; O_3	**Increment**: 1 ppm **Relative Risk (Lower CI, Upper CI); lag:** Total mortality: 0.993 (0.950, 1.037); 0-4 Cardiovascular mortality: 0.965 (0.892, 1.044); 0-4
Author: Hong et al. (2002, 024690) **Period of Study:** 1/1995-12/1998 **Location:** Seoul, Korea	**Health Outcome (ICD9):** Mortality: Stroke (160-169) **Study Design:** Time series **Statistical Analyses:** Poisson GAM **Age Groups Analyzed:** All ages	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 1.2 (0.5) ppm **Range (Min, Max):** (0.4, 3.4) **Copollutant: correlation** PM_{10}: r = 0.22; NO_2: r = 0.64; SO_2: r = 0.90; O_3: r = -0.35	**Increment:** 0.3 ppm **% Increase (Lower CI, Upper CI); lag:** CO: 2.2% (0.4, 4.1); 2 CO (stratified by PM_{10} concentration): <median concentration of PM_{10}: 1.1; 2 ≥ median concentration of PM_{10}: 3.6; 2
Author: Hong et al. (1999, 008087) **Period of Study:** 1/1995-8/1996 **Location:** Inchon, South Korea	**Health Outcome (ICD9):** Mortality: Total (nonaccidental) (<800); respiratory; cardiovascular **Study Design:** Time series **Statistical Analyses:** Poisson GAM; LOESS **Age Groups Analyzed:** All ages	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 15.2 (7.1) ppb **Range (Min, Max):** (2.9, 51.2) **Copollutant:** PM_{10}; NO_2; SO_2; O_3	**Increment: 100 ppb** **β (SE); lag:** Total Mortality CO 0.0019 (0.0015); 1 0.0024 (0.0041); 0-4 CO, PM_{10}, NO_2, SO_2, O_3 -0.0009 (0.0019); 1 -0.0018 (0.0043); 0-4 Cardiovascular Mortality CO 0.0019 (0.0073); 1 -0.0008 (0.0028); 0-4 CO, PM_{10}, NO_2, SO_2, O_3 -0.0053 (0.0078); 1 -0.0037 (0.0033); 0-4 Respiratory Mortality CO 0.0148 (0.0065); 1 0.0063 (0.0171); 0-4 CO, PM_{10}, NO_2, SO_2, O_3 0.0121 (0.0079); 1 -0.0034 (0.0183); 0-4
Author: Keatinge et al. (2001, 017063) **Period of Study:** 1976-1995 **Location:** London, England	**Health Outcome (ICD9):** Mortality: Nonaccidental causes (<800) **Study Design:** Time series **Statistical Analyses:** Single- and multiple-delay regression **Age Groups Analyzed:** All ages	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit**: NR **Range (Min, Max):** NR **Copollutant:** SO_2; PM_{10}	The study did not present quantitative results for CO.

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Kettunen et al. (2007, 091242) **Period of Study:** 1998-2004 **Location:** Helsinki, Finland	**Health Outcome (ICD10):** Mortality: Stroke (I60-I61, I63-I64) **Study Design:** Time series **Statistical Analyses:** Poisson GAM, penalized thin-plate splines **Age Groups Analyzed:** ≥ 65 yr	**Pollutant:** CO **Averaging Time**: Max 8-h ma **Median (SD) unit:** Cold Season: 0.5 mg/m^3 Warm Season: 0.4 mg/m^3 **Range (Min, Max):** Cold Season: (0.1, 2.4) Warm Season: (0.1, 1.1) **Copollutant: correlation** Cold Season: $PM_{2.5}$: r = 0.32; UFP: r = 0.47 Warm Season: $PM_{2.5}$: r = 0.24; UFP: r = 0.39	**Increment:** 0.2 mg/m^3 **% Increase (Lower CI, Upper CI); lag:** Cold Season 0.47 (-3.29 to 4.39); 0; / -0.63 (-4.39 to 3.28); 1; -2.69 (-6.46 to 1.24); 2; / -0.19 (-3.93 to 3.69); 3 Warm Season 3.95 (-3.78 to 12.30); 0; / 8.33 (0.63 to 16.63); 1; 6.97 (-0.59 to 15.11); 2; / 7.54 (-0.05 to 15.71); 3
Author: Klemm et al. (2004, 056585) **Period of Study:** 8/1998-7/2000 **Location:** Fulton County and DeKalb County, GA (ARIES)	**Health Outcome (ICD9):** Mortality: Nonaccidental (<800); cardiovascular (390-459); respiratory (460-519); cancer (140-239) **Study Design:** Time series **Statistical Analyses:** Poisson GLM, natural cubic splines **Age Groups Analyzed:** <65 yr; ≥ 65 yr	**Pollutant:** CO **Averaging Time:** 1-h max **Median (SD) unit:** 1,310 (939.13) ppb **Range (Min, Max**): (303.58, 7400) **Copollutant:** $PM_{2.5}$; $PM_{10-2.5}$; O_3; NO_2; SO_2; Acid; EC; OC; SO_4; Oxygenated HCs; NMHCs; NO_3	**Increment:** NR β (SE); lag: Quarterly Knots: 0.00002 (0.00001); 0-1 Monthly Knots: 0.00002 (0.00001); 0-1 Biweekly Knots: 0.00001 (0.00002); 0-1
Author: Knox et al. (2008, 193776) **Period of Study:** 1996-2004 **Location:** 352 English local authorities	**Health Outcome:** Mortality **Study Design:** Cross sectional **Statistical Analyses:** Linear regression **Age Groups Analyzed:** NR **Sample Description:** Data from Oxford Cancer Intelligence Unit	**Averaging Time:** NR **Meuan (SD) nit:** NR **Range (Min, Max):** NR **Copollutant:** NR	**Increment:** NR Significant (p<0.01) correlations (r) between CO and diseases: Lung cancer: 0.28, Stomach cancer: 0.20, Oesophagus cancer: -0.20, Prostate cancer: -0.25, Brain cancer: -0.24, Melanoma: -0.24, Hodgkin's: -0.19, Peripheral vascular disease: 0.15, Stroke: 0.16, Rheumatic heart disease: 0.27, Peptic ulcer: 0.28, Diabetes: 0.17, COPD: 0.25, Asthma: 0.14, Pneumonia: 0.44, Multiple sclerosis: -0.16, Motorneurone disease: -0.24, Parkinsons disease: -0.15 Significant (p<0.01) socially standardized correlations between diseases and exposures: Lung cancer: 0.25, Stomach cancer: 0.18, RHD: 0.19, Pneumonia: 0.37, COPD: 0.17, Peptic ulcer: 0.16 Lags examined: NR

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Kwon et al. (2001, 016699) **Period of Study:** 1994-1998 **Location:** Seoul, Korea	**Health Outcome (ICD9):** Mortality: CHF (428); cardiovascular (390-459) **Study Design:** 1. Time-series 2. Bi-directional case-crossover **Statistical Analyses:** 1. Poisson GLM, LOESS 2. Conditional logistic regression **Age Groups Analyzed:** <55 yr 55-64 yr 65-74 yr 75-84 yr ≥ 85 yr	**Pollutant:** CO **Averaging Time:** 1-h avg **Mean (SD) unit:** 12.4 ppb **Range (Min, Max):** (4.1, 38.0) **Copollutant correlation:** PM_{10}: r = 0.713; NO_2: r = 0.744; SO_2: r = 0.843; O_3: r = -0.367	**Increment:** 0.59 ppm **Odds Ratio (Lower CI, Upper CI); lag:** From GAM approach CHF patients: 1.054 (0.991-1.121); 0; 0 General Population: 1.022 (1.017- 1.029); 0 From case-crossover design CHF patients: 1.033 (0.946-1.127); 0 General Population: 1.007 (0.997- .016); 0 Modifiers and CHF patients (case-crossover design) Gender Male: 1.025 (0.890-1.180); 0 Female: 1.035 (0.925-1.157); 0 Age Group: <75: 0.948 (0.890-1.180); 0 ≥ 75: 1.116 (0.989-1.258); 0 Time from admission to death 4 or less wk: 1.088 (0.907-1.306); 0 >4 wk: 1.017 (0.920-1.124); 0 Total mortality: 1.033 (0.946-1.127); 0 Cardiovascular mortality: 1.033 (0.920-1.160); 0 Cardiac death: 1.052 (0.919-1.204); 0 Two-pollutant model in CHF patients (case-crossover design) CO alone: 1.054 (0.991-1.121); 0 CO, PM_{10}: 1.096 (0.981-1.224); 0 CO, NO_2: 1.022 (0.932-1.122); 0 CO, SO_2: 1.014 (0.909-1.131); 0 CO, O_3: 1.056 (0.992-1.124); 0
Author: Lee et al. (2007, 093042) **Period of Study:** 1/2000-12/2004 **Location:** Seoul, Korea	**Health Outcome (ICD10):** Mortality: Nonaccidental (A00-R99) **Study Design:** Time series **Statistical Analyses:** Poisson GAM **Age Groups Analyzed:** All ages	**Pollutant:** CO **Averaging Time:** Max 8-h ma **Mean (SD) unit:** w/ Asian dust days: 0.92 (0.42) ppm w/o Asian dust days:0.92 (0.41) ppm Asian dust days only: 1.00 (0.47) ppm **Range (Min, Max):** NR **Copollutant:** PM_{10}; NO_2; SO_2; O_3	**Increment**: 0.54 ppm **% Increase (Lower CI, Upper CI); lag:** Model with Asian Dust Days: 3.3% (2.5-4.1); 1 Model without Asian dust days: 3.3% (2.5-4.2); 1
Author: Lipfert et al. (2000, 004088) **Period of Study:** 5/1992-9/1995 **Location:** Philadelphia, PA, three nearby suburban Pennsylvania counties, and three nearby New Jersey counties	**Health Outcome (ICD9):** Mortality: Respiratory (460-519); cardiac (390-448); Cancer; other causes (<800) **Study Design:** Time series **Statistical Analyses:** Step-wise regression **Age Groups Analyzed:** <65 yr ≥ 65 yr	**Pollutant:** CO **Averaging Time**: 24-h avg; 1-h max **Mean (SD) unit:** Camden: 24-h avg: 0.75 (0.40) ppm Philadelphia: 24-h avg: 0.63 (0.40) ppm 1-h max: 1.44 (1.04) **Range (Min, Max):** Camden: (0.10, 3.8) Philadelphia: 24-h avg: (0.10, 3.3) 1-h max: (0.0, 7.8) **Copollutant:** NO; NO_2; O_3; SO_2; SO_4^{2-}; PM_{10}; $PM_{2.5}$	**Increment:** NR **Attributable Risk; lag:** Peak CO All-cause Philadelphia: 0.0054; 0-1 4 Pennsylvania Counties: 0.0081; 0-1 Pennsylvania + NJ: 0.0085; 0-1 CO All seven counties in Pennsylvania and New Jersey All ages Respirator y: -0.0067; Cardiac: 0.0131; Other: 0.0078 All-cause: <65: 0.0148; 0-1; ≥ 65: 0.0054; 0-1 Joint model with CO Philadelphia: 0.0059; 0-1 4 Pennsylvania Counties: 0.0089; 0-1 Pennsylvania + NJ: 0.0096; 0-1 Cardiac: 0.0135; 0-1; Other causes: 0.0084 <65: 0.0154; 0-1; ≥ 65: 0.0060; 0-1

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Lippmann et al. (2000, 011938) **Period of Study:** 1985-1990 1992-1994 **Location:** Detroit, MI and Windsor, ON	**Health Outcome (ICD9):** Mortality: Total (nonaccidental) (<800); circulatory (390-459); respiratory (460-519) **Study Design:** Time series **Statistical Analyses:** Poisson GLM **Age Groups Analyzed:** ≥ 65 yr	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 1985-1990: 0.9 ppm 1992-1994: 0.72 ppm **Range (5th, 95th):** 1985-1990: (.46, 1.61) 1992-1994: (0.36, 1.2) **Copollutant correlation:** 1985-1990 PM_{10}: r = 0.35; TSP: r = 0.28; TSP-PM_{10}: r = 0.02; TSP-SO_4^{2-}: r = 0.18; O_3: r = -0.22; SO_2: r = 0.36; NO_2: r = 0.58 1992-1994 PM_{10}: r = 0.38; $PM_{2.5}$: r = 0.38; $PM_{10-2.5}$: r = 0.24; H+: r = 0.16; SO_4^{2-}:r = 0.32; O_3: r = 0.16; SO_2: r = 0.42; NO_2: r = 0.68	**Increment:** 1985-1990: 11.5 ppm; 1992-1994: 8.4 ppm Relative Risk (Lower CI, Upper CI); lag: 1985-1990 Total Mortality: 0.9842 (0.9667-1.002); 0 1.0103 (0.9926-1.0284); 1 1.0075 (0.9898-1.0254); 2 1.0145 (0.9967-1.0326); 3 0.9968 (0.9789-1.0151); 0-1 1.0105 (0.9925-1.0288); 1-2 1.0134 (0.9954-1.0317); 2-3 1.0003 (0.9823-1.0187); 0-2 1.0152 (0.9971-1.0336); 1-3 1.0053 (0.9873-1.0236); 0-3 Circulatory Mortality: 0.9818 (0.9574-1.0068); 0 0.9991 (0.9745-1.0243); 1 0.9980 (0.9735-1.0232); 2 1.0088 (0.9841-1.0341); 3 0.9888 (0.9640-1.0144); 0-1 0.9981 (0.9732-1.0237); 1-2 1.0042 (0.9792-1.0298); 2-3 0.9900 (0.9650-1.0157); 0-2 1.0029 (0.9777-1.0287); 1-3 0.9944 (0.9692-1.0202); 0-3 Respiratory Mortality; 0.9644 (0.9042-1.0287); 0 1.0142 (0.9518-1.0808); 1 1.0483 (0.9845-1.1164); 2 1.0468 (0.9828-1.1149); 3 0.9868 (0.9248-1.053); 0-1 1.0372 (0.9730-1.1056); 1-2 1.0554 (0.9904-1.1246); 2-3 1.0088 (0.9457-1.0762); 0-2 1.0466 (0.9817-1.1158); 1-3 1.0205 (0.9569-1.0884); 0-3 Total minus respiratory and circulatory mortality: 0.9939 (0.9668-1.0217); 0 1.0278 (1.0001-1.0562); 1 1.0178 (0.9902-1.0461); 2 1.0227 (0.9948-1.0514); 3 1.0127 (0.9860-1.0412); 0-1 1.0269 (0.9989-1.0556); 1-2 1.0249 (0.9968-1.0538); 2-3 1.0172 (0.9893-1.0458); 0-2 1.0322 (1.0041-1.0612); 1-3 1.0229 (0.9950-1.0516); 0-3 1992-1994 Total Mortality 0.9933 (0.9636-1.024); 0 1.0162 (0.9860-1.0473); 1 1.0116 (0.9816-1.0426); 2 0.9947 (0.9648-1.0254); 3 1.0056 (0.9756-1.0366); 0-1 1.0165 (0.9864-1.0476); 1-2 1.0038 (0.9739-1.0476); 2-3 1.0098 (0.9796-1.0409); 0-2 1.0104 (0.9862-1.0414); 1-3 1.0064 (0.9755-1.0382); 0-3 Circulatory Mortality 1.0076 (0.9640-1.0531); 0 1.0307 (0.9865-1.0768); 1 1.0142 (0.9705-1.0598); 2 0.9523 (0.9102-0.9964); 3 1.0229 (0.9788-1.0688); 0-1 1.0267 (0.9827-1.0727); 1-2 0.9802 (0.9375-1.0248); 2-3 1.0243 (0.9801-1.0726); 0-2 0.9987 (0.9553-1.0441); 1-3 1.0019 (0.9573-1.0487); 0-3

Study	Design	Concentrations	Effect Estimates (95% CI)
			Respiratory Mortality 0.9894 (0.8912-1.0984); 0 0.9474 (0.8521-1.0533); 1 0.9652 (0.8682-1.0732); 2 0.9931 (0.8934-1.1040); 3 0.9626 (0.8668-1.0691); 0-1 0.9485 (0.8535-1.0541); 1-2 0.9752 (0.8775-1.0838); 2-3 0.9555 (0.8802-1.0615); 0-2 0.9567 (0.8607-1.0635); 1-3 0.9584 (0.9604-1.0675); 0-3 Total minus respiratory and circulatory mortality: 0.9769 (0.9332-1.0227); 0 1.0135 (0.9682-1.0609); 1 1.0195 (0.9747-1.0664); 2 1.0429 (0.9974-1.0905); 3 0.9940 (0.9494-1.0406); 0-1 1.0197 (0.9746-1.0670); 1-2 1.0371 (0.9918-1.0845); 2-3 1.0045 (0.9596-1.0515); 0-2 1.0353 (0.9896-1.0831); 1-3 1.0215 (0.9749-1.0702); 0-3
Author: Maheswaran et al. (2005, 090769) **Period of Study:** 1994-1998 **Location:** Sheffield, United Kingdom	**Health Outcome (ICD9):** Mortality: CHD (410-414) **Study Design:** Ecological **Statistical Analyses:** Poisson **Age Groups Analyzed:** ≥ 45 yr	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** NR **Range (Min, Max):** NR **Copollutant:** NO_X; PM_{10} **Notes:** Quintiles represent the following mean CO concentrations and category limits: 5: 482 µg/m^3 (≥ 455) 4: 443 µg/m^3 (≥ 433 to <455) 3: 426 µg/m^3 (≥ 419 to <433) 2: 405 µg/m^3 (≥ 387 to <419) 1: 360 µg/m^3 (<387)	**Increment:** NR **Rate Ratios (Lower CI, Upper CI):** CO Adjusted for sex and age Quintile: 5 (highest): 1.24 (1.14, 1.36) 4: 1.30 (1.19, 1.41) 3: 1.15 (1.05, 1.25) 2: 1.08 (0.99, 1.17) 1: (lowest): 1.00 CO Adjusted for sex, age, deprivation, and smoking Quintile: 5 (highest): 1.05 (0.95, 1.16); 4: 1.16 (1.06, 1.28); 3: 1.04 (0.95, 1.14); 2: 1.03 (0.94, 1.13); 1 (lowest): 1.00 CO Adjusted for sex, age, deprivation, and smoking (spatially smoothed using a 1 km radius) Quintile: 5 (highest): 1.07 (0.96, 1.18); 4: 1.13 (1.03, 1.24); 3: 1.04 (0.95, 1.14); 2: 1.01 (0.92, 1.10); 1 (lowest): 1.00

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Maheswaran et al. (2005, 088683) **Period of Study:** 1994-1998 **Location:** Sheffield, United Kingdom	**Health Outcome (ICD9):** Mortality: Stroke deaths (430-438) **Study Design:** Ecological **Statistical Analyses:** Poisson **Age Groups Analyzed:** ≥ 45 yr	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** Quintile: 5: 482 µg/m^3; 4: 443 µg/m^3; 3: 426 µg/m^3; 2: 405 µg/m^3; 1: 360 µg/m^3 **Range (Min, Max):** NR **Copollutant correlation:** PM_{10}: r = 0.88; NO_X: r = 0.87 **Notes:** Quintiles represent the following mean CO concentrations and category limits: 5: 482 µg/m^3 (≥ 455) 4: 443 µg/m^3 (≥ 433 to <455) 3: 426 µg/m^3 (≥ 419 to <433) 2: 405 µg/m^3 (≥ 387 to <419) 1: 360 µg/m^3 (<387)	**Increment:** NR **Rate Ratios (Lower CI, Upper CI); lag:** RR for mortality and CO modeled outdoor air pollution Adjusted for sex and age Quintile: 5 (highest): 1.35 (1.19, 1.53); 4: 1.40 (1.24, 1.58); 3: 1.08 (0.95, 1.23); 2: 1.10 (0.97, 1.24); 1 (lowest): 1.00 Adjusted for sex, age, deprivation, and smoking Quintile: 5 (highest): 1.26 (1.10, 1.46); 4: 1.32 (1.15, 1.50); 3: 1.07 (0.93, 1.22); 2: 1.12 (0.99, 1.28); 1 (lowest): 1.00 Not spatially smoothed CO outdoor air pollution Quintile: 5 (highest): 1.26 (1.10, 1.46); 4: 1.32 (1.15, 1.50); 3: 1.07 (0.93, 1.22); 2: 1.12 (0.99, 1.28); 1 (lowest): 1.00 Spatially smoothed using a 1-km radius Quintile: 5 (highest): 1.16 (1.01, 1.34); 4: 1.22 (1.07, 1.39); 3: 0.95 (0.83, 1.09); 2: 0.97 (0.85, 1.11); 1 (lowest): 1.00
Author: Mar et al. (2000, 001760) **Period of Study:** 1995-1997 **Location:** Phoenix, AZ	**Health Outcome (ICD9):** Mortality: Total (nonaccidental) (<800); cardiovascular (390-449) **Study Design:** Time series **Statistical Analyses:** Poisson **Age Groups Analyzed:** >65 yr	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 1.5 (0.8) ppm **Range (Min, Max):** 1995: (0.5, 4.0) ppm 1996: (0.3, 4.0) ppm 1997: (0.3, 3.7) ppm **Copollutant correlation:** $PM_{2.5}$: r = 0.85; PM_{10}: r = 0.53; $PM_{10-2.5}$: r = 0.34; NO_2: r = 0.87; O_3: r =-0.40; SO_2: r =0.53	**Increment:** 1.19 ppm **Relative Risk (Lower CI, Upper CI); lag:** Total Mortality (CO exposure): 1.06 (1.02, 1.09); 0; 1.05 (1.01, 1.09); 1 Cardiovascular Mortality (CO exposure): 1.05 (1.00, 1.11); 0; 1.10 (1.04, 1.15); 1; 1.07 (1.02, 1.12); 2; 1.07 (1.02, 1.12); 3; 1.08 (1.03, 1.13); 4

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Moolgavkar et al. (2000, 012054) **Period of Study:** 1987-1995 **Location:** Cook County, IL Los Angeles County, CA Maricopa County, AZ	**Health Outcome (ICD9):** Mortality: Circulatory (390-448); cardiovascular (390-429); cerebrovascular (430-448); COPD (490-496); asthma (493) **Study Design:** Time series **Statistical Analyses:** Poisson GAM, spline smoother **Age Groups Analyzed:** All ages	**Pollutant:** CO **Averaging Time:** 24-h avg **Median unit:** Cook county: 993 ppb Los Angeles: 1347 ppb Maricopa: 1240 ppb **Range (Min, Max):** Cook county: (224, 3912) Los Angeles: (237, 5955) Maricopa: (269, 4777) **Copollutant correlation:** PM_{10}: Cook: r = 0.30; LA: r = 0.45; Maricopa: r = 0.20 NO_2: Cook: r = 0.63; LA: r = 0.80; Maricopa: r = 0.66 SO_2: Cook: r = 0.35; LA: r = 0.78; Maricopa: r = 0.53 O_3: Cook: r = -0.28; LA: r = -0.52; Maricopa: r = -0.61	**Increment:** 1 ppm **% Change (Lower CI, Upper CI); lag:** CVD Mortality Cook County CO -1.07 (-2.67, 0.54); 0; / 1.25 (-0.36, 2.87); 1; 1.49 (-0.09, 3.07); 2; / 1.90 (0.32, 3.48); 3; 1.44 (-0.16, 3.03); 4; / 0.72 (-0.89, 2.32); 5 Los Angeles County CO 3.47 (2.94, 4.00); 0; / 3.93 (3.41, 4.46); 1; 4.08 (3.56, 4.60); 2; / 3.76 (3.24, 4.28); 3; 2.91 (2.37, 3.44); 4; / 2.63 (2.09, 3.17); 5 CO, PM_{10} 2.27 (0.88, 3.66); 0; / 4.33 (2.96, 5.69); 1; 4.72 (3.38, 6.05); 2; / 4.26 (2.90, 5.63); 3; 2.49 (1.10, 3.88); 4; / 5.93 (4.60, 7.27); 5 CO and $PM_{2.5}$ 0.43 (-1.35, 2.20); 0; / 2.88 (1.16, 4.60); 1; 4.65 (2.93, 6.37); 2; / 5.93 (4.20, 7.65); 3; 3.88 (2.13, 5.63); 4; / 5.85 (4.12, 7.58); 5 Maricopa County CO 0.81 (-0.79, 2.39); 0; / 2.20 (0.61, 3.79); 1; 3.05 (1.49, 4.61); 2; / 3.78 (2.27, 5.28); 3; 3.73 (2.27, 5.19); 4; / 2.25 (0.76, 3.72); 5 COPD Mortality Cook County CO -2.65 (-7.05, 1.75); 0; / 2.80 (-1.60, 7.19); 1; 0.98 (-3.34, 5.31); 2; / 2.20 (-2.12, 6.53); 3; 1.31 (-3.06, 5.68); 4; / 1.59 (-2.78, 5.97); 5 Los Angeles County CO 3.78 (2.31, 5.25); 0; / 5.23 (3.78, 6.69); 1; 5.71 (4.26, 7.17); 2; / 5.42 (3.95, 6.89); 3; 4.01 (2.51, 5.50); 4; / 3.82 (2.31, 5.33); 5 Maricopa County CO 1.29 (-2.19, 4.76); 0; / 4.63 (1.17, 8.09); 1; 0.07 (-3.36, 3.50); 2; / 3.00 (-0.30, 6.30); 3; 6.21 (3.02, 9.40); 4; / 3.27 (0.04, 6.50); 5 Cerebrovascular Disease Mortality Cook County -0.41 (-3.30, 2.47); 0; / 3.13 (0.23, 6.02); 1; 2.12 (-0.73, 4.97); 2; / 1.00 (-1.85, 3.86); 3; 2.50 (-0.36, 5.37); 4; / 1.88 (-1.00, 4.76); 5 Los Angeles County 3.31 (2.32, 4.31); 0; / 3.88 (2.89, 4.87); 1; 3.23 (2.25, 4.22); 2; / 2.65 (1.66, 3.65); 3; 2.11 (1.11, 3.12); 4; / 2.04 (1.02, 3.06); 5 Maricopa County 0.26 (-2.65, 3.16); 0; / 3.50 (0.60, 6.41); 1; 3.52 (0.66, 6.38); 2; / 4.61 (1.85, 7.37); 3; 4.78 (2.10, 7.46); 4; / 5.15 (2.45, 7.84); 5 **Notes:** Total Mortality effect estimates were not presented quantitatively.

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Moolgavkar et al. (2003, 051316) **Period of Study:** 1987-1995 **Location:** Cook County, Illinois & Los Angeles County, California	**Health Outcome (ICD9):** Mortality: Total (nonaccidental) (<800); circulatory (390-448) **Study Design:** Time series **Statistical Analyses:** Poisson GAM **Age Groups Analyzed:** All Ages	**Pollutant:** CO **Averaging Time:** 24-h avg **Median unit:** Cook County: 993 ppb LA County: 1347 ppb **Range (Min, Max):** Cook County: (224, 3912) ppb LA County: (237, 5955) ppb **Copollutant correlation:** Cook County: NO_2: r = 0.63; O_3: r = -0.22; SO_2: r = 0.35; PM_{10}: r = 0.30 LA County: NO_2: r = 0.80; O_3: r = -0.52; SO_2: r = 0.78; PM_{10}: r = 0.45; $PM_{2.5}$: r = 0.58	**Increment:** 1 ppm **% Increase (t-statistic); lag** Total Mortality Cook County CO: 0.6% (1.2); 0; / 2.5% (5.4); 1; / 1.2% (2.6); 2; 1.5% (3.2); 3; / 1.1% (2.5); 4; / 0.6% (1.3); 5 CO, PM_{10}: -0.5% (-1.0); 0; / 2.2% (4.3); 1; / 1.1% (2.2); 2; 1.0% (1.9); 3; / 1.1% (2.1); 4; / 1.4% (2.7); 5 Total Mortality Los Angeles County CO: 1.3% (7.4); 0; / 1.9% (10.5); 1; / 1.6% (8.9); 2; 1.4% (8.1); 3; / 1.0% (5.9); 4; / 0.7% (4.1); 5 CO, PM_{10}: 0% (0); 0; / 2.2% (4.8); 1; / 1.4% (3.1); 2; 0.8% (1.8); 3; / 0.7% (1.6); 4; / 1.3% (3.0); 5 CO, $PM_{2.5}$: -0.1% (-1.5); 0; / 1.5% (2.5); 1; / 2.4% (3.8); 2; 0.3% (0.5); 3; / 1.6% (2.8); 4; / 1.5% (2.6); 5 Total Mortality (Season-specific) Cook County Spring (CO): 0.8% (0.9); 0; / 2.4% (2.9); 1; / 0% (0); 2; 1.2% (1.5); 3; / 0.8% (1.0); 4; / -0.1% (-0.2); 5 Summer (CO): 1.2% (1.0); 0; / 3.6% (3.0); 1; / 4.2% (3.6); 2; -0.3% (-0.2); 3; / -1.1% (-1.0); 4; /-0.7% (-0.6); 5 Fall (CO): 1.2% (1.5); 0; / 2.1% (2.7); 1; / 0% (0); 2; 0% (0); 3; /-0.5% (-0.6); 4; / -0.7% (-0.9); 5 Winter (CO): -0.7% (-1.0); 0; / 1.8% (2.3); 1; / -0.2% (-0.3); 2; 0.5% (0.6); 3; / 1.2% (1.5); 4; / 1.0% (1.3); 5 Los Angeles County Total Mortality (Season-specific) Spring (CO): 3.6% (6.3); 0; / 3.5% (6.2); 1; / 1.9% (3.4); 2; 0.6% (1.0); 3; / -0.5% (-0.8); 4; / -0.7% (-1.2); 5 Summer (CO): 3.0% (3.0); 0; / 4.7% (4.6); 1; / 5.2% (5.1); 2; 4.1% (3.8); 3; / 1.9% (1.8); 4; / 1.4% (1.3); 5 Fall (CO): 1.8% (4.6); 0; / 2.0% (5.1); 1; / 1.0% (2.6); 2; 0.6% (1.5); 3; / 0.4% (1.2); 4; / 0.2% (0.6); 5 Winter (CO): 0% (0); 0; / 0.8% (2.5); 1; / 0.9% (3.1); 2; 1.0% (3.4); 3; / 0.5% (1.7); 4; / 0.5% (1.6); 5 CVD Mortality Cook County CO: -1.1% (-1.5); 0; / 1.8% (2.5); 1; / 1.5% (2.2); 2; 1.6% (2.4); 3; / 1.4% (2.1); 4; / 0.7% (1.0); 5 CO, PM_{10}: -2.1% (-2.6); 0; / 1.5% (1.8); 1; / 1.4% (1.7); 2; 0.1% (1.1); 3; / 1.4% (1.9); 4; / 1.6% (2.1); 5 CVD Mortality Los Angeles County CO: 1.6% (6.3); 0; / 1.9% (7.6); 1; / 1.6% (6.6); 2; 1.9% (8.2); 3; / 1.6% (7.1); 4; / 1.4% (6.1); 5 CO, PM_{10}: -0.8% (-1.2); 0; / 1.9% (3.0); 1; / 2.7% (4.3); 2; 1.3% (2.2); 3; / 0.5% (0.9); 4; / 2.8% (4.7); 5 CO, $PM_{2.5}$: -2.2% (-2.7); 0; / 1.5% (1.8); 1; / 1.9% (2.0); 2; 1.9% (2.2); 3; / 2.1% (2.6); 4; / 3.7%(4.5); 5

Study	Design	Concentrations	Effect Estimates (95% CI)
			CVD Mortality (Season Specifid) Cook County Spring (CO): 0.7% (0.5); 0; / 1.4% (1.1); 1; / 0.3% (0.3); 2; 1.1% (0.9); 3; / 0.4% (3.1); 4; / 0.1% (0.6); 5 Summer (CO): -2.6% (-1.4); 0; / 2.5% (1.4); 1; / 6.5% (3.7); 2; 0.9% (0.5); 3; / -1.9% (-1.1); 4; / -1.0% (-0.6); 5 Fall (CO): 0% (0); 0; / 2.9% (2.5); / 1; 0% (0); 2; 0% (0); 3; /-0.8% (-0.7); / 4; 0% (0); 5 Winter (CO): -2.5% (-2.2); 0; / 0.7% (0.6); 1; / 0% (0); 2; 1.3% (1.1); 3; / 0.8% (0.7); 4; / 0.4% (0.4); 5 Los Angeles County CVD Mortality (Season-specific) Spring (CO): 3.0% (3.7); 0; / 3.3% (4.1); 1; / 2.3% (2.9); 2; 0.7% (0.9); 3; / -1.2% (-1.6); 4; / 0% (0); 5 Summer (CO): 4.0% (2.8); 0; / 5.2% (3.5); 1; / 6.3% (4.3); 2; 5.0% (3.3); 3; / 3.1% (2.0); 4; / 3.6% (2.3); 5 Fall (CO): 2.3% (4.2); 0; / 2.1% (3.7); 1; / 1.1% (1.9); 2; 1.2% (2.2); 3; / 1.5% (2.9); 4; / 1.0% (1.8); 5 Winter (CO): 0.3% (0.8); / 0; 0.7% (1.7); 1; / 0.8% (2.0); 2; 1.4% (3.4); 3; / 1.0% (2.3); 4; / 1.1% (2.5); 5
Author: Ostro et al. (1999, 006610) **Period of Study:** 1989-1992 **Location:** Coachella Valley, California	**Health Outcome (ICD9):** Mortality: Total (nonaccidental) (<800); respiratory (460-519); cardiovascular (393-440) **Study Design:** Time series **Statistical Analyses:** Poisson GAM; LOESS **Age Groups Analyzed:** >50 yr	**Pollutant:** CO **Averaging Time:** 1-h max **Mean (SD) unit:** 1.35 ppm **Range (Min, Max):** (0, 6.0) **Copollutant correlation:** PM_{10}: r = -0.18; O_3: r = -0.47; NO_2: r = 0.65	**Increment:** NR **β (SE); lag:** CO: 0.0371 (0.0157); 2 CO, PM_{10}: 0.0300 (0.0194); 2
Author: Penttinen et al. (2004, 087432) **Period of Study:** 1988-1996 **Location:** Helsinki, Finland	**Health Outcome (ICD9):** Mortality: Total (nonaccidental) (<800); respiratory (460-519); cardiovascular (393-440) **Study Design:** Time series **Statistical Analyses:** Poisson GAM, LOESS **Age Groups Analyzed:** All ages 15-64 yr 65-74 yr ≥ 75	**Pollutant:** CO **Averaging Time:** Max 8-h avg **Median unit:** 1.2 mg/m^3 **Range (Min, Max):** (0, 12.4) **Copollutant correlation:** O_3: r = -0.46; NO_2: r = 0.59; SO_2: r = 0.55; PM_{10}: r = 0.45; TSP: r = 0.26; TSP Blackness: r = 0.26	**Increment:** 1 mg/m^3 **% Increase (Lower CI, Upper CI); lag:** Total Mortality -1.50% (-2.78, -0.22); 0 0.15% (-1.09, 1.39); 1 -1.00% (-2.80, 0.81); 0-3 Cardiovascular Mortality -2.48% (-4.30, -0.66); 0 -0.84% (-2.61, 0.93); 1 -1.87% (-4.43, 0.69); 0- Respiratory Mortality -0.48% (-4.84, 3.87); 0 -0.14% (-4.43, 4.15); 1 -1.49% (-7.73, 4.74); 0-3
Author: Peters et al. (2000, 001756) **Period of Study:** 1982-1994 **Location:** Northern Bavaria (Rural Germany) and the Coal Basin of the Czech Republic	**Health Outcome (ICD9):** Mortality: Total (non-accidental) (<800); Cardiovascular (390-459); Respiratory (460-519); Cancer (140-239) **Study Design:** Time-series **Statistical Analyses:** (1) Poisson Regression Models by logistic regression analyses with a cubic function; (2) Poisson GAM, natural splines **Age Groups Analyzed:** All Ages	**Pollutant:** CO **Averaging Time:** 24-h avg Mean (SD) unit: Coal Basin: 0.58 (0.39) mg/m^3 Northeast Bavaria: 0.88 (0.69) mg/m^3 Range (Min, Max): Coal Basin: (-0.1, 2.88) Northeast Bavaria: (0.1, 6.2) **Copollutant correlation:** SO_2: r = 0.37; TSP: r = 0.37; NO_2: r = 0.32; O_3: r = -0.57; PM_{10}: r = 0.44; $PM_{2.5}$: r = 0.42	Increment: 1 mg/m^3 Relative Risk (Lower CI, Upper CI); lag: Coal Basin of the Czech Republic Total Mortality: 1.016 (0.998, 1.035); 0; / 1.016 (0.998, 1.034); 1; 1.013 (0.996, 1.030); 2; / 1.012 (0.995, 1.028); 3 Northeast Bavaria Total Mortality: 1.014 (0.994, 1.034); 0; / 1.023 (1.005, 1.041); 1; 1.013 (0.995, 1.031); 2; / 1.003 (0.985, 1.021); 3 CVD Mortality: 1.018 (0.994, 1.044); 0; / 1.012 (0.987, 1.038); 1; 1.016 (0.991, 1.041); 2; / 1.004 (0.980, 1.029); 3

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Rainham et al. (2003, 053202) **Period of Study:** 1980-1996 **Location:** Toronto, ON, Canada	**Health Outcome (ICD9):** Mortality: Cardiac (390-459); Respiratory (480-519); Total (non-accidental) (<800) **Study Design:** Time-series **Statistical Analyses:**Poisson GAM, natural cubic splines **Age Groups Analyzed:** <65 ≥ 65	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 1.0 (0.4) ppm **Range (Min, Max):** (0.0, 4.0) **Copollutant:** O_3; NO_2; SO_2	The study did not present quantitative results for CO.
Author: Roemer et al. (2001, 019391) **Period of Study:** 1/1987-11/1998 **Location:** Amsterdam	**Health Outcome (ICD9):** Mortality: Total (non-accidental) (<800) **Study Design:** Time-series **Statistical Analyses:** Poisson GAM **Age Groups Analyzed:** All ages	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** Air pollution background: 836 µg/m^3 Air pollution traffic: 1805 µg/m^3 **Range (10th, 90th):** Air pollution background: (448, 1315) µg/m^3 Air pollution traffic: (727, 3192) µg/m^3 **Copollutant:** BS; PM_{10}; SO_2; NO_2; NO; O_3	**Increment:** Lag 1 and 2: 100 µg/m^3 Lag 0-6: 50 µg/m^3 **Relative Risk (Lower CI, Upper CI); lag:** Total Population using Background sites 1.002 (1.000-1.004); 1; 1.001 (0.999-1.003); 2; 1.001 (1.000-1.003); 0-6 Traffic Population using Background Sites 1.003 (0.997-1.008); 1; 1.008 (1.003-1.013); 2; 1.003 (0.999-1.007); 0-6 Total population using Traffic Sites 1.000 (1.000-1.001); 1; 1.000 (0.999-1.001); 2; 1.000 (1.000-1.001); 0-6

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Samet et al. (2000, 013132) **Period of Study:** 1987-1994 **Location:** 20 U.S. Cities: Los Angeles, CA; New York, NY; Chicago, IL; Dallas, TX; Houston, TX; San Diego, CA; Anaheim, CA; Phoenix, AZ; Detroit, MI; Miami, FL; Philadelphia, PA; Minneapolis, MN; Seattle, WA; San Jose, CA; Cleveland, OH; San Bernardino, CA; Pittsburgh, PA; Oakland, CA; Atlanta, GA; San Antonio, TX	**Health Outcome (ICD9):** Mortality: Cardiovascular (390-459); Respiratory (460-519); Other (non-accidental) (<800) **Study Design:** Time-series **Statistical Analyses:** Two-stage log linear regression model **Age Groups Analyzed:** <65 65-74 ≥ 75	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** Los Angeles: 15.1 ppm New York: 20.4 ppm Chicago: 7.9 ppm Dallas: 7.4 ppm Houston: 8.9 ppm San Diego: 11.0 ppm Anaheim: 12.3 ppm Phoenix: 12.6 ppm Detroit: 6.6 ppm Miami: 10.6 ppm Philadelphia: 11.8 ppm Minneapolis: 11.8 ppm Seattle: 17.8 ppm San Jose: 9.4 ppm Cleveland: 8.5 ppm San Bernardino: 10.3 ppm Pittsburgh: 12.2 ppm Oakland: 9.1 ppm Atlanta: 8.0 ppm San Antonio: 10.1 ppm Range (10th, 90th): Los Angeles: (5.9, 28.3) New York: (14.8, 27.6) Chicago: (4.5, 11.9) Dallas: (3.6, 12.0) Houston: (4.0, 14.2) San Diego: (4.5, 20.5) Anaheim: (3.7, 25.2) Phoenix: (5.4, 22.6) Detroit: (3.2, 11.1) Miami: (6.5, 15.9) Philadelphia: (7.0, 17.2) Minneapolis: (7.0, 17.0) Seattle: (10.5, 26.4) San Jose: (1.7, 21.3) Cleveland: (3.7, 13.8) San Bernardino: (4.0, 17.5) Pittsburgh: (6.1, 19.8) Oakland: (2.9, 17.0) Atlanta: (3.2, 14.3) San Antonio: (4.1, 17.3) **Copollutant correlation:** PM_{10}: r = 0.45; O_3: r = -0.19; NO_2: r = 0.64; SO_2: r = 0.41	This study did not provide quantitative results for CO.
Author: Samoli et al. (2007, 098420) **Period of Study:** 1990-1997 **Location:** 19 European Cities (APHEA2)	**Health Outcome (ICD9):** Mortality: Total (non-accidental) (<800); Cardiovascular (390-459) **Study Design:** Time-series **Statistical Analyses:** Poisson and two-stage hierarchical model **Age Groups Analyzed:** All ages	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean Range (unit–mg/m3):** Athens: 6.1; Barcelona: 0.9; Basel: 0.6; Birmingham: 1.0; Budapest: 5.1; Geneva: 1.5; Helsinki: 1.2; Ljubljana: 1.6; London: 1.4; Lyon: 3.8; Milano: 5.4; Netherlands: 0.6; Prague: 0.9; Rome: 4.1; Stockholm: 0.8; Teplice: 0.7; Torino: 5.5; Valencia: 4.1; Zurich: 1.2 **Range (10th, 90th):** Athens: (3.5, 9.2) Barcelona: (0.4, 1.7) Basel: (0.4, 1.1) Birmingham: (0.5, 1.6) Budapest: (3.3, 7.4) Geneva: (0.8, 2.6) Helsinki: (0.7, 1.9) Ljubljana: (0.6, 3.0) London: (0.7, 2.2) Lyon: (2.0, 6.0) Milano: (2.9, 8.7) Netherlands: (0.4, 1.2) Prague: (0.5, 1.5)	**Increment:** 1 mg/m^3 **% Increase (Lower CI, Upper CI); lag:** Non-accidental mortality 8 Degrees of Freedom per yr Fixed Effects: CO: 0.59% (0.41-0.78); 0-1 CO, BS: 0.35% (-0.03 to 0.72); 0-1 CO, PM_{10}: 0.48% (0.24-0.72); 0-1 CO, SO_2: 0.44% (0.21-0.67); 0-1 CO, O_3: 0.66% (0.46-0.86); 0-1 CO, NO_2: 0.27% (0.03-0.51); 0-1 Random Effects: CO: 0.66% (0.27-1.05); 0-1 CO, BS: 0.45% (-0.01 to 0.92); 0-1 CO, PM_{10}: 0.58% (0.12-1.04); 0-1 CO, SO_2: 0.46% (0.07-0.85); 0-1 CO, O_3: 0.76% (0.45-1.06); 0-1 CO, NO_2: 0.30% (-0.11 to 0.71); 0-1 PACF: (Partial Autocorrelation Function) Plot Fixed Effects: CO: 1.00% (0.83-1.18); 0-1 CO, BS: 0.67% (0.30-1.04); 0-1 CO, PM_{10}: 0.78% (0.55-1.00); 0-1 CO, SO_2: 0.68% (0.47-0.90); 0-1 CO, O_3: 1.12% (0.93-1.31); 0-1 CO, NO_2: 0.72% (0.50-0.95); 0-1

Study	Design	Concentrations	Effect Estimates (95% CI)
		Rome: (2.5, 5.9) Stockholm: (0.5, 1.2) Teplice: (0.3, 1.2) Torino: (2.8, 9.1) Valencia: (2.4, 5.9) Zurich: (0.7, 2.0) **Copollutant correlation:** PM_{10}: r = 0.16 to 0.70 BS: r = 0.67 to 0.82 SO_2: r = 0.35 to 0.82 NO_2: r = 0.03 to 0.68 O_3: r = -0.25 to -0.65	Random Effects: CO: 1.20% (0.63-1.77); 0-1 CO, BS: 0.77% (0.28-1.26); 0-1 CO, PM_{10}: 1.09% (0.36-1.83); 0-1 CO, SO_2: 0.75% (0.26-1.26); 0-1 CO, O_3: 1.37% (0.81-1.95); 0-1 CO, NO_2: 0.88% (0.22-1.55); 0-1 Cardiovascular Mortality 8 Degrees of Freedom per Year Fixed Effects: CO: 0.80% (0.53-1.07); 0-1 CO, BS: 0.49% (-0.04 to 1.02); 0-1 CO, PM_{10}: 0.73% (0.39-1.07); 0-1 CO, SO_2: 0.72% (0.39-1.04); 0-1 CO, O_3: 0.91% (0.62-1.20); 0-1 CO, NO_2: 0.44% (0.10-0.79); 0-1 Random Effects: CO: 0.81% (0.36-1.26); 0-1 CO, BS: 0.49% (-0.04 to 1.02); 0-1 CO, PM_{10}: 0.73% (0.39-1.07); 0-1 CO, SO_2: 0.68% (-0.03 to 1.40); 0-1 CO, O_3: 1.02% (0.58-1.46); 0-1 CO, NO_2: 0.43% (-0.06 to 0.93); 0-1 PACF (Partial Autocorrelation Function) Fixed Effects: CO: 1.06% (0.80-1.32); 0-1 CO, BS: 0.83% (0.31-1.35); 0-1 CO, PM_{10}: 0.95% (0.62-1.27); 0-1 CO, SO_2: 0.91% (0.59-1.22); 0-1 CO, O_3: 1.28% (1.01-1.56); 0-1 CO, NO_2: 0.68% (0.35-1.00); 0-1 Random Effects: CO: 1.25% (0.30-2.21); 0-1 CO, BS: 0.83% (0.31-1.35); 0-1 CO, PM_{10}: 1.13% (0.60-1.67); 0-1 CO, SO_2: 0.86% (0.06-1.66); 0-1 CO, O_3: 1.62% (0.72-2.52); 0-1 CO, NO_2: 0.84% (-0.03 to 1.71); 0-1 Effect Modifiers Non-accidental Mortality 8 Degrees of Freedom per Year Number of CO monitors: 25th Percentile: 0.71% (0.48-0.94); 0-1 75th Percentile: 0.54% (0.34-0.74); 0-1 Mean PM_{10} Levels: 25th Percentile: 0.37% (0.08-0.66); 0-1 75th Percentile: 0.49% (0.28-0.69); 0-1 Standardized Mortality Rate: 25th Percentile: 0.79% (0.55-1.03); 0-1 75th Percentile: 0.44% (0.22-0.66); 0-1 Western cities: 0.75% (0.47-1.03); 0-1 Southern cities: 0.61% (0.32-0.91); 0-1 Eastern cities: 0.03% (-0.47 to 0.53); 0-1 PACF (Partial Autocorrelation Function) Number of CO monitors: 25th Percentile: 1.18% (0.96-1.39); 0-1 75th Percentile: 0.92% (0.73-1.11); 0-1 Mean PM_{10} Levels: 25th Percentile: 0.74% (0.46-1.02); 0-1 75th Percentile: 1.07% (0.87-1.27); 0-1 Standardized Mortality Rate: 25th Percentile: 1.29% (1.06-1.52); 0-1 75th Percentile: 0.77% (0.56-0.98); 0-1 Western cities: 1.15% (0.90-1.40); 0-1 Southern cities: 1.08% (0.79-1.38); 0-1 Eastern cities: 0.27% (-0.20 to 0.74); 0-1 Cardiovascular Mortality 8 Degrees of Freedom per Year Mean O_3: 25th Percentile: 1.04% (0.67-1.41); 0-1 75th Percentile: 0.82% (0.55-1.10); 0-1 Standardized Mortality Rate: 25th Percentile: 1.06% (0.71-1.42); 0-1 75th Percentile: 0.61% (0.30-0.93); 0-1

Study	Design	Concentrations	Effect Estimates (95% CI)
			Population >75 yr of age (%): 25th Percentile: 0.58% (0.25-0.92); 0-1 75th Percentile: 0.94% (0.64-1.24); 0-1 Western cities: 1.06% (0.67-1.46); 0-1 Southern cities: 0.70% (0.26-1.14); 0-1 Eastern cities: 0.21% (-0.48 to 0.90); 0-1 PACF (Partial Autocorrelation Function) Mean O_3: 25th Percentile: 1.32% (0.96-1.68); 0-1 75th Percentile: 1.09% (0.83-1.14); 0-1 Standardized Mortality Rate: 25th Percentile: 1.40% (1.06-1.75); 0-1 75th Percentile: 0.85% (0.55-1.14); 0-1 Population >75 yr of age (%): 25th Percentile: 0.74% (0.41-1.06); 0-1 75th Percentile: 1.25% (0.96-1.54); 0-1 Western cities: 1.38% (1.00-1.76); 0-1 Southern cities: 0.90% (0.47-1.33); 0-1 Eastern cities: 0.48% (-0.14 to 1.11); 0-1
Author: Schwartz et al. (1999, 017915) **Period of Study:** 1989-1995 **Location:** Spokane, WA	**Health Outcome (ICD9):** Mortality: Total (nonaccidental) (<800) **Study Design:** Time series **Statistical Analyses:** Poisson GAM **Age Groups Analyzed:** All ages	**Pollutant:** CO **Averaging Time:** 1-h avg **Mean (SD) unit:** Dust Storm Days: 09/08/1990: 6.37 ppm 09/12/1990: 3.40 ppm 10/04/1990: 3.15 ppm 11/09/1990: 2.45 ppm 11/23/1990: 2.50 ppm 09/13/1991: 4.60 ppm 10/16/1991: 2.10 ppm 10/21/1991: 2.20 ppm 09/04/1992: 3.43 ppm 09/12/1992: 1.80 ppm 09/13/1992: 1.65 ppm 09/25/1992: 2.95 ppm 09/26/1992: 4.30 ppm 10/08/1992: 3.85 ppm 09/11/1993: 1.88 ppm 11/3/1993: 5.33 ppm 07/24/1994: 2.10 ppm 08/30/1996: 2.85 ppm **Range (Min, Max):** NR **Copollutant:** PM_{10}	The study did not present quantitative results for CO.
Author: Sharovsky et al. (2004, 156976) **Period of Study:** 1996-1998 **Location:** Sao Paulo, Brazil	**Health Outcome (ICD10):** Mortality: MI (I.21) **Study Design:** Time series **Statistical Analyses:** Poisson GAM, LOESS **Age Groups Analyzed:** 35-109 yr	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 3.7 (1.6) ppm **Range (Min, Max):** (1.0, 11.8) **Copollutant: correlation** SO_2: r = 0.73; PM_{10}: r = 0.51	**Increment:** NR **β x 100 (SE); lag:** CO: 1.42 (1.01) CO, SO_2, PM_{10}: 0.97 (1.27) **Notes:** The study did not present the lag used for CO.
Author: Slaughter et al. (2005, 073854) **Period of Study:** 1/1995-6/2001 **Location:** Spokane, WA	**Health Outcome (ICD9):** Mortality: Total (nonaccidental) (<800); respiratory (460-519); asthma (493); COPD (491, 492, 494, 496); pneumonia (480-487); acute upper respirator y tract infections (464-466, 490); cardiac outcomes (390-459) **Study Design:** Time series **Statistical Analyses:** Log-linear Poisson GLM, natural splines for calendar time **Age Groups Analyzed:** All ages	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** Areas in Spokane Hamilton St: 1.73 (0.46) ppm Backdoor Tavern: 1.29 (0.23) ppm Spokane Club: 1.41 (0.32) ppm Third and Washington: 1.82 (0.33) ppm Rockwood: 0.42 (0.15) ppm **Range (Min, Max):** NR **Copollutant correlation:** PM_1: r = 0.63; $PM_{2.5}$: r = 0.62; PM_{10}: r = 0.32; $PM_{10-2.5}$: r = 0.32	The study did not present quantitative results for CO.

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Stieb et al. (2003, 056908) **Period of Study**: 1985-2000 **Location:** All locations	**Health Outcome (ICD9):** Mortality: Nonaccidental **Study Design:** Meta-analysis **Statistical Analyses:** NR **Age Groups Analyzed:** All ages	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** NR IQR (25th, 75th): NR **Copollutant:** NR	**Increment:** 1.1 ppm % Excess Mortality (Lower CI, Upper CI); lag: Non-GAM: Single-pollutant model (4 studies): 4.7% (1.1-8.4) Multi-pollutant model (1 study): 0.0% (-3.8 to 3.8) GAM: Single-pollutant model (18 studies): 1.6% (1.1-2.1) Multi-pollutant model (11 studies): 0.7% (-0.1 to 1.5)
Author: Stölzel et al. (2007, 091374) **Period of Study:** 9/1995-8/2001 **Location:** Erfurt, Germany	**Health Outcome (ICD9):** Mortality: Total (nonaccidental) (<800); cardio-respiratory (390-459, 460-519, 785, 786) **Study Design:** Time series **Statistical Analyses:** Poisson GAM **Age Groups Analyzed:** All ages	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 0.47 (0.39) mg/m^3 IQR (25th, 75th): (0.23, 0.57) **Copollutant correlation:** MC0.1-0.5: r = 0.58; MC0.01-2.5: r = 0.57; PM_{10}: r = 0.50; NO: r = 0.70; NO_2: r = 0.71	**Increment:** 0.34 mg/m^3 **Relative Risk (Lower CI, Upper CI); lag:** Total (non-accidental) 1.000 (0.977-1.023); 0; 1.002 (0.980-1.024); 1; 1.013 (0.991-1.035); 2; 1.007 (0.986-1.029); 3; 1.012 (0.990-1.034); 4; 0.995 (0.974-1.017); 5
Author: Sunyer et al. (2001, 019367) **Period of Study:** 1990-1995 **Location:** Barcelona, Spain	**Health Outcome (ICD9):** Mortality: COPD (491, 492, 494, 496) **Study Design:** Bidirectional case crossover **Statistical Analyses:** Conditional logistic regression **Age Groups Analyzed:** >35 yr	**Pollutant:** CO **Averaging Time:** 8-h avg **Mean (SD) unit:** NR **Range (Min, Max):** NR **Copollutant:** PM_{10}; NO_2; O_3	**Increment:** 4.5 $\mu g/m^3$ **Odds Ratio (Lower CI, Upper CI); lag:** CO: 1.052 (0.990-1.117); 0-2 CO, PM_{10}: 1.017 (0.947-1.091); 0-2
Author: Sunyer et al. (2002, 034835) **Period of Study:** 1985-1995 **Location:** Barcelona, Spain	**Health Outcome (ICD9):** Mortality: Respiratory mortality **Study Design:** Case crossover **Statistical Analyses:** Conditional logistic regression **Age Groups Analyzed:** >14 yr **Study population:** Asthmatic individuals: 5,610	**Pollutant:** CO **Averaging Time:** 24-h avg **Median (SD) unit:** 7.7 $\mu g/m^3$ **Range (Min, Max):** (0.6, 66.0) **Copollutant:** PM_{10}; BS; NO_2; O_3; SO_2	**Increment:** 7.2 $\mu g/m^3$ **Odds Ratio (Lower CI, Upper CI); lag:** Asthmatic individuals with 1 ED visit 1.127 (0.895-1.418); 0-2 Asthmatic individuals with >1 ED visit 1.125 (0.773-1.638); 0-2 Asthma/COPD individuals with >1 ED visit 0.815 (0.614-1.082); 0-2
Author: Tsai et al. (2003, 050480) **Period of Study:** 1994-2000 **Location:** Kaohsiung, Taiwan	**Health Outcome (ICD9):** Mortality: Total (nonaccidental) (<800); respiratory (460-519); circulatory (390-459) **Study Design:** Bidirectional case crossover **Statistical Analyses:** Conditional logistic regression **Age Groups Analyzed:** All ages	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 0.827 ppm **Range (Min, Max):** (0.226, 1.770) **Copollutant:** PM_{10}; SO_2; NO_2; O_3	**Increment:** 0.313 ppm **Odds Ratio (Lower CI, Upper CI); lag:** Total (nonaccidental): 1.003 (0.968-1.039); 0-2 Respiratory: 1.011 (0.883-1.159); 0-2 Circulatory: 0.986 (0.914-1.063); 0-2
Author: Tsai et al. (2006, 090709) **Period of Study:** 1994-2000 **Location:** Kaohsiung, Taiwan	Health Outcome (ICD9): Mortality: Total (nonaccidental) (<800) **Study Design:** Case crossover **Statistical Analyses:** Conditional logistic regression **Age Groups Analyzed:** 27 days old to <1 yr of age	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit**: 8.27 ppm **Range (Min, Max):** (2.26, 17.70) **Copollutant:** PM_{10}; SO_2; O_3; NO_2	**Increment:** 0.31 ppm **Odds Ratio (Lower CI, Upper CI); lag:** Postneonatal Mortality 1.051 (0.304-3.630); 0-2

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Vedal et al. (2003, 039044) **Period of Study:** 1/1994-12/1996 **Location:** Vancouver, BC, Canada	**Health Outcome (ICD9):** Mortality: Total (nonaccidental) (<800); respiratory (460-519); cardiovascular (390-459) **Study Design:** Time series **Statistical Analyses:** Poisson GAM, LOESS **Age Groups Analyzed:** All ages	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 0.6 (0.2) ppm **Range (Min, Max):** (0.3, 1.9) **Copollutant correlation:** Summer: PM_{10}:r = 0.71; O_3: r = 0.12; NO_2: r = 0.81; SO_2: r = 0.67 Winter: PM_{10}: r = 0.76; O_3: r = -0.65; NO_2: r = 0.78; SO_2: r = 0.83	The study did not present quantitative results for CO.
Author: Villeneuve et al. (2003, 055051) **Period of Study:** 1986-1999 **Location:** Vancouver, BC, Canada	Health Outcome (ICD9): Mortality: Nonaccidental (<800); cardiovascular (401-440); respiratory (460-519); cancer (140-239) **Study Design:** Time series **Statistical Analyses:** Poisson, natural splines **Age Groups Analyzed:** ≥ 65 yr	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 1.0 ppm **Range (Min, Max):** (0.2, 4.9) **Copollutant:** $PM_{2.5}$; PM_{10}; $PM_{10-2.5}$; TSP; SO_4; CO; COH; O_3; NO_2; SO_2	**Increment:** 1.1 ppb **% Increase (Lower CI, Upper CI); lag:** Non-accidental 0.5% (-1.9 to 2.9); 0-2; / -0.3% (-2.2 to 1.7); 0; 0.6% (-1.3 to 2.6); 1; / 0.5% (-1.4 to 2.5); 2 Cardiovascular 2.3% (-1.6 to 6.3); 0-2; / 1.6% (-1.5 to 4.7); 0; 1.2% (-2.0 to 4.5); 1; / 1.5% (-1.5 to 4.4); 2 Respiratory -1.0% (-7.3 to 5.8); 0-2; / 1.3% (-4.4 to 7.3); 0; -0.1% (-5.3 to 5.4); 1; -/ 2.8% (-7.8 to 2.6); 2 Cancer -2.8% (-7.6 to 2.4); 0-2; / -3.0% (-6.9 to 1.1); 0; -1.6% (-5.6 to 2.4); 1; / -0.5% (-4.7 to 3.8); 2
Author: Wang et al. (2008, 179974) **Period of Study:** Daily CO content: 2000-2005 (data from Beijing Environment Protection Bureau), Death rate: 2000-2003 **Location:** Beijing, China	**Health Outcome:** Mortality **Study Design:** Time series, Granger causality, Back propagation neural network model, MIV **Statistical Analyses:** Eviews 3.1, SAS 9.0, Matlab 7.0 **Age Groups Analyzed:** NR **Sample Description:** Death rate of respiratory diseases in Beijing from China Centers for Disease Control and Prevention	**Averaging Time:** NR **Mean (SD) unit:** NR **Range (Min, Max):** NR **Copollutant:** NR	**Increment:** NR Granger causality: Acute respiratory diseases probability: 0.03122 COPD probability: 0.00047 Change of death rate of acute respiratory diseases: Increasing 10%: +0.437, Decreasing 10%: -0.386 Change of death rate of COPD: Increasing 10%: +0.181, Decreasing 10%: -0.316 **Lags examined:** 10

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Wichmann et al. (2000, 013912) **Period of Study:** 9/1995-12/1998 **Location:** Erfurt, Germany	**Health Outcome (ICD9):** Mortality: Nonaccidental (<800); cardiovascular (401-440); respiratory (460-519) **Study Design:** Time series **Statistical Analyses:** Poisson GAM, LOESS **Age Groups Analyzed:** <70 70-79 ≥ 80	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 0.6 (0.5) mg/m^3 **Range (Min, Max):** (0.10, 2.50) **Copollutant:** correlation $PM_{2.5}$: r = 0.62; PM_{10}: r = 0.58; TSP: r = 0.57; SO_2: r = 0.59; NO_2: r = 0.71	**Increment:** 0.5 ppm **Relative Risk (Lower CI, Upper CI); lag:** Single-Day Lag CO: 1.055 (1.003-1.110); 4 Polynomial Distributed Lag Multi-pollutant model: 1.076 (1.017-1.138); 4 Total Mortality CO: 1.012 (0.977-1.049); 0 Log-transformed: 1.016 (0.962-1.073); 0 1.004 (0.969-1.040); 1 Log-transformed: 1.027 (0.973-1.083); 1 1.020 (0.984-1.057); 2 Log-transformed: 1.024 (0.970-1.081); 2 1.019 (0.984-1.055); 3 Log-transformed: 1.037 (0.984-1.093); 3 1.029 (0.995-1.063); 4 Log-transformed: 1.055 (1.003-1.110); 4 0.997 (0.965-1.031); 5 Log-transformed: 1.014 (0.966-1.065); 5 Total Mortality (Season-specific): Log-transformed Winter: 1.002 (0.922-1.088); 4 Spring: 1.019 (0.942-1.102); 4 Summer: 1.085 (1.018-1.156); 4 Fall: 1.111 (1.039-1.188); 4 Winter-specific: Log-transformed 10/95-3/96: 1.046 (0.949-1.153); 4 10/96-3/97: 1.091 (0.998-1.193); 4 10/97-3/98: 1.028 (0.966-1.095); 4 One-pollutant Model: Log-transformed CO: 1.055 (1.003-1.110); 4
Author: Yang et al. (2004, 055603) **Period of Study:** 1994-1998 **Location:** Taipei, Taiwan	**Health Outcome (ICD9):** Mortality: Nonaccidental (<800); circulatory (390-459); respiratory (460-519) **Study Design:** Bidirectional case crossover **Statistical Analyses:** Conditional logistic regression **Age Groups Analyzed:** All ages	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 1.16 ppm **Range (Min, Max):** (0.24, 4.42) **Copollutant:** PM_{10}; SO_2; NO_2; O_3	**Increment:** 0.52 ppm **Odds Ratio (Lower CI, Upper CI); lag:** Non-accidental: 1.005 (0.980-1.031); 0-2 Respiratory: 1.014 (0.925-1.110); 0-2 Circulatory: 0.996 (0.948-1.046); 0-2

Table C-8. Studies of long-term CO exposure and mortality.

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Krewski et al. (2009, 191193) **Period of Study:** 1983-2000 **Location:** United States	**Health Outcome:** Mortality **Study Design:** Cohort **Statistical Analyses:** Random effects Cox model **Age Groups Analyzed:** 30+ yrs **Sample Description:** 508,538 adults living in large US cities	**Averaging Time:** 1980 annual avg **Mean (SD) unit:** 1.68 (0.66) ppm **Range (min, max):** 0.19, 3.95 **Copollutant:** PM_{15}, $PM_{2.5}$, SO_2, SO_4, TSP, O_3, NO_2	**Increment:** 1ppm HR Estimate [Lower CI, Upper CI]: **Lags examined:** NR All Causes: 1.00 (0.99, 1.01) Cardiopulmonary: 1.00 (0.99, 1.01) IHD: 1.01 (0.99, 1.03) Lung Cancer: 0.99 (0.97, 1.03) All Other Causes: 0.99 (0.98, 1.01)
Author: Lipfert et al. (2000, 004087) **Period of Study:** 1975-1996 **Location:** 32 Veterans Hospitals, USA	Mortality **Health Outcome (ICD9):** Nonaccidental **Study Design:** Cohort **Study Population:** ~90,000 hypertensive male U.S. veterans **Statistical Analyses:** Staged regression **Age Groups Analyzed:** NR	**Pollutant:** CO **Averaging Time:** 95th Percentile Annual avg **Mean (SD) unit:** 1960-1974: 10.82 (5.15) ppm 1975-1981: 7.64 (2.94) ppm 1982-1988: 3.42 (0.95) ppm 1989-1996: 2.36 (0.67) ppm **Range (Min, Max):** 1960-1974: (0.94, 35.30) 1975-1981: (0.43, 22.38) 1982-1988: (0.30, 15.20) 1989-1996: (0.30, 7.10) **Copollutants; correlation:** 1960-1974: O_3: r = 0.004; NO_2: r = 0.690; SO_4^{2-}: r = 0.469 1975-1981: O_3: r = 0.109; NO_2: r = 0.249; SO_4^{2-}: r = -0.155; IP SO_4^{2-}: r = 0.356; $PM_{2.5}$: r = 0.634; $PM_{10-2.5}$: r = 0.498; PM_{15}: r = 0.626 1982-1988 O_3: r = 0.158; NO_2: r = 0.413; SO_4^{2-}: r = -0.518; IP SO_4^{2-}: r = 0.075; $PM_{2.5}$: r = 0.296; $PM_{10-2.5}$: r = 0.135 PM_{15}: r = 0.284 1989-1996 O_3: r = 0.397; NO_2: r = 0.492; SO_4^{2-}: r = -0.551	**Increment:** NR Coefficient: Baseline Model Exposure Period: up to 1975 Single Period: -0.000 Deaths, 1976-81: 0.0043 Deaths, 1982-88: -0.0002 Deaths after 1988: -0.0041 Exposure Period: 1975-81 Single Period: -0.013 Deaths, 1976-81: -0.0170 Deaths, 1982-88: -0.0217 Deaths after 1988: -0.0240 Exposure Period: 1982-88 Single Period: -0.028 Deaths, 1976-81: -0.0294 Deaths, 1982-88: -0.0484 Deaths after 1988: -0.0424 Exposure Period: 1989-96 Single Period: -0.046 Deaths, 1976-81: -0.0590 Deaths, 1982-88: -0.0581 Deaths after 1988: -0.0536 Final Model w/ Ecological Variables Exposure Period: up to 1975 Single Period: -0.001 Deaths, 1976-81: 0.0013 Deaths, 1982-88: -0.0022 Deaths after 1988: -0.0061 Exposure Period: 1975-81 Single Period: -0.008 Deaths, 1976-81: -0.0128 Deaths, 1982-88: -0.0186 Deaths after 1988: -0.0203 Exposure Period: 1982-88 Single Period: -0.009 Deaths, 1976-81: -0.0007 Deaths, 1982-88: -0.0246 Deaths after 1988: -0.0216 Exposure Period: 1989-96 Single Period: -0.009 Deaths, 1976-81: -0.0106 Deaths, 1982-88: -0.0136 Deaths after 1988: -0.0078 **Notes:** Mortality risks based on mean concentrations of pollutants less estimated background weighted by the number of subjects in each county, but The study did not present this value for each pollutant.

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Lipfert and Morris (2002, 019217) **Period of Study:** 1960-1997 **Location:** U.S. counties	Mortality **Health Outcome (ICD9):** Nonaccidental **Study Design:** Ecological/ cross sectional **Statistical Analyses:** Staged regression **Age Groups Analyzed:** 15-44 yr 45-64 yr 65-74 yr 75-84 yr ≥ 85 yr	**Pollutant:** CO **Averaging Time:** Annual avg **Mean (SD) unit:** 1960-1969: 13.81 (8.47) ppm 1970-1974:9.64 (5.63) ppm 1979-1981:5.90 (3.54) ppm 1989-1991:2.69 (1.22) ppm 1995-1997:1.72 (0.76) ppm R**ange (Min, Max):** NR **Copollutant:** TSP SO_4^{2-} SO_2 NO_2 O_3	**Increment:** NR Attributable risk (SE): Attributable Risks of mortality (1960-4) Peak CO 1960-1964, All locations Ages 15-44: 0.1299 (0.0341) Ages 45-64: 0.0340 (0.0280) Ages 65-74: -0.0058 (0.0220) Ages 75-84: 0.0121 (0.0188) Ages ≥ 85: 0.0374 (0.0225) Log Mean: 0.0365 (0.0149) Attributable Risks of mortality (1970-4) Peak CO 1970-1974, All locations Ages 15-44: 0.0553 (0.0240) Ages 45-64: 0.0181 (0.0148) Ages 65-74: -0.0146 (0.0134) Ages 75-84: -0.0128 (0.0098) Ages ≥ 85: -0.0151 (0.0093) Log Mean: 0.0038 (0.0086) Attributable Risks of mortality (1979-81) Peak CO 1979-1981, All locations Ages 15-44: 0.0054 (0.0174) Ages 45-64: -0.0060 (0.0141) Ages 65-74: -0.0251 (0.0105) Ages 75-84: -0.0331 (0.0086) Ages ≥ 85: -0.0123 (0.0079) Log Mean: -0.0183 (0.0077) Peak CO 1970-1974, All locations Ages 15-44: 0.0218 (0.0200) Ages 45-64: 0.0327 (0.0161) Ages 65-74: -0.0136 (0.0119) Ages 75-84: -0.0250 (0.0105) Ages ≥ 85: -0.0202 (0.0085) Log Mean: -0.0048 (0.0077) Peak CO 1960-1969, All locations Ages 15-44: 0.0506 (0.0478) Ages 45-64: 0.0704 (0.0337) Ages 65-74: 0.0100 (0.0211) Ages 75-84: -0.0124 (0.0143) Ages ≥ 85: 0.0187 (0.0135) Log Mean: 0.0084 (0.0149) Peak CO 1979-1981, CO 1970-1974 Ages 15-44: 0.0244 (0.0209) Ages 45-64: 0.0016 (0.0181) Ages 65-74: -0.0183 (0.0128) Ages 75-84: -0.0382 (0.0108) Ages ≥ 85: -0.0201 (0.0089) Log Mean: -0.0165 (0.0089) Peak CO 1979-1981, CO 1960-1969 Ages 15-44: 0.0748 (0.0679) Ages 45-64: 0.0844 (0.0496) Ages 65-74: 0.0144 (0.0259) Ages 75-84: -0.0158 (0.0168) Ages ≥ 85: -0.0073 (0.0170) Log Mean: 0.0109 (0.0218) Peak CO 1979-1981, CO 1960-1969 Ages 15-44: 0.1191 (0.0709) Ages 45-64: 0.1163 (0.0491) Ages 65-74: 0.0177 (0.0310) Ages 75-84: -0.0120 (0.0212) Ages ≥ 85: -0.0040 (0.0202) Log Mean: 0.0211 (0.0231) Attributable Risks of mortality (1989-91) Peak CO 1989-1991, All locations Ages 15-44: 0.0404 (0.0322) Ages 45-64: -0.0262 (0.0162) Ages 65-74: -0.0397 (0.0115) Ages 75-84: -0.0464 (0.0097) Ages ≥ 85: -0.0209 (0.0073) Log Mean: -0.0178 (0.0098) Peak CO 1979-1981, All locations

Study	Design	Concentrations	Effect Estimates (95% CI)
			Ages 15-44: 0.0522 (0.0227) Ages 45-64: -0.0047 (0.0121) Ages 65-74: -0.0165 (0.0078) Ages 75-84: -0.0268 (0.0068) Ages ≥ 85: -0.0027 (0.0055) Log Mean: -0.0020 (0.0065) Peak CO 1970-1974, All locations Ages 15-44: 0.0685 (0.0274) Ages 45-64: 0.0022 (0.0148) Ages 65-74: -0.0051 (0.0091) Ages 75-84: -0.0158 (0.0079) Ages ≥ 85: -0.0069 (0.0060) Log Mean: 0.0038 (0.0077) Peak CO 1960-1969, All locations Ages 15-44: 0.0578 (0.0713) Ages 45-64: 0.0583 (0.0347) Ages 65-74: 0.0007 (0.0174) Ages 75-84: -0.0245 (0.0130) Ages ≥ 85: -0.0138 (0.0113) Log Mean: 0.0041 (0.0176) Attributable Risks of mortality (1995-97) Peak CO 1995-1997, All locations Ages 15-44: 0.0344 (0.0256) Ages 45-64: -0.0203 (0.0198) Ages 65-74: -0.0346 (0.0146) Ages 75-84: -0.0378 (0.0161) Ages ≥ 85: -0.0283 (0.0119) Log Mean: -0.0188 (0.0103) Peak CO 1989-1991, All locations Ages 15-44: 0.0289 (0.0248) Ages 45-64: -0.0192 (0.0192) Ages 65-74: -0.0466 (0.0140) Ages 75-84: -0.0497 (0.0147) Ages ≥ 85: -0.0301 (0.0108) Log Mean: -0.0240 (0.0096) Peak CO 1979-1981, All locations Ages 15-44: 0.0336 (0.0176) Ages 45-64: -0.0037 (0.0135) Ages 65-74: -0.0298 (0.0096) Ages 75-84: -0.0301 (0.0105) Ages ≥ 85: -0.0087 (0.0078) Log Mean: -0.0094 (0.0071) Peak CO 1970-1974, All locations Ages 15-44: 0.0464 (0.0202) Ages 45-64: 0.0202 (0.0155) Ages 65-74: -0.0032 (0.0112) Ages 75-84: -0.0157 (0.0122) Ages ≥ 85: -0.0142 (0.0084) Log Mean: 0.0007 (0.0077) Peak CO 1960-1969, All locations Ages 15-44: 0.0679 (0.0441) Ages 45-64: 0.0772 (0.0405) Ages 65-74: 0.0059 (0.0173) Ages 75-84: -0.0085 (0.0213) Ages ≥ 85: -0.0158 (0.0162) Log Mean: 0.0162 (0.0149)

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Lipfert et al. (2006, 088218) **Period of Study:** 1976-2001 **Location:** 32 Veterans Hospitals, USA	Mortality **Health Outcome (ICD9):** Nonaccidental **Study Design:** Cohort **Study Population:** ~70,000 hypertensive male U.S. veterans **Statistical Analyses:** Cox proportional-hazards model **Age Groups Analyzed:** NR	**Pollutant:** CO **Averaging Time:** 95th Percentile Annual avg **Mean (SD) unit:** 1976-1981: 7.6 (2.9) ppm 1982-1988: 3.4 (9.5) ppm 1989-1996: 2.4 (0.67) ppm 1997-2001: 1.6 (5.6) ppm **Range (Min, Max):** NR **Copollutants correlation:** ln(VKTA): r = -0.06 Avg NO_2: r = 0.43 Peak O_3: r = 0.08 Peak SO_2: r = -0.05 $PM_{2.5}$: r = 0.08 SO_4^{2-}: r = -0.16 **Note:** VKTA = annual vehicle-km traveled/km^2	**Increment**: 2 ppm **Relative risk (Lower CI, Upper CI):** CO: 1.032 (0.954-1.117) CO, lnVKTA: 0.999 (0.923-1.081) CO, lnVKTA, NO_2: 1.012 (0.923-1.110) CO, lnVKTA, NO_2+O_3: 1.023 (0.939-1.115)
Author: Lipfert et al. (2006, 088756) **Period of Study:** 1997-2002 **Location:** 32 Veterans Hospitals, USA	Mortality **Health Outcome (ICD9):** Nonaccidental **Study Design:** Cohort **Study Population:** ~18,000 hypertensive male U.S. veterans **Statistical Analyses:** Cox proportional-hazards model **Age Groups Analyzed:** NR	Pollutant: CO **Averaging Time:** 95th Percentile Annual avg **Mean (SD) unit:** 1999-2001: 1.63 (0.84) ppm 1999-2001 (STN sites only): 1.73 (0.77) Range (Min, Max): 1999-2001: (0.40, 6.7) 1999-2001 (STN sites only): (0.47, 4.2) **Copollutants correlation:** ln(traffic density): r = -0.199 $PM_{2.5}$: r = 0.040; As: r = 0.148 Cr: r = 0.448; Cu: r = 0.177 Fe: r = -0.138; Pb: r = 0.420 Mn: r = 0.357; Ni: r = 0.090 Se: r = -0.110; V: r = 0.230 Zn: r = 0.472; OC: r = 0.470 EC: r = 0.234; SO_4^{2-}: r = -0.123 NO_3-: r = -0.088 $PM_{2.5}$ comp.: r = 0.133 NO_2: r = 0.418 Peak O_3: r = 0.172 Peak SO_2: r = 0.405	**Increment:** NR **β coefficient (SE); t-statistic:** -0.00000536 (0.0000324); -0.165
Author: Jerrett et al. (2003, 087380) **Period of Study:** 1982-1989 **Location:** 107 U.S. cities	Mortality **Health Outcome (ICD9):** Cardiovascular; CHD; Cerebrovascular disease **Study Design:** Cohort **Study Population:** 65,893 postmenopausal women without previous CVD **Statistical Analyses:** Cox proportional-hazards model **Age Groups Analyzed:** ≥ 30 yr	**Pollutant:** CO **Averaging Time:** Annual avg **Mean (SD) unit:** 1.56 ppm **Range (Min, Max):** (0.19, 3.95) **Copollutants correlation:** Sulfates: r = -0.07 NO_2 O_3 SO_2	**Increment:** 1 ppm Relative risk (Lower CI, Upper CI): CO: 0.98 (0.92-1.03) CO, Sulfates: 0.97 (0.92-1.03)

Study	Design	Concentrations	Effect Estimates (95% CI)
Author: Miller et al. (2007, 090130) **Period of Study:** 1994-1998 **Location:** 36 U.S. cities	Mortality **Health Outcome (ICD9):** Cardiovascular; CHD; Cerebrovascular disease **Study Design:** Cohort **Study Population:** 65,893 postmenopausal women without previous CVD **Statistical Analyses:** Cox proportional-hazards model **Age Groups Analyzed:** 50-79 yr	**Pollutant:** CO **Averaging Time:** Annual avg **Mean (SD) unit**: NR **Range (Min, Max):** NR **Copollutants:** $PM_{2.5}$ $PM_{10-2.5}$ SO_2 NO_2 O_3	**Increment:** 1 ppm **Hazard ratio (Lower CI, Upper CI):** All subjects CO: 1.0 (0.81-1.22) Only subjects with non-missing exposure data CO: 0.92 (0.71-1.21) CO, $PM_{2.5}$, $PM_{10-2.5}$, SO_2, NO_2, O_3: 0.93 (0.67, 1.30)
Author: Pope et al. (2002, 024689) **Period of Study:** 1980-1998 **Location:** All 50 States, Washington DC, and Puerto Rico (ACS-CPS-II)	Mortality **Health Outcome** (ICD9): Total (nonaccidental) (<800); lung cancer (162); cardiopulmonary (401-440, 460-519) **Study Design:** Prospective cohort **Statistical Analyses:** Cox proportional hazards model **Age Groups Analyzed:** ≥ 30 yr	**Pollutant:** CO **Averaging Time:** 24-h avg **Mean (SD) unit:** 1980: 1.7 (0.7) ppm 1982-1998: 1.1 (0.4) ppm **Range (Min, Max):** NR **Copollutant:** $PM_{2.5}$; PM_{10}; TSP; SO_2; NO_2; O_3	The study presents results for CO graphically.

References

Abe T; Tokuda Y; Ohde S; Ishimatsu S; Nakamura T; Birrer RB (2009). The relationship of short-term air pollution and weather to ED visits for asthma in Japan. Am J Emerg Med, 27: 153-159. 190536

Andersen ZJ; Loft S; Ketzel M; Stage M; Scheike T; Mette MN; Bisgaard H (2008). Ambient Air Pollution Triggers Wheezing Symptoms in Infants. Thorax, 63: 710-716. 096150

Andersen ZJ; Wahlin P; Raaschou-Nielsen O; Scheike T; Loft S (2007). Ambient particle source apportionment and daily hospital admissions among children and elderly in Copenhagen. J Expo Sci Environ Epidemiol, 17: 625-636. 093201

Anderson HR; Bremner SA; Atkinson RW; Harrison RM; Walters S (2001). Particulate matter and daily mortality and hospital admissions in the west midlands conurbation of the United Kingdom: associations with fine and coarse particles, black smoke and sulphate. Occup Environ Med, 58: 504-510. 017033

Atkinson RW; Bremner SA; Anderson HR; Strachan DP; Bland JM; Ponce de Leon A (1999). Short-term associations between emergency hospital admissions for respiratory and cardiovascular disease and outdoor air pollution in London. Arch Environ Occup Health, 54: 398-411. 007882

Baccarelli A; Zanobetti A; Martinelli I; Grillo P; Hou L; Giacomini S; Bonzini M; Lanzani G; Mannucci PM; Bertazzi PA; Schwartz J (2007). Effects of exposure to air pollution on blood coagulation. J Thromb Haemost, 5: 252-260. 090733

Ballester F; Rodriguez P; Iniguez C; Saez M; Daponte A; Galan I; Taracido M; Arribas F; Bellido J; Cirarda FB; Canada A; Guillen JJ; Guillen-Grima F; Lopez E; Perez-Hoyos S; Lertxundi A; Toro S (2006). Air pollution and cardiovascular admisisons association in Spain: results within the EMECAS project. J Epidemiol Community Health, 60: 328-336. 088746

Ballester F; Tenias JM; Perez-Hoyos S (2001). Air pollution and emergency hospital admissions for cardiovascular diseases in Valencia, Spain. J Epidemiol Community Health, 55: 57-65. 013257

Barnett AG; Williams GM; Schwartz J; Best TL; Neller AH; Petroeschevsky AL; Simpson RW (2006). The effects of air pollution on hospitalizations for cardiovascular disease in elderly people in Australian and New Zealand cities. Environ Health Perspect, 114: 1018-1023. 089770

Bedeschi E; Campari C; Candela S; Collini G; Caranci N; Frasca G; Galassi C; Francesca G; Vigotti MA (2007). Urban air pollution and respiratory emergency visits at pediatric unit, Reggio Emilia, Italy. J Toxicol Environ Health A Curr Iss, 70: 261-265. 090712

Bell ML; Ebisu K; Belanger K (2007). Ambient air pollution and low birth weight in Connecticut and Massachusetts. Environ Health Perspect, 115: 1118-24. 091059

Bell ML; Levy JK; Lin Z (2008). The effect of sandstorms and air pollution on cause-specific hospital admissions in Taipei, Taiwan. Occup Environ Med, 65: 104-111. 091268

Bell ML; Peng RD; Dominici F; Samet JM (2009). Emergency admissions for cardiovascular disease and ambient levels of carbon monoxide: Results for 126 U.S. urban counties, 1999-2005. Circulation, 120: 949-955. 193780

Bellini P; Baccini M; Biggeri A; Terracini B (2007). The meta-analysis of the Italian studies on short-term effects of air pollution (MISA): Old and new issues on the interpretation of the statistical evidences. Environmetrics, 18: 219-229. 097787

Berger A; Zareba W; Schneider A; Ruckerl R; Ibald-Mulli A; Cyrys J; Wichmann HE; Peters A (2006). Runs of ventricular and supraventricular tachycardia triggered by air pollution in patients with coronary heart disease. J Occup Environ Med, 48: 1149-58. 098702

Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at http://epa.gov/hero. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISAs) and the Integrated Risk Information System (IRIS).

Berglind N; Bellander T; Forastiere F; von Klot S; Aalto P; Elosua R; Kulmala M; Lanki T; Löwel H; Peters A; Picciotto S; Salomaa V; Stafoggia M; Sunyer J; Nyberg F (2009). Ambient air pollution and daily mortality among survivors of myocardial infarction. Epidemiology, 20: 110-118. 190068

Bhattacharyya N (2009). Air quality influences the prevalence of hay fever and sinusitis. Laryngoscope, 119: 429-433. 180154

Biggeri A; Baccini M; Bellini P; Terracini B (2005). Meta-analysis of the Italian studies of short-term effects of air pollution (MISA), 1990-1999. Int J Occup Environ Health, 11: 107-122. 087395

Botter DA; Jorgensen B; Peres AAQ (2002). A longitudinal study of mortality and air pollution for Sao Paulo, Brazil. J Expo Sci Environ Epidemiol, 12: 335-343. 011922

Braga ALF; Saldiva PHN; Pereira LAA; Menezes JJC; Conceicao GMC; Lin CA; Zanobetti A; Schwartz J; Dockery DW (2001). Health effects of air pollution exposure on children and adolescents in Sao Paulo, Brazil. Pediatr Pulmonol, 31: 106-113. 016275

Brauer M; Lencar C; Tamburic L; Koehoorn M; Demers P; Karr C (2008). A cohort study of traffic-related air pollution impacts on birth outcomes. Environ Health Perspect, 116: 680-686. 156292

Bremner SA; Anderson HR; Atkinson RW; McMichael AJ; Strachan DP; Bland JM; Bower JS (1999). Short term associations between outdoor air pollution and mortality in London 1992-4. Occup Environ Med, 56: 237-244. 007601

Briet M; Collin C; Laurent S; Tan A; Azizi M; Agharazii M; Jeunemaitre X; Alhenc-Gelas F; Boutouyrie P (2007). Endothelial function and chronic exposure to air pollution in normal male subjects. Hypertension, 50: 970-976. 093049

Burnett RT; Brook J; Dann T; Delocla C; Philips O; Cakmak S; Vincent R; Goldberg MS; Krewski D (2000). Association between particulate- and gas-phase components of urban air pollution and daily mortality in eight Canadian cities. Inhal Toxicol, 12: 15-39. 010273

Burnett RT; Smith-Doiron M; Stieb D; Cakmak S; Brook JR (1999). Effects of particulate and gaseous air pollution on cardiorespiratory hospitalizations. Arch Environ Occup Health, 54: 130-139. 017269

Burnett RT; Smith-Doiron M; Stieb D; Raizenne ME; Brook JR; Dales RE; Leech JA; Cakmak S; Krewski D (2001). Association between ozone and hospitalization for acute respiratory diseases in children less than 2 years of age. Am J Epidemiol, 153: 444-452. 093439

Burnett RT; Stieb D; Brook JR; Cakmak S; Dales R; Raizenne M; Vincent R; Dann T (2004). Associations between short-term changes in nitrogen dioxide and mortality in Canadian cities. Arch Environ Occup Health, 59: 228-236. 086247

Cakmak S; Dales RE; Judek S (2006). Respiratory health effects of air pollution gases: modification by education and income. Arch Environ Occup Health, 61: 5-10. 093272

Cakmak S; Dales RE; Vidal CB (2007). Air pollution and mortality in Chile: Susceptibility among the elderly. Environ Health Perspect, 115: 524-7. 091170

Chan C-C; Chuang K-J; Chien L-C; Chen W-J; Chang W-T (2006). Urban air pollution and emergency admissions for cerebrovascular diseases in Taipei, Taiwan. Eur Heart J, 27: 1238-1244. 090193

Chan C-C; Chuang K-J; Su T-C; Lin L-Y (2005). Association between nitrogen dioxide and heart rate variability in a susceptible population. Eur J Cardiovasc Prev Rehabil, 12: 580-586. 088988

Chang C-C; Tsai S-S; Ho S-C; Yang C-Y (2005). Air pollution and hospital admissions for cardiovascular disease in Taipei, Taiwan. Environ Res, 98: 114-119. 080086

Chen L; Jennison BL; Yang W; Omaye ST (2000). Elementary school absenteeism and air pollution. Inhal Toxicol, 12: 997-1016. 011931

Chen L; Yang W; Jennison BL; Goodrich A; Omaye ST (2002). Air pollution and birth weight in northern Nevada, 1991-1999. Inhal Toxicol, 14: 141-157. 024945

Chen P-C; Lai Y-M; Chan C-C; Hwang J-S; Yang C-Y; Wang J-D (1999). Short-term effect of ozone on the pulmonary function of children in primary school. Environ Health Perspect, 107: 921-925. 011149

Cheng M-F; Tsai S-S; Wu T-N; Chen P-S; Yang C-Y (2007). Air pollution and hospital admissions for pneumonia in a tropical city: Kaohsiung, Taiwan. J Toxicol Environ Health A Curr Iss, 70: 2021-2026. 093034

Chiu HF; Cheng MH; Yang CY (2009). Air pollution and hospital admissions for pneumonia in a subtropical city: Taipei, Taiwan. Inhal Toxicol, 21: 32-37. 190249

Cho B; Choi J; Yum YT (2000). Air pollution and hospital admissions for respiratory disease in certain areas of Korea. J Occup Health, 42: 185-191. 099051

Chock DP; Winkler SL; Chen C (2000). A study of the association between daily mortality and ambient air pollutant concentrations in Pittsburgh, Pennsylvania. J Air Waste Manag Assoc, 50: 1481-1500. 010407

Chuang KJ; Coull BA; Zanobetti A; Suh H; Schwartz J; Stone PH; Litonjua A; Speizer FE; Gold DR (2008). Particulate Air Pollution as a Risk Factor for ST-Segment Depression in Patients With Coronary Artery Disease. Circulation, 118: 1314-1320. 155731

Cifuentes LA; Vega J; Kopfer K; Lave LB (2000). Effect of the fine fraction of particulate matter versus the coarse mass and other pollutants on daily mortality in Santiago, Chile. J Air Waste Manag Assoc, 50: 1287-1298. 010351

Conceicao GMS; Miraglia SGEK; Kishi HS; Saldiva PHN; Singer JM (2001). Air pollution and child mortality: a time-series study in Sao Paulo, Brazil. Environ Health Perspect, 1093: 347-350. 016628

D'Ippoliti D; Forastiere F; Ancona C; Agabiti N; Fusco D; Michelozzi P; Perucci CA (2003). Air pollution and myocardial infarction in Rome: a case-crossover analysis. Epidemiology, 14: 528-535. 074311

Dales R (2004). Ambient carbon monoxide may influence heart rate variability in subjects with coronary artery disease. J Occup Environ Med, 46: 1217-1221. 099036

Delfino RJ: Staimer N; Tjoa T; Gillen DL; Polidori A; Arhami M; Kleinman MT; Vaziri ND; Longhurst J; Sioutas C (2009). Air pollution exposures and circulating biomarkers of effect in a susceptible population: clues to potential causal component mixtures and mechanisms. Environ Health Perspect, 117: 1232-1238. 200844

Delfino RJ; Gone H; Linn WS; Pellizzari ED; Hu Y (2003). Asthma symptoms in Hispanic children and daily ambient exposures to toxic and criteria air pollutants. Environ Health Perspect, 111: 647-656. 050460

Delfino RJ; Staimer N; Tjoa T; Polidori A; Arhami M; Gillen DL; Kleinman MT; Vaziri ND; Longhurst J; Zaldivar F; Sioutas C (2008). Circulating biomarkers of inflammation, antioxidant activity, and platelet activation are associated with primary combustion aerosols in subjects with coronary artery disease. Environ Health Perspect, 116: 898-906. 156390

De Hartog JJ; Hoek G; Peters A; Timonen KL; Ibald-Mulli A; Brunekreef B; Heinrich J; Tiittanen P; Van Wijnen JH; Kreyling W; Kulmala M; Pekkanen J (2003). Effects of fine and ultrafine particles on cardiorespiratory symptoms in elderly subjects with coronary heart disease: the ULTRA study. Am J Epidemiol, 157: 613-623. 001061

De Leon SF; Thurston GD; Ito K (2003). Contribution of respiratory disease to nonrespiratory mortality associations with air pollution. Am J Respir Crit Care Med, 167: 1117-1123. 055688

Dockery DW; Luttmann-Gibson H; Rich DQ; Link MS; Mittleman MA; Gold DR; Koutrakis P; Schwartz JD; Verrier RL (2005). Association of air pollution with increased incidence of ventricular tachyarrhythmias recorded by implanted cardioverter defibrillators. Environ Health Perspect, 113: 670-674. 078995

Dominici F; McDermott A; Daniels M; Zeger SL; Samet JM (2003). Mortality among residents of 90 cities. In: Revised analyses of time-series studies of air pollution and health. Health Effects Institute. Boston, MA. HEI Special Report. http://www.healtheffects.org/Pubs/TimeSeries.pdf. 056116

Estrella B; Estrella R; Oviedo J; Narvaez X; Reyes MT; Gutierrez M; Naumova EN (2005). Acute respiratory diseases and carboxyhemoglobin status in school children of Quito, Ecuador. Environ Health Perspect, 113: 607-11. 099124

Fairley D (1999). Daily mortality and air pollution in Santa Clara County, California: 1989-1996. Environ Health Perspect, 107: 637-641. 000896

Farhat SCL; Paulo RLP; Shimoda TM; Conceicao GMS; Lin CA; Braga ALF; Warth MPN; Saldiva PHN (2005). Effect of air pollution on pediatric respiratory emergency room visits and hospital admissions. Braz J Med Biol Res, 38: 227-235. 089461

Fischer P; Hoek G; Brunekreef B; Verhoeff A; van Wijnen J (2003). Air pollution and mortality in the Netherlands: are the elderly more at risk? Eur Respir J, 40: 34S-38S. 043739

Fischer PH; Steerenberg PA; Snelder JD; Van Loveren H; Van Amsterdam JGC (2002). Association between exhaled nitric oxide, ambient air pollution and respiratory health in school children. Int Arch Occup Environ Health, 75: 348-353. 025731

Forastiere F; Stafoggia M; Picciotto S; Bellander T; D'Ippoliti D; Lanki T; Von Klot S; Nyberg F; Paatero P; Peters A; Pekkanen J; Sunyer J; Perucci CA (2005). A case-crossover analysis of out-of-hospital coronary deaths and air pollution in Rome, Italy. Am J Respir Crit Care Med, 172: 1549-1555. 086323

Forastiere F; Stafoggia M; Tasco C; Picciotto S; Agabiti N; Cesaroni G; Perucci CA (2007). Socioeconomic status, particulate air pollution, and daily mortality: differential exposure or differential susceptibility. Am J Ind Med, 50: 208-216. 090720

Fung KY; Khan S; Krewski D; Chen Y (2006). Association between air pollution and multiple respiratory hospitalizations among the elderly in Vancouver, Canada. Inhal Toxicol, 18: 1005-1011. 089789

Fung KY; Luginaah I; Gorey KM; Webster G (2005). Air pollution and daily hospital admissions for cardiovascular diseases in Windsor, Ontario. Can J Public Health, 96: 29-33. 074322

Fusco D; Forastiere F; Michelozzi P; Spadea T; Ostro B; Arca M; Perucci CA (2001). Air pollution and hospital admissions for respiratory conditions in Rome, Italy. Eur Respir J, 17: 1143-1150. 020631

Gilboa SM; Mendola P; Olshan AF; Langlois PH; Savitz DA; Loomis D; Herring AH; Fixler DE (2005). Relation between ambient air quality and selected birth defects, seven county study, Texas, 1997-2000. Am J Epidemiol, 162: 238-252. 087892

Gold DR; Litonjua A; Schwartz J; Lovett E; Larson A; Nearing B; Allen G; Verrier M; Cherry R; Verrier R (2000). Ambient pollution and heart rate variability. Chest, 101: 1267-1273. 011432

Gold DR; Litonjua AA; Zanobetti A; Coull BA; Schwartz J; MacCallum G; Verrier RL; Nearing BD; Canner MJ; Suh H; Stone PH (2005). Air pollution and ST-segment depression in elderly subjects. Environ Health Perspect, 113: 883-887. 087558

Goldberg MS; Burnett RT; Bailar JC III; Brook J; Bonvalot Y; Tamblyn R; Singh R; Valois M-F (2001). The association between daily mortality and ambient air particle pollution in Montreal, Quebec 1 Nonaccidental mortality. Environ Res, 86: 12-25. 016548

Goldberg MS; Burnett RT; Valois M-F; Flegel K; Bailar JC III; Brook J; Vincent R; Radon K (2003). Associations between ambient air pollution and daily mortality among persons with congestive heart failure. Environ Res, 91: 8-20. 035202

Goldberg MS; Burnett RT; Yale JF; Valois MF; Brook JR (2006). Associations between ambient air pollution and daily mortality among persons with diabetes and cardiovascular disease. Environ Res, 100: 255-267. 088641

Goldberg MS; Giannetti N; Burnett RT; Mayo NE; Valois MF; Brophy JM (2008). A panel study in congestive heart failure to estimate the short-term effects from personal factors and environmental conditions on oxygen saturation and pulse rate. Occup Environ Med, 65: 659-666. 180380

Goss CH; Newsom SA; Schildcrout JS; Sheppard L; Kaufman JD (2004). Effect of ambient air pollution on pulmonary exacerbations and lung function in cystic fibrosis. Am J Respir Crit Care Med, 169: 816-821. 055624

Gouveia N; Bremner SA; Novaes HMD (2004). Association between ambient air pollution and birth weight in Sao Paulo, Brazil. J Epidemiol Community Health, 58: 11-17. 055613

Gouveia N; Fletcher T (2000). Respiratory diseases in children and outdoor air pollution in Sao Paulo, Brazil: a time series analysis. Occup Environ Med, 57: 477-483. 010436

Gouveia N; Fletcher T (2000). Time series analysis of air pollution and mortality: effects by cause, age and socioeconomic status. J Epidemiol Community Health, 54: 750-755. 012132

Guo YL; Lin Y-C; Sung F-C; Huang S-L; Ko Y-C; Lai J-S; Su H-J; Shaw C-K; Lin R-S; Dockery DW (1999). Climate, traffic-related air pollutants, and asthma prevalence in middle-school children in Taiwan. Environ Health Perspect, 107: 1001-1006. 010937

Gwynn RC; Burnett RT; Thurston GD (2000). A time-series analysis of acidic particulate matter and daily mortality and morbidity in the Buffalo, New York, region. Environ Health Perspect, 108: 125-133. 074109

Ha E-H; Hong Y-C; Lee B-E; Woo B-H; Schwartz J; Christiani DC (2001). Is air pollution a risk factor for low birth weight in Seoul? Epidemiology, 12: 643-648. 019390

Ha E-H; Lee J-T; Kim H; Hong Y-C; Lee (2003). Infant susceptibility of mortality to air pollution in Seoul, South Korea. Pediatrics, 111: 284-290. 042552

Hajat S; Anderson HR; Atkinson RW; Haines A (2002). Effects of air pollution on general practitioner consultations for upper respiratory diseases in London. Occup Environ Med, 59: 294-299. 030358

Hajat S; Armstrong B; Wilkinson P; Busby A; Dolk H (2007). Outdoor air pollution and infant mortality: Analysis of daily time-series data in 10 English cities. J Epidemiol Community Health, 61: 719-722. 093276

Hajat S; Haines A; Goubet SA; Atkinson RW; Anderson HR (1999). Association of air pollution with daily GP consultations for asthma and other lower respiratory conditions in London. Thorax, 54: 597-605. 000924

Hapcioglu B; Issever H; Kocyigit E; Disci R; Vatansever S; Ozdilli K (2006). The effect of air pollution and meteorological parameters on chronic obstructive pulmonary disease at an Istanbul hospital. Indoor Built Environ, 15: 147-153. 093263

Henrotin JB; Besancenot JP; Bejot Y; Giroud M (2007). Short-term effects of ozone air pollution on ischaemic stroke occurrence: A case-crossover analysis from a 10-year population-based study in Dijon, France. Occup Environ Med, 64: 439-445. 093270

Hinwood AL; De Klerk N; Rodriguez C; Jacoby P; Runnion T; Rye P; Landau L; Murray F; Feldwick M; Spickett J (2006). The relationship between changes in daily air pollution and hospitalizations in Perth, Australia 1992-1998: A case-crossover study. Int J Environ Health Res, 16: 27-46. 088976

Hirsch T; Weiland SK; Von Mutius E; Safeca AF; Grafe H; Csaplovics E; Duhme H; Keil U; Leupold W (1999). Inner city air pollution and respiratory health and atopy in children. Eur Respir J, 14: 669-677. 003537

Ho W-C; Hartley WR; Myers L; Lin M-H; (2007). Air pollution, weather, and associated risk factors related to asthma prevalence and attack rate. Environ Res, 104: 402-409. 093265

Hoek G; Brunekreef B; Fischer P; Van Wijnen J (2001). The association between air pollution and heart failure, arrhythmia, embolism, thrombosis, and other cardiovascular causes of death in a time series study. Epidemiology, 12: 355-357. 016550

Hoek G; Brunekreef B; Verhoeff A; Van Wijnen J; Fischer P (2000). Daily mortality and air pollution in the Netherlands. J Air Waste Manag Assoc, 50: 1380-1389. 010350

Holguin F; Tellez-Rojo MM; Hernandez M; Cortez M; Chow JC; Watson JG; Mannino D; Romieu I (2003). Air pollution and heart rate variability among the elderly in Mexico City. Epidemiology, 14: 521-527. 057326

Honda Y; Nitta H; Ono M (2003). Low level carbon monoxide and mortality of persons aged 65 or older in Tokyo, Japan 1976-1990. Eisei Kagaku, 49: 454-458. 193774

Hong Y-C; Lee J-T; Kim H; Ha E-H; Schwartz J; Christiani DC (2002). Effects of air pollutants on acute stroke mortality. Environ Health Perspect, 110: 187-191. 024690

Hong Y-C; Lee J-T; Kim H; Kwon H-J (2002). Air pollution: A new risk factor in ischemic stroke mortality. Stroke, 33: 2165-2169. 035060

Hong Y-C; Leem J-H; Ha E-H; Christiani DC (1999). PM10 exposure, gaseous pollutants, and daily mortality in Inchon, South Korea. Environ Health Perspect, 107: 873-8. 008087

Hong YC; Leem JH; Ha EH (1999). Air pollution and daily mortality in Inchon, Korea. J Korean Med Sci, 14: 239-244. 011195

Hosseinpoor AR; Forouzanfar MH; Yunesian M; Asghari F; Naieni KH; Farhood D (2005). Air pollution and hospitalization due to angina pectoris in Tehran, Iran: A time-series study. Environ Res, 99: 126-131. 087413

Huynh M; Woodruff TJ; Parker JD; Schoendorf KC (2006). Relationships between air pollution and preterm birth in California. Paediatr Perinat Epidemiol, 20: 454-461. 091240

Hwang B-F; Jaakkola JJK; Lee Y-L; Lin Y-C; Guo Y-LL (2006). Relation between air pollution and allergic rhinitis in Taiwanese schoolchildren. Respir Res, 7: 23. 088971

Hwang B-F; Lee Y-L; Lin Y-C; Jaakkola JJK; Guo YL (2005). Traffic related air pollution as a determinant of asthma among Taiwanese school children. Thorax, 60: 467-473. 089454

Hwang BF; Jaakkola JJ (2008). Ozone and other air pollutants and the risk of oral clefts. Environ Health Perspect, 116: 1411-1415. 193794

Hwang J-S; Chan C-C (2002). Effects of air pollution on daily clinic visits for lower respiratory tract illness. Am J Epidemiol, 155: 1-10. 023222

Ibald-Mulli A; Stieber J; Wichmann H-E; Koenig W; Peters A (2001). Effects of air pollution on blood pressure: A population-based approach. Am J Public Health, 91: 571-577. 016030

Ibald-Mulli A; Timonen KL; Peters A; Heinrich J; Wolke G; Lanki T; Buzorius G; Kreyling WG; De Hartog J; Hoek G; Ten Brink HM; Pekkanen J (2004). Effects of particulate air pollution on blood pressure and heart rate in subjects with cardiovascular disease: a multicenter approach. Environ Health Perspect, 112: 369-377. 087415

Ito K; Thurston GD; Silverman RA; (2007). Association between coarse particles and asthma emergency department (ED) visits in New York City. Presented at American Thoracic Society international conference 2007, San Francisco, CA. 091262

Jalaludin B; Mannes T; Morgan G; Lincoln D; Sheppeard V; Corbett S (2007). Impact of ambient air pollution on gestational age is modified by season in Sydney, Australia. Environ Health, 6: 16. 156601

Jalaludin B; Morgan G; Lincoln D; Sheppeard V; Simpson R; Corbett S (2006). Associations between ambient air pollution and daily emergency department attendances for cardiovascular disease in the elderly (65+ years), Sydney, Australia. J Expo Sci Environ Epidemiol, 16: 225-237. 189416

Jayaraman G; Nidhi (2008). Air pollution and associated respiratory morbidity in Delhi. Health Care Manag Sci, 11: 132-138. 180352

Jerrett M; Burnett RT; Willis A; Krewski D; Goldberg MS; DeLuca P; Finkelstein N (2003). Spatial analysis of the air pollution-mortality relationship in the context of ecologic confounders. J Toxicol Environ Health A Curr Iss, 66: 1735-1777. 087380

Karr C; Lumley T; Schreuder A; Davis R; Larson T; Ritz B; Kaufman J (2007). Effects of subchronic and chronic exposure to ambient air pollutants on infant bronchiolitis. Am J Epidemiol, 165: 553-560. 090719

Karr C; Lumley T; Shepherd K; Davis R; Larson T; Ritz B; Kaufman J (2006). A case-crossover study of wintertime ambient air pollution and infant bronchiolitis. Environ Health Perspect, 114: 277-281. 088751

Keatinge WR; Donaldson GC (2001). Mortality related to cold and air pollution in London after allowance for effects of associated weather patterns. Environ Res, 86: 209-216. 017063

Kettunen J; Lanki T; Tiittanen P; Aalto PP; Koskentalo T; Kulmala M; Salomaa V; Pekkanen J (2007). Associations of fine and ultrafine particulate air pollution with stroke mortality in an area of low air pollution levels. Stroke, 38: 918-922. 091242

Kim SY; O'Neill MS; Lee JT; Cho Y; Kim J; Kim H (2007). Air pollution, socioeconomic position, and emergency hospital visits for asthma in Seoul, Korea. Int Arch Occup Environ Health, 80: 701-710. 092837

Klemm RJ; Lipfert FW; Wyzga RE; Gust C (2004). Daily mortality and air pollution in Atlanta: two years of data from ARIES. Inhal Toxicol, 16 Suppl 1: 131-141. 056585

Knox EG (2008). Atmospheric pollutants and mortalities in English local authority areas. J Epidemiol Community Health, 62: 442-447. 193776

Koken PJM; Piver WT; Ye F; Elixhauser A; Olsen LM; Portier CJ (2003). Temperature, air pollution, and hospitalization for cardiovascular diseases among elderly people in Denver. Environ Health Perspect, 111: 1312-1317. 049466

Kontos AS; Fassois SD; Deli MF (1999). Short-term effects of air pollution on childhood respiratory illness in Piraeus, Greece, 1987-1992: nonparametric stochastic dynamic analysis. Environ Res, 81: 275-296. 011326

Krewski D; Jerrett M; Burnett RT; Ma R; Hughes E; Shi Y; Turner MC; Pope AC III; Thurston G; Calle EE; Thun MJ (2009). Extended follow-up and spatial analysis of the American Cancer Society study linking particulate air pollution and mortality. Health Effects Institute. Cambridge, MA. Report Nr. 140. 191193

Kwon H-J; Cho S-H; Nyberg F; Pershagen G (2001). Effects of ambient air pollution on daily mortality in a cohort of patients with congestive heart failure. Epidemiology, 12: 413-419. 016699

Lagorio S; Forastiere F; Pistelli R; Iavarone I; Michelozzi P; Fano V; Marconi A; Ziemacki G; Ostro BD (2006). Air pollution and lung function among susceptible adult subjects: a panel study. Environ Health, 5: 11. 089800

Lanki T; Pekkanen J; Aalto P; Elosua R; Berglind N; D'Ippoliti D; Kulmala M; Nyberg F; Peters A; Picciotto S; Salomaa V; Sunyer J; Tiittanen P; Von Klot S; Forastiere F; for the HEAPSS Study Group (2006). Associations of traffic-related air pollutants with hospitalisation for first acute myocardial infarction: the HEAPSS study. Occup Environ Med, 63: 844-851. 089788

Lee BE; Ha EH; Park HS; Kim YJ; Hong YC; Kim H; Lee JT (2003). Exposure to air pollution during different gestational phases contributes to risks of low birth weight. Hum Reprod, 18: 638-643. 043202

Lee I-M; Tsai S-S; Chang C-C; Ho C-K; Yang C-Y (2007). Air pollution and hospital admissions for chronic obstructive pulmonary disease in a tropical city: Kaohsiung, Taiwan. Inhal Toxicol, 19: 393-398. 090707

Lee J-T; Kim H; Song H; Hong Y-C; Cho Y-S; Shin S-Y; Hyun Y-J; Kim Y-S (2002). Air pollution and asthma among children in Seoul, Korea. Epidemiology, 13: 481-484. 034826

Lee J-T; Son J-Y; Cho Y-S (2007). A comparison of mortality related to urban air particles between periods with Asian dust days and without Asian dust days in Seoul, Korea, 2000-2004. Environ Res, 105: 409-13. 093042

Lee JT; Kim H; Cho YS; Hong YC; Ha EH; Park H (2003). Air pollution and hospital admissions for ischemic heart diseases among individuals 64+ years of age residing in Seoul, Korea. Arch Environ Health, 58: 617-623. 095552

Lee JT; Son JY; Kim H; Kim SY (2006). Effect of air pollution on asthma-related hospital admissions for children by socioeconomic status associated with area of residence. Arch Environ Occup Health, 61: 123-130. 098248

Lee Y-L; Shaw C-K; Su H-J; Lai J-S; Ko Y-C; Huang S-L; Sung F-C; Guo Y-L (2003). Climate, traffic-related air pollutants and allergic rhinitis prevalence in middle-school children in Taiwan. Eur Respir J, 21: 964-970. 049201

Leem J-H; Kaplan BM; Shim YK; Pohl HR; Gotway CA; Bullard SM; Rogers JF; Smith MM; Tylenda CA (2006). Exposures to air pollutants during pregnancy and preterm delivery. Environ Health Perspect, 114: 905-910. 089828

Levy D; Sheppard L; Checkoway H; Kaufman J; Lumley T; Koenig J; Siscovick D (2001). A case-crossover analysis of particulate matter air pollution and out-of-hospital primary cardiac arrest. Epidemiology, 12: 193-199. 017171

Liao D; Duan Y; Whitsel EA; Zheng Z-J; Heiss G; Chinchilli VM; Lin H-M (2004). Association of higher levels of ambient criteria pollutants with impaired cardiac autonomic control: a population-based study. Am J Epidemiol, 159: 768-777. 056590

Liao D; Heiss G; Chinchilli VM; Duan Y; Folsom AR; Lin HM; Salomaa V (2005). Association of criteria pollutants with plasma hemostatic/inflammatory markers: a population-based study. J Expo Sci Environ Epidemiol, 15: 319-328. 088677

Lin C-M; Li C-Y; Yang G-Y; Mao I-F (2004). Association between maternal exposure to elevated ambient sulfur dioxide during pregnancy and term low birth weight. Environ Res, 96: 41-50. 089503

Lin CA; Martins MA; Farhat SCL; Pope CA III; Conceicao GMS; Anastacio VM; Hatanaka M; Andrade WC; Hamaue WR; Bohm GM; Saldiva PHN (1999). Air pollution and respiratory illness of children in Sao Paulo, Brazil. Paediatr Perinat Epidemiol, 13: 475-488. 040437

Lin CA; Pereira LAA; Nishioka DC; Conceicao GMS; Graga ALF; Saldiva PHN (2004). Air pollution and neonatal deaths in Sao Paulo, Brazil. Braz J Med Biol Res, 37: 765-770. 095787

Lin M; Chen Y; Burnett RT; Villeneuve PJ; Krewski D (2003). Effect of short-term exposure to gaseous pollution on asthma hospitalisation in children: a bi-directional case-crossover analysis. J Epidemiol Community Health, 57: 50-55. 042549

Lin M; Chen Y; Villeneuve PJ; Burnett RT; Lemyre L; Hertzman C; McGrail KM; Krewski D (2004). Gaseous air pollutants and asthma hospitalization of children with low household income in Vancouver, British Columbia, Canada. Am J Epidemiol, 159: 294-303. 055600

Lin M; Stieb DM; Chen Y (2005). Coarse particulate matter and hospitalization for respiratory infections in children younger than 15 years in Toronto: a case-crossover analysis. Pediatrics, 116: 235-240. 087828

Linn WS; Szlachcic Y; Gong H Jr; Kinney PL; Berhane KT (2000). Air pollution and daily hospital admissions in metropolitan Los Angeles. Environ Health Perspect, 108: 427-434. 002839

Lipfert FW; Baty JD; Miller JP; Wyzga RE (2006). PM2.5 constituents and related air quality variables as predictors of survival in a cohort of U.S. military veterans. Inhal Toxicol, 18: 645-657. 088756

Lipfert FW; Morris SC (2002). Temporal and spacial relationships between age-specific mortality and ambient air quality in the United States: preliminary results for counties, 1960-97. Occup Environ Med, 59: 156-174. 019217

Lipfert FW; Morris SC; Wyzga RE (2000). Daily mortality in the Philadelphia metropolitan area and size-classified particulate matter. J Air Waste Manag Assoc, 50: 1501-1513. 004088

Lipfert FW; Perry HM Jr; Miller JP; Baty JD; Wyzga RE; Carmody SE (2000). The Washington University-EPRI veterans' cohort mortality study: preliminary results. Inhal Toxicol, 4: 41-73. 004087

Lipfert FW; Wyzga RE; Baty JD; Miller JP (2006). Traffic density as a surrogate measure of environmental exposures in studies of air pollution health effects: long-term mortality in a cohort of US veterans. Atmos Environ, 40: 154-169. 088218

Lippmann M; Ito K; Nadas A; Burnett RT (2000). Association of particulate matter components with daily mortality and morbidity in urban populations. Health Effects Institute. Cambridge, MA. 011938

Liu S; Krewski D; Shi Y; Chen Y; Burnett R (2007). Association between maternal exposure to ambient air pollutants during pregnancy and fetal growth restriction. J Expo Sci Environ Epidemiol, 17: 426-432. 090429

Liu S; Krewski D; Shi Y; Chen Y; Burnett RT (2003). Association between gaseous ambient air pollutants and adverse pregnancy outcomes in Vancouver, Canada. Environ Health Perspect, 111: 1773-1778. 089548

Ljungman P; Bellander T; Schneider A; Breitner S; Forastiere F; Hampel R; Illig T; Jacquemin B; Katsouyanni K; von Klot S (2009). Modification of the interleukin-6 response to air pollution by interleukin-6 and fibrinogen polymorphisms. Environ Health Perspect, 117: 1373-1379. 191983

Luginaah IN; Fung KY; Gorey KM; Webster G; Wills C (2005). Association of ambient air pollution with respiratory hospitalization in a government designated "area of concern": the case of Windsor, Ontario. Environ Health Perspect, 113: 290-296. 057327

Maheswaran R; Haining RP; Brindley P; Law J; Pearson T; Fryers PR; Wise S; Campbell MJ (2005). Outdoor air pollution and stroke in Sheffield, United Kingdom: A small-area level geographical study. Stroke, 36: 239-243. 088683

Maheswaran R; Haining RP; Brindley P; Law J; Pearson T; Fryers PR; Wise S; Campbell MJ (2005). Outdoor air pollution, mortality, and hospital admissions from coronary heart disease in Sheffield, UK: A small-area level ecological study. Eur Heart J, 26: 2543-2549. 090769

Maisonet M; Bush TJ; Correa A; Jaakkola JJK (2001). Relation between ambient air pollution and low birth weight in the northeastern United States. Environ Health Perspect, 1093: 351-356. 016624

Mann JK; Tager IB; Lurmann F; Segal M; Quesenberry CP Jr; Lugg MM; Shan J; Van den Eeden SK (2002). Air pollution and hospital admissions for ischemic heart disease in persons with congestive heart failure or arrhythmia. Environ Health Perspect, 110: 1247-1252. 036723

Mannes T; Jalaludin B; Morgan G; Lincoln D; Sheppeard V; Corbett S (2005). Impact of ambient air pollution on birth weight in Sydney, Australia. Occup Environ Med, 62: 524-530. 087895

Mar TF; Norris GA; Koenig JQ; Larson TV (2000). Associations between air pollution and mortality in Phoenix, 1995-1997. Environ Health Perspect, 108: 347-353. 001760

Martins LC; Latorre MRDO; Saldiva PHN; Braga ALF (2002). Air pollution and emergency room visits due to chronic lower respiratory diseases in the elderly: An ecological time-series study in Sao Paulo, Brazil. J Occup Environ Med, 44: 622-627. 035059

Masjedi MR; Jamaati HR; Dokouhaki P; Ahmadzadeh Z; Taheri SA; Bigdeli M; Izadi S; Rostamian A; Aagin K; Ghavam SM (2003). The effects of air pollution on acute respiratory conditions. Respirology, 8: 213-230. 052100

McGowan JA; Hider PN; Chacko E; Town GI (2002). Particulate air pollution and hospital admissions in Christchurch, New Zealand. Aust N Z J Public Health, 26: 23-29. 030325

Medeiros A; Gouveia N (2005). Relacao entre baixo peso ao nascer e a poluicao do ar no Municipio de Sao Paulo [Relationship between low birthweight and air pollution in the city of Sao Paulo, Brazil]. Rev Saude Publica, 39: 965-972. 089824

Meng YY; Wilhelm M; Rull RP; English P; Ritz B (2007). Traffic and outdoor air pollution levels near residences and poorly controlled asthma in adults. Ann Allergy Asthma Immunol, 98: 455-463. 093275

Metzger KB; Klein M; Flanders WD; Peel JL; Mulholland JA; Langberg JJ; Tolbert PE (2007). Ambient air pollution and cardiac arrhythmias in patients with implantable defibrillators. Epidemiology, 18: 585-592. 092856

Metzger KB; Tolbert PE; Klein M; Peel JL; Flanders WD; Todd KH; Mulholland JA; Ryan PB; Frumkin H (2004). Ambient air pollution and cardiovascular emergency department visits. Epidemiology, 15: 46-56. 044222

Migliaretti G; Dalmasso P; Gregori D (2007). Air pollution effects on the respiratory health of the resident adult population in Turin, Italy. Int J Environ Health Res, 17: 369-379. 193772

Miller KA; Siscovick DS; Sheppard L; Shepherd K; Sullivan JH; Anderson GL; Kaufman JD (2007). Long-term exposure to air pollution and incidence of cardiovascular events in women. N Engl J Med, 356: 447-458. 090130

Min JY; Paek D; Cho SI; Min KB (2009). Exposure to environmental carbon monoxide may have a greater negative effect on cardiac autonomic function in people with metabolic syndrome. Sci Total Environ, 407: 4807-4811. 199514

Moolgavkar SH (2000). Air pollution and daily mortality in three US counties. Environ Health Perspect, 108: 777-784. 012054

Moolgavkar SH (2000). Air pollution and hospital admissions for chronic obstructive pulmonary disease in three metropolitan areas in the United States. Inhal Toxicol, 12: 75-90. 010274

Moolgavkar SH (2003). Air pollution and daily deaths and hospital admissions in Los Angeles and Cook counties. Health Effects Institute. Boston, MA. 042864

Moolgavkar SH (2003). Air pollution and daily mortality in two US counties: season-specific analyses and exposure-response relationships. Inhal Toxicol, 15: 877-907. 051316

Moon JS; Kim YS; Kim JH; Son BS; Kim DS; Yang W (2009). Respiratory health effects among schoolchildren and their relationship to air pollutants in Korea. Int J Environ Health Res, 19: 31-48. 190297

Mortimer K; Neugebauer R; Lurmann F; Alcorn S; Balmes J; Tager I (2008). Air pollution and pulmonary function in asthmatic children: Effects of prenatal and lifetime exposures. Epidemiology, 19: 550-557. 122163

Mortimer K; Neugebauer R; Lurmann F; Alcorn S; Balmes J; Tager I (2008). Early-Lifetime exposure to air pollution and allergic sensitization in children with asthma. J Asthma, 45: 874-881. 187280

Nautiyal J 3rd; Garg ML; Kumar MS; Khan AA; Thakur JS; Kumar R (2007). Air pollution and cardiovascular health in Mandi-Gobindgarh, Punjab, India - a pilot study. Int J Environ Health Res, 4: 268-82. 190301

Neidell MJ (2004). Air pollution, health, and socio-economic status: The effect of outdoor air quality on childhood asthma. J Health Econ, 23: 1209-1236. 057330

Nkwocha EE; Egejuru RO (2008). Effects of industrial air pollution on the respiratory health of children. Int J Environ Sci Tech, 5: 509-516. 190304

Norris G; Young-Pong SN; Koenig JQ; Larson TV; Sheppard L; Stout JW (1999). An association between fine particles and asthma emergency department visits for children in Seattle. Environ Health Perspect, 107: 489-493. 040774

O'Connor GT; Neas L; Vaughn B; Kattan M; Mitchell H; Crain EF; Evans R 3rd; Gruchalla R; Morgan W; Stout J; Adams GK; Lippmann M (2008). Acute respiratory health effects of air pollution on children with asthma in US inner cities. J Allergy Clin Immunol, 121: 1133-1139. 156818

Ostro BD; Hurley S; Lipsett MJ (1999). Air pollution and daily mortality in the Coachella Valley, California: A study of PM10 dominated by coarse particles. Environ Res, 81: 231-238. 006610

Park H; Lee B; Ha E-H; Lee J-T; Kim H; Hong Y-C (2002). Association of air pollution with school absenteeism due to illness. Arch Pediatr Adolesc Med, 156: 1235-1239. 093798

Park JW; Lim YH; Kyung SY; An CH; Lee SP; Jeong SH; Ju S-Y (2005). Effects of ambient particulate matter on peak expiratory flow rates and respiratory symptoms of asthmatics during Asian dust periods in Korea. Respirology, 10: 470-476. 088673

Park SK; O'Neill MS; Vokonas PS; Sparrow D; Schwartz J (2005). Effects of air pollution on heart rate variability: The VA normative aging study. Environ Health Perspect, 113: 304-309. 057331

Parker JD; Woodruff TJ; Basu R; Schoendorf KC (2005). Air pollution and birth weight among term infants in California. Pediatrics, 115: 121-128. 087462

Peel JL; Metzger KB; Klein M; Flanders WD; Mulholland JA; Tolbert PE (2007). Ambient air pollution and cardiovascular emergency department visits in potentially sensitive groups. Am J Epidemiol, 165: 625-633. 090442

Peel JL; Tolbert PE; Klein M; Metzger KB; Flanders WD; Knox T; Mulholland JA; Ryan PB; Frumkin H (2005). Ambient air pollution and respiratory emergency department visits. Epidemiology, 16: 164-174. 056305

Pekkanen J; Brunner EJ; Anderson HR; Tiittanen P; Atkinson RW (2000). Daily concentrations of air pollution and plasma fibrinogen in London. Occup Environ Med, 57: 818-822. 013250

Penttinen P; Tiittanen P; Pekkanen J (2004). Mortality and air pollution in metropolitan Helsinki, 1988-1996. Scand J Work Environ Health, 2: 19-27. 087432

Penttinen P; Timonen KL; Tiittanen P; Mirme A; Ruuskanen J; Pekkanen J (2001). Ultrafine particles in urban air and respiratory health among adult asthmatics. Eur Respir J, 17: 428-435. 030335

Pereira Filho MA; Pereira LAA; Arbex FF; Arbex M; Conceição GM; Santos UP; Lopes AC; Saldiva PHN; Braga ALF; Cendon S (2008). Effect of air pollution on diabetes and cardiovascular diseases in São Paulo, Brazil. Braz J Med Biol Res, 41: 526-532. 190260

Peters A; Dockery DW; Muller JE; Mittleman MA (2001). Increased particulate air pollution and the triggering of myocardial infarction. Circulation, 103: 2810-2815. 016546

Peters A; Liu E; Verrier RL; Schwartz J; Gold DR; Mittleman M; Baliff J; Oh JA; Allen G; Monahan K; Dockery DW (2000). Air pollution and incidence of cardiac arrhythmia. Epidemiology, 11: 11-17. 011347

Peters A; Perz S; Doring A; Stieber J; Koenig W; Wichmann H-E (1999). Increases in heart rate during an air pollution episode. Am J Epidemiol, 150: 1094-1098. 011554

Peters A; Skorkovsky J; Kotesovec F; Brynda J; Spix C; Wichmann HE; Heinrich J (2000). Associations between mortality and air pollution in central Europe. Environ Health Perspect, 108: 283-287. 001756

Pope CA III; Burnett RT; Thun MJ; Calle EE; Krewski D; Ito K; Thurston GD (2002). Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. JAMA, 287: 1132-1141. 024689

Rabinovitch N; Zhang LN; Murphy JR; Vedal S; Dutton SJ; Gelfand EW (2004). Effects of wintertime ambient air pollutants on asthma exacerbations in urban minority children with moderate to severe disease. J Allergy Clin Immunol, 114: 1131-1137. 096753

Rainham DGC; Smoyer-Tomic KE (2003). The role of air pollution in the relationship between a heat stress index and human mortality in Toronto. Environ Res, 93: 9-19. 053202

Ranzi A; Gambini M; Spattini A; Galassi C; Sesti D; Bedeschi M; Messori A; Baroni A; Cavagni G; Lauriola P (2004). Air pollution and respiratory status in asthmatic children: Hints for a locally based preventive strategy AIRE study. Eur J Epidemiol, 19: 567-576. 089500

Rich DQ; Kim MH; Turner JR; Mittleman MA; Schwartz J; Catalano PJ; Dockery DW (2006). Association of ventricular arrhythmias detected by implantable cardioverter defibrillator and ambient air pollutants in the St Louis, Missouri metropolitan area. Occup Environ Med, 63: 591-596. 089814

Rich DQ; Mittleman MA; Link MS; Schwartz J; Luttmann-Gibson H; Catalano PJ; Speizer FE; Gold DR; Dockery DW (2006). Increased risk of paroxysmal atrial fibrillation episodes associated with acute increases in ambient air pollution. Environ Health Perspect, 114: 120-123. 088427

Rich DQ; Schwartz J; Mittleman MA; Link M; Luttmann-Gibson H; Catalano PJ; Speizer FE; Dockery DW (2005). Association of short-term ambient air pollution concentrations and ventricular arrhythmias. Am J Epidemiol, 161: 1123-1132. 079620

Rich KE; Petkau J; Vedal S; Brauer M (2004). A case-crossover analysis of particulate air pollution and cardiac arrhythmia in patients with implantable cardioverter defibrillators. Inhal Toxicol, 16: 363-372. 055631

Riojas-Rodriguez H; Escamilla-Cejudo JA; Gonzalez-Hermosillo JA; Tellez-Rojo MM; Vallejo M; Santos-Burgoa C; Rojas-Bracho L (2006). Personal PM2.5 and CO exposures and heart rate variability in subjects with known ischemic heart disease in Mexico City. J Expo Sci Environ Epidemiol, 16: 131-137. 156913

Ritz B; Wilhelm M; Hoggatt KJ; Ghosh JK (2007). Ambient air pollution and preterm birth in the environment and pregnancy outcomes study at the University of California, Los Angeles. Am J Epidemiol, 166: 1045-1052. 096146

Ritz B; Wilhelm M; Zhao Y (2006). Air pollution and infant death in southern California, 1989-2000. Pediatrics, 118: 493-502. 089819

Ritz B; Yu F; Chapa G; Fruin S (2000). Effect of air pollution on preterm birth among children born in Southern California between 1989 and 1993. Epidemiology, 11: 502-511. 012068

Ritz B; Yu F; Fruin S; Chapa G; Shaw GM; Harris JA (2002). Ambient air pollution and risk of birth defects in Southern California. Am J Epidemiol, 155: 17-25. 023227

Rodriguez C; Tonkin R; Heyworth J; Kusel M; De Klerk N; Sly PD; Franklin P; Runnion T; Blockley A; Landau L; Hinwood AL (2007). The relationship between outdoor air quality and respiratory symptoms in young children. Int J Environ Health Res, 17: 351-360 . 092842

Roemer WH; Van Wijnen JH (2001). Daily mortality and air pollution along busy streets in Amsterdam, 1987-1998. Epidemiology, 12: 649-653. 019391

Rosenlund M; Bellander T; Nordquist T; Alfredsson L (2009). Traffic-generated air pollution and myocardial infarction. Epidemiology, 20: 265-71. 190309

Rosenlund M; Berglind N; Pershagen G; Hallqvist J; Jonson T; Bellander T (2006). Long-term exposure to urban air pollution and myocardial infarction. Epidemiology, 17: 383-390. 089796

Ruckerl R; Greven S; Ljungman P; Aalto P; Antoniades C; Bellander T; Berglind N; Chrysohoou C; Forastiere F; Jacquemin B; von Klot S; Koenig W; Kuchenhoff H; Lanki T; Pekkanen J; Perucci CA; Schneider A; Sunyer J; Peters A (2007). Air pollution and inflammation (interleukin-6, C-reactive protein, fibrinogen) in myocardial infarction survivors. Environ Health Perspect, 115: 1072-1080. 156931

Ruckerl R; Ibald-Mulli A; Koenig WSchneider A; Woelke G; Cyrys J; Heinrich J; Marder V; Frampton M; Wichmann HE; Peters A (2006). Air pollution and markers of inflammation and coagulation in patients with coronary heart disease. Environ Health Perspect, 173: 432-441. 088754

Rudez G; Janssen NA; Kilinc E; Leebeek FW; Gerlofs-Nijland ME; Spronk HM; ten Cate H; Cassee FR; de Maat MP (2009). Effects of ambient air pollution on hemostasis and inflammation. Environ Health Perspect, 117: 995-1001. 193783

Salam MT; Millstein J; Li Y-F; Lurmann FW; Margolis HG; Gilliland FD (2005). Birth outcomes and prenatal exposure to ozone, carbon monoxide, and particulate matter: results from the Children's Health Study. Environ Health Perspect, 113: 1638-1644. 087885

Samet JM; Dominici F; Curriero FC; Coursac I; Zeger SL (2000). Fine particulate air pollution and mortality in 20 US cities, 1987-1994. N Engl J Med, 343: 1742-1749. 013132

Samoli E; Touloumi G; Schwartz J; Anderson HR; Schindler C; Forsberg B; Vigotti MA; Vonk J; Kosnik M; Skorkovsky J; Katsouyanni K (2007). Short-term effects of carbon monoxide on mortality: An analysis within the APHEA project. Environ Health Perspect, 115: 1578-1583. 098420

Sari I; Zengin S; Ozer O; Davutoglu V; Yildirim C; Aksoy M (2008). Chronic carbon monoxide exposure increases electrocardiographic P-wave and QT dispersion. Inhal Toxicol, 20: 879-84. 190315

Sarnat SE; Suh HH; Coull BA; Schwartz J; Stone PH; Gold DR (2006). Ambient particulate air pollution and cardiac arrhythmia in a panel of older adults in Steubenville, Ohio. Occup Environ Med, 63: 700-706. 090489

Sauerzapf V; Jones AP; Cross J (2009). Environmental factors and hospitalisation for chronic obstructive pulmonary disease in a rural county of England. J Epidemiol Community Health, 63: 324-328. 180082

Schildcrout JS; Sheppard L; Lumley T; Slaughter JC; Koenig JQ; Shapiro GG (2006). Ambient air pollution and asthma exacerbations in children: An eight-city analysis. Am J Epidemiol, 164: 505-517. 089812

Schwartz J; Litonjua A; Suh H; Verrier M; Zanobetti A; Syring M; Nearing B; Verrier R; Stone P; MacCallum G; Speizer FE; Gold DR (2005). Traffic related pollution and heart rate variability in a panel of elderly subjects. Thorax, 60: 455-461. 074317

Schwartz J; Norris G; Larson T; Sheppard L; Claiborne C; Koenig J (1999). Episodes of high coarse particle concentrations are not associated with increased mortality. Environ Health Perspect, 107: 339-342. 017915

Sharovsky R; Cesar LA; Ramires JA (2004). Temperature, air pollution, and mortality from myocardial infarction in Sao Paulo, Brazil. Braz J Med Biol Res, 37: 1651-1657. 156976

Sheppard L; Levy D; Norris G; Larson TV; Koenig JQ (1999). Effects of ambient air pollution on nonelderly asthma hospital admissions in Seattle, Washington, 1987-1994. Epidemiology, 10: 23-30. 086921

Silkoff PE; Zhang L; Dutton S; Langmack EL; Vedal S; Murphy J; Make B (2005). Winter air pollution and disease parameters in advanced chronic obstructive pulmonary disease panels residing in Denver, Colorado. J Allergy Clin Immunol, 115: 337-344. 087471

Singh V; Khandelwal R; Gupta AB (2003). Effect of air pollution on peak expiratory flow rate variability. J Asthma, 40: 81-86. 052686

Slaughter JC; Kim E; Sheppard L; Sullivan JH; Larson TV; Claiborn C (2005). Association between particulate matter and emergency room visits, hospital admissions and mortality in Spokane, Washington. J Expo Sci Environ Epidemiol, 15: 153-159. 073854

Slaughter JC; Lumley T; Sheppard L; Koenig JQ; Shapiro GG (2003). Effects of ambient air pollution on symptom severity and medication use in children with asthma. Ann Allergy Asthma Immunol, 91: 346-353. 086294

Sole D; Camelo-Nunes IC; Wandalsen GF; Pastorino AC; Jacob CMA; Gonzalez C; Wandalsen NF; Rosario Filho NA; Fischer GB; Naspitz CK (2007). Prevalence of symptoms of asthma, rhinitis, and atopic eczema in Brazilian adolescents related to exposure to gaseous air pollutants and socioeconomic status. J Investig Allergol Clin Immunol, 17: 6-13. 090706

Son JY; Cho YS; Lee JT (2008). Effects of air pollution on postneonatal infant mortality among firstborn infants in Seoul, Korea: case-crossover and time-series analyses. Arch Environ Occup Health, 63: 108-13. 190323

Steerenberg PA; Nierkens S; Fischer PH; Van Loveren H; Opperhuizen A; Vos JG; Van Amsterdam JG (2001). Traffic-related air pollution affects peak expiratory flow, exhaled nitric oxide, and inflammatory nasal markers. Arch Environ Occup Health, 56: 167-174. 017157

Steinvil A; Kordova-Biezuner L; Shapira I; Berliner S; Rogowski O (2008). Short-term exposure to air pollution and inflammation-sensitive biomarkers. Environ Res, 106: 51-61. 188893

Stieb DM; Beveridge RC; Brook JR; Smith-Doiron M; Burnett RT; Dales RE; Beaulieu S; Judek S; Mamedov A (2000). Air pollution, aeroallergens and cardiorespiratory emergency department visits in Saint John, Canada. J Expo Sci Environ Epidemiol, 10: 461-477. 011675

Stieb DM; Judek S; Burnett RT (2003). Meta-analysis of time-series studies of air pollution and mortality: Update in relation to the use of generalized additive models. J Air Waste Manag Assoc, 53: 258-261. 056908

Stölzel M; Breitner S; Cyrys J; Pitz M; Wolke G; Kreyling W; Heinrich J; Wichmann H-E; Peters A (2007). Daily mortality and particulate matter in different size classes in Erfurt, Germany. J Expo Sci Environ Epidemiol, 17: 458-467. 091374

Strickland MJ; Klein M; Correa A; Reller MD; Mahle WT; Riehle-Colarusso TJ; Botto LD; Flanders WD; Mulholland JA; Siffel C; Marcus M; Tolbert PE (2009). Ambient air pollution and cardiovascular malformations in Atlanta, Georgia, 1986-2003. Am J Epidemiol, 169: 1004-14. 190324

Sullivan J; Ishikawa N; Sheppard L; Siscovick D; Checkoway H; Kaufman J (2003). Exposure to ambient fine particulate matter and primary cardiac arrest among persons with and without clinically recognized heart disease. Am J Epidemiol, 157: 501-509. 043156

Sun HL; Chou MC; Lue KH (2006). The relationship of air pollution to ED visits for asthma differ between children and adults. Am J Emerg Med, 24: 709-713. 090768

Sunyer J; Basagana X (2001). Particles, and not gases, are associated with the risk of death in patients with chronic obstructive pulmonary disease. Int J Epidemiol, 30: 1138-1140. 019367

Sunyer J; Basagana X; Belmonte J; Anto JM (2002). Effect of nitrogen dioxide and ozone on the risk of dying in patients with severe asthma. Thorax, 57: 687-693. 034835

Symons JM; Wang L; Guallar E; Howell E; Dominici F; Schwab M; Ange BA; Samet J; Ondov J; Harrison D; Geyh A (2006). A case-crossover study of fine particulate matter air pollution and onset of congestive heart failure symptom exacerbation leading to hospitalization. Am J Epidemiol, 164: 421-433. 091258

Szyszkowicz M (2007). Air pollution and emergency department visits for ischemic heart disease in Montreal, Canada. Int J Occup Med Environ Health, 20: 167-173. 193793

Tarkiainen TH; Timonen KL; Vanninen EJ; Alm S; Hartikainen JEK; Pekkanen J (2003). Effect of acute carbon monoxide exposure on heart rate variability in patients with coronary artery disease. Clin Physiol Funct Imaging, 23: 98-102. 053625

Tenias JM; Ballester F; Perez-Hoyos S; Rivera ML (2002). Air pollution and hospital emergency room admissions for chronic obstructive pulmonary disease in Valencia, Spain. Arch Environ Occup Health, 57: 41-47. 026077

Thompson AJ; Shields MD; Patterson CC (2001). Acute asthma exacerbations and air pollutants in children living in Belfast, Northern Ireland. Arch Environ Occup Health, 56: 234-241. 073513

Timonen KL; Pekkanen J; Tiittanen P; Salonen RO (2002). Effects of air pollution on changes in lung function induced by exercise in children with chronic respiratory symptoms. Occup Environ Med, 59: 129-134. 025653

Timonen KL; Vanninen E; De Hartog J; Ibald-Mulli A; Brunekreef B; Gold DR; Henrich J; Hoek G; Lanki T; Peters A; Tarkiainen T; Tiittanen P; Kreyling W; Pekkanen J (2006). Effects of ultrafine and fine particulate and gaseous air pollution on cardiac autonomic control in subjects with coronary artery disease: The ULTRA study. J Expo Sci Environ Epidemiol, 16: 332-341. 088747

Tolbert PE; Klein M; Peel JL; Sarnat SE; Sarnat JA (2007). Multipollutant modeling issues in a study of ambient air quality and emergency department visits in Atlanta. J Expo Sci Environ Epidemiol, 17: S29-S35. 090316

Trapasso LM; Keith L (1999). Relationships between selected meteorological/pollution parameters and hospital admissions for asthma in south central kentucky . J Ky Acad Sci, 60: 73-77. 180127

Tsai S-S; Chen C-C; Hsieh H-J; Chang C-C; Yang C-Y (2006). Air pollution and postneonatal mortality in a tropical city: Kaohsiung, Taiwan. Inhal Toxicol, 18: 185-189. 090709

Tsai S-S; Cheng M-H; Chiu H-F; Wu T-N; Yang C-Y (2006). Air pollution and hospital admissions for asthma in a tropical city: Kaohsiung, Taiwan. Inhal Toxicol, 18: 549-554. 089768

Tsai S-S; Goggins WB; Chiu H-F; Yang C-Y (2003). Evidence for an association between air pollution and daily stroke admissions in Kaohsiung, Taiwan. Stroke, 34: 2612-2616. 080133

Tsai S-S; Huang C-H; Goggins WB; Wu T-N; Yang C-Y (2003). Relationship between air pollution and daily mortality in a tropical city: Kaohsiung, Taiwan. J Toxicol Environ Health A Curr Iss, 66: 1341-1349. 050480

Vedal S; Brauer M; White R; Petkau J (2003). Air pollution and daily mortality in a city with low levels of pollution. Environ Health Perspect, 111: 45-51. 039044

Vedal S; Rich K; Brauer M; White R; Petkau J (2004). Air pollution and cardiac arrhythmias in patients with implantable cardiovascular defibrillators. Inhal Toxicol, 16: 353-362. 055630

Vigotti MA; Chiaverini F; Biagiola P; Rossi G (2007). Urban air pollution and emergency visits for respiratory complaints in Pisa, Italy. J Toxicol Environ Health A Curr Iss, 70: 266-269. 090711

Villeneuve PJ; Burnett RT; Shi Y; Krewski D; Goldberg MS; Hertzman C; Chen Y; Brook J (2003). A time-series study of air pollution, socioeconomic status, and mortality in Vancouver, Canada. J Expo Sci Environ Epidemiol, 13: 427-435. 055051

Villeneuve PJ; Chen L; Stieb D; Rowe BH (2006). Associations between outdoor air pollution and emergency department visits for stroke in Edmonton, Canada. Eur J Epidemiol, 21: 689-700. 090191

Villeneuve PJ; Doiron M-S; Stieb D; Dales R; Burnett RT; Dugandzic R (2006). Is outdoor air pollution associated with physician visits for allergic rhinitis among the elderly in Toronto, Canada? Allergy, 61: 750-758. 091179

Von Klot S; Wolke G; Tuch T; Heinrich J; Dockery DW; Schwartz J; Kreyling WG; Wichmann HE; Peters A (2002). Increased asthma medication use in association with ambient fine and ultrafine particles. Eur Respir J, 20: 691-702. 034706

Von Klot S; Peters A; Aalto P; Bellander T; Berglind N; D'Ippoliti D; Elosua R; Hormann A; Kulmala M; Lanki T; Lowel H; Pekkanen J; Picciotto S; Sunyer J; Forastiere F; Health Effects of Particles on Susceptible Subpopulations (HEAPSS) Study Group (2005). Ambient air pollution is associated with increased risk of hospital cardiac readmissions of myocardial infarction survivors in five European cities. Circulation, 112: 3073-3079. 088070

Wang Q; Liu Y; Pan X (2008). Atmosphere pollutants and mortality rate of respiratory diseases in Beijing. Sci Total Environ, 391: 143-148. 179974

Wang T-N; Ko Y-C; Chao Y-Y; Huang C-C; Lin R-S (1999). Association between indoor and outdoor air pollution and adolescent asthma from 1995 to 1996 in Taiwan. Environ Res, 81: 239-247. 008105

Wellenius GA; Bateson TF; Mittleman MA; Schwartz J (2005). Particulate air pollution and the rate of hospitalization for congestive heart failure among medicare beneficiaries in Pittsburgh, Pennsylvania. Am J Epidemiol, 161: 1030-1036. 087483

Wellenius GA; Schwartz J; Mittleman MA (2005). Air pollution and hospital admissions for ischemic and hemorrhagic stroke among medicare beneficiaries. Stroke, 36: 2549-2553. 088685

Wellenius GA; Yeh GY; Coull BA; Suh HH; Phillips RS; Mittleman MA (2007). Effects of ambient air pollution on functional status in patients with chronic congestive heart failure: a repeated-measures study. Environ Health, 6: 1-7. 092830

Wheeler A; Zanobetti A; Gold DR; Schwartz J; Stone P; Suh HH (2006). The relationship between ambient air pollution and heart rate variability differs for individuals with heart and pulmonary disease. Environ Health Perspect, 114: 560-566. 088453

Wichmann H-E; Spix C; Tuch T; Wolke G; Peters A; Heinrich J; Kreyling WG; Heyder J (2000). Daily mortality and fine and ultrafine particles in Erfurt, Germany Part I: role of particle number and particle mass. Health Effects Institute. Boston, MA. 013912

Wilhelm M; Meng YY; Rull RP; English P; Balmes J; Ritz B (2008). Environmental public health tracking of childhood asthma using California health interview survey, traffic, and outdoor air pollution data. Environ Health Perspect, 116: 1254-1260. 191912

Wilhelm M; Ritz B (2005). Local variations in CO and particulate air pollution and adverse birth outcomes in Los Angeles County, California, USA. Environ Health Perspect, 113: 1212-1221. 088668

Woodruff TJ; Darrow LA; Parker JD (2008). Air pollution and postneonatal infant mortality in the United States, 1999-2002. Environ Health Perspect, 116: 110-115. 098386

Xirasagar S; Lin HC; Liu TC (2006). Seasonality in pediatric asthma admissions: the role of climate and environmental factors. Eur J Pediatr, 165: 747-752. 093267

Yang C-Y; Chang C-C; Chuang H-Y; Tsai S-S; Wu T-N; Ho C-K (2004). Relationship between air pollution and daily mortality in a subtropical city: Taipei, Taiwan. Environ Int, 30: 519-523. 055603

Yang C-Y; Chen Y-S; Yang C-H; Ho S-C (2004). Relationship between ambient air pollution and hospital admissions for cardiovascular diseases in Kaohsiung, Taiwan. J Toxicol Environ Health A Curr Iss, 67: 483-493. 094376

Yang CY (2008). Air pollution and hospital admissions for congestive heart failure in a subtropical city: Taipei, Taiwan. J Toxicol Environ Health A Curr Iss, 71: 1085-1090. 157160

Yang CY; Chen CC; Chen CY; Kuo HW (2007). Air pollution and hospital admissions for asthma in a subtropical city: Taipei, Taiwan. J Toxicol Environ Health A Curr Iss, 70: 111-117. 092848

Yang CY; Chen CJ (2007). Air pollution and hospital admissions for chronic obstructive pulmonary disease in a subtropical city: Taipei, Taiwan. J Toxicol Environ Health A Curr Iss, 70: 1214-1219. 092847

Yang Q; Chen Y; Krewski D; Burnett RT; Shi Y; McGrail KM (2005). Effect of short-term exposure to low levels of gaseous pollutants on chronic obstructive pulmonary disease hospitalizations. Environ Res, 99: 99-105. 090184

Yang Q; Chen Y; Krewski D; Shi Y; Burnett RT; McGrail KM (2004). Association between particulate air pollution and first hospital admission for childhood respiratory illness in Vancouver, Canada. Arch Environ Occup Health, 59: 14-21. 087488

Yang Q; Chen Y; Shi Y; Burnett RT; McGrail KM; Krewski D (2003). Association between ozone and respiratory admissions among children and the elderly in Vancouver, Canada. Inhal Toxicol, 15: 1297-1308. 055621

Yu O; Sheppard L; Lumley T; Koenig JQ; S (2000). Effects of ambient air pollution on symptoms of asthma in Seattle-area children enrolled in the CAMP study. Environ Health Perspect, 108: 1209-1214. 013254

Zanobetti A; Canner MJ; Stone PH; Schwartz J; Sher D; Eagan-Bengston E; Gates KA; Hartley LH; Suh H; Gold DR (2004). Ambient pollution and blood pressure in cardiac rehabilitation patients. Circulation, 110: 2184-2189. 087489

Zanobetti A; Schwartz J (2006). Air pollution and emergency admissions in Boston, MA. J Epidemiol Community Health, 60: 890-895. 090195

Annex D. Controlled Human Exposure Studies

Table D-1. Controlled human exposure studies.

Study	Subjects	Exposure	Findings
Adir et al. (1999, 001026)	15 healthy nonsmokers **Gender:** M **Age:** 22-34 yr	**Inhaled Concentration:** Not provided **Exposure Duration:** 3 min 45 s **COHb Concentration**: 4-6% **COHb Analysis:** CO-oximeter (IL-282) Exposures to CO and room air were separated by 1 mo, with the order of exposure randomly assigned.	Exposure to CO resulted in a decrease in postexposure exercise duration (Bruce protocol) relative to clean air exposure in 13 out of 15 subjects (p = 0.0012). Statistically significant decreases in METs were also reported following CO exposure (p = 0.0001). No CO-induced changes in HR, BP, ECG parameters, or myocardial perfusion were observed.
Bathoorn et al. (2007, 193963)	19 former smokers with COPD **Gender:** 18 M/1 F **Age:** 66-70 yr	**Inhaled Concentration:** 100 ppm (9 subjects) or 125 ppm (10 subjects) **Exposure Duration:** 2 h on each of 4 consecutive days **COHb Concentration**: 2.7% (following 4th day exposure) **COHb Analysis:** Not provided Exposures to CO and room air conducted were separated by at least 1 wk, using a randomized crossover design.	Following the 4th day of exposure, CO inhalation reduced sputum eosinophils relative to room air and also increased the provocative concentration of methacholine required to cause a 20% reduction in FEV_1. Neither of these effects were shown to reach statistical significance. No changes in sputum neutrophils, white blood cell counts or serum C-reactive protein (CRP) were observed. Although this study appears to demonstrate some evidence of an anti-inflammatory effect of CO among subjects with COPD, it must be noted that 2 of these patients experienced exacerbations of COPD during or following CO exposure, with 1 patient requiring hospitalization 2 mo after exposure (initial symptoms first experienced 1 wk postexposure).
Hanada et al. (2003, 193915)	20 healthy adults **Gender:** M **Age:** 26 ± 1 yr	**Inhaled Concentration:** Not provided **Exposure Duration:** 20 min **COHb Concentration**: 20-24% **COHb Analysis:** CO-oximeter (OSM-3) 15 subjects exposed for 20 min (10 min rest, 5 min handgrip exercise, 2 min postexercise ischemia, 3 min recovery) under the following 4 conditions: (1) normoxia (inspiratory O_2 fraction 21.4%); (2) hypoxia (inspiratory O_2 fraction 10.3%); (3) CO + normoxia; and (4) CO + hyperoxia (inspiratory O_2 fraction 95.9%). Trials involving exposure to CO were conducted last in this sequence. Each of the 4 conditions was separated from the next by 20 min of rest. 5 subjects served as controls (4 consecutive 20 min periods of normoxia).	Blood oxygenation, BP, HR and respiratory rate were measured during exposure. Muscle sympathetic nerve activity (MSNA) and leg hemodynamics were evaluated in two subsets of the study group (n = 8 and 7, respectively). Arterial oxygen saturation (pulse oximetry) was significantly lower, and resting HR and ventilation significantly higher during the period of hypoxia compared to the other periods; none of these measures were affected by exposure to CO. MSNA was shown to increase during hypoxia and CO exposure relative to normoxia. Neither hypoxia nor CO was found to affect leg blood flow or vasoconstriction.

Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at http://epa.gov/hero. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISAs) and the Integrated Risk Information System (IRIS).

Study	Subjects	Exposure	Findings
Kizakevich et al. (2000, 052691)	16 healthy nonsmokers **Gender:** M **Age:** 18-29 yr	**Inhaled Concentration:** Initial short term (4-6 min) exposure to 1,000 or 3,000 pap, followed by exposures to 27, 55, 83, or 100 ppm to maintain COHb concentration. **Exposure Duration:** 4-6 min at 1,000 or 3,000 pap, followed by 20 min at 27, 55, 83, or 100 ppm. **Target COHb Concentrations**: 5, 10, 15, and 20% **COHb Analysis:** CO-oximeter (IL-282) Subjects exposed on 4 separate days to increasing CO concentrations during either upper-body exercise (hand-crank) or lower-body exercise (treadmill). Targeted COHb concentrations were initially attained using short-term (4-6 min) exposures to CO at concentrations of 1,000 or 3,000 ppm. Chamber exposures were then conducted at CO concentrations required to maintain COHb levels of <2% (room air), 5% (27 ppm), 10% (55 ppm), 15% (83 ppm), and 20% (100 ppm).	At all levels of upper- and lower-body exercise, exposures to CO resulted in increases in HR, cardiac output, and cardiac contractility relative to clean-air exposures. Increases in HR reached statistical significance at COHb concentrations ≥ 5%, and increases in both cardiac output and cardiac contractility reached statistical significance at COHb concentrations ≥ 10%. CO exposure during exercise was not observed to cause ventricular arrhythmias or affect ECG wave shape (no evidence of ST-segment depression) at COHb concentrations ≤ 20%.
Mayr et al. (2005, 193984)	13 healthy nonsmokers **Gender:** M **Age:** 18-38 yr	**Inhaled Concentration:** 500 ppm **Exposure Duration:** 1 h **COHb Concentration**: 7% **COHb Analysis:** CO-oximeter (AVL 912) Subjects exposed to both CO and clean air with exposures separated by a 6-wk period. Immediately following exposure, subjects were administered an intravenous bolus dose (2 ng/kg) of lipopolysaccharide (LPS).	Infusion of LPS significantly increased plasma concentrations of TNF-α, CRP, IL-6, and IL-8, with no difference in the inflammatory response between clean-air and CO exposures.
Morse et al. (2008, 097980)	12 healthy nonsmokers **Gender:** M **Age:** 25 ± 2.9 yr	**Inhaled Concentration:** 3,000 ppm **Exposure Duration:** 3-8 min **COHb Concentration**: 6.2% **COHb Analysis:** Electrochemical sensor (Smokerlyzer) measuring CO in exhaled breath Exposures conducted on2 separate occasions to room air (6 min) and CO. Subjects were exposed to CO until COHb reached 6% (3- to 8-min exposures).	Leg strength and muscle fatigue were evaluated immediately following exposure. CO exposure did not affect muscle strength (maximal voluntary isometric contraction) but did cause a statistically significant increase in muscle fatigue ($p < 0.05$).
Ren et al. (2001, 193850)	12 healthy adults (10 nonsmokers and 1 smoker) **Gender:** 9 M/3 F **Age:** 20-32 yr	**Inhaled Concentration:** 0.4% (4,000 ppm) **Exposure Duration:** 10-30 min at 0.4% followed by ~ 8-h with periodic exposure to maintain COHb concentration **COHb Concentration**: 10% **COHb Analysis:** Not provided Each subject underwent 4 different 8-h experimental protocols: (1) isocapnic hypoxia (end-tidal PO_2 held at 55 mmHg); (2) withdrawal of 500 mL of venous blood at the start of an 8-h period; (3) CO exposure at a concentration required to maintain a COHb level of 10%; and (4) a control exposure where subjects breathed room air with no intervention.	A statistically significant increase in ventilation was observed following hypoxia, but no such increase was found following any of the other 3 protocols, including exposure to CO. One subject felt faint during the blood withdrawal protocol and did not complete the study.

Study	Subjects	Exposure	Findings
Resch et al. (2005, 193853)	15 healthy nonsmokers **Gender:** M **Age:** 27 ± 4 yr	**Inhaled Concentration:** 500 ppm **Exposure Duration:** 1 h **COHb Concentration**: ~ 10% **COHb Analysis:** CO-oximeter (AVL 912) Exposures to CO and synthetic air control were separated by a period of at least 1 wk.	COHb levels averaged 5.6% after 30 min and 9.4% after 60 min of exposure. Statistically significant increases in retinal blood flow, retinal vessel diameter, and choroidal blood flow were observed with CO exposure relative to synthetic air at both time points. Exposure to CO did not affect oxygen saturation of arterial blood.
Vesely et al. (2004, 194000)	10 healthy nonsmokers **Gender:** M **Age:** 22-52 yr	**Inhaled Concentration:** 1,200 ppm **Exposure Duration:** 30-45 min **COHb Concentration**: 10% **COHb Analysis:** CO-oximeter (OSM-3) Prior to and following exposure, subjects performed hypoxic and hyperoxic rebreathing tests. Four subjects were exposed to hypoxic conditions first, while 6 subjects were exposed to hyperoxic conditions first, both prior to and following CO exposure.	Ventilation rate was observed to significantly increase during hypoxic rebreathing relative to hyperoxic rebreathing. However, exposure to CO had no effect on ventilation under either hypoxic or hyperoxic conditions. The authors concluded that exposure to low levels of CO does not significantly affect chemoreflex sensitivity of the CO_2-induced stimulation of ventilation.
Zevin et al. (2001, 021120)	12 healthy smokers **Gender:** M **Age:** 27-47 yr	**Inhaled Concentration:** 1,200-1,500 ppm **Exposure Duration:** 10 min each h, 16 h each day, over 7 days **COHb Concentration**: 5-6% **COHb Analysis:** CO-oximeter (Ciba Corning 2500) Exposures were conducted over 21 consecutive days under3 different protocols, with each protocol lasting 7 days. In 1 protocol, subjects smoked 20 cigarettes per day, 1 every 45 min. In the other 2 protocols, every 45 min (20 times per day) subjects breathed either air or CO from a 1-liter bag once per min for 10 min at a time. Subjects completed all 3 protocols, with 6 subjects exposed sequentially to CO, smoking, then air, and the other 6 exposed sequentially to air, smoking, then CO.	COHb levels were similar during smoking and exposure to CO, with average concentrations of 6% and 5%, respectively. Blood was drawn on day 4 of each exposure and analyzed for CRP, plasma platelet factor 4, and white blood cell count. Plasma levels of CRP and platelet factor 4 were significantly elevated with smoking but not with CO exposure, relative to air control. HR and BP were evaluated on day 3 of each protocol. Cigarette smoke but not CO was observed to significantly increase HR, while no difference in BP was observed between any of the 3 exposures.

References

Adir Y; Merdler A; Haim SB; Front A; Harduf R; Bitterman H (1999). Effects of exposure to low concentrations of carbon monoxide on exercise performance and myocardial perfusion in young healthy men. Occup Environ Med, 56: 535-538. 001026

Bathoorn E; Slebos DJ; Postma DS; Koeter GH; van Oosterhout AJ; van der Toorn M; Boezen HM; Kerstjens HA (2007). Anti-inflammatory effects of inhaled carbon monoxide in patients with COPD: A pilot study. Eur Respir J, 30: 1131-1137. 193963

Hanada A; Sander M; González-Alonso J (2003). Human skeletal muscle sympathetic nerve activity, heart rate and limb haemodynamics with reduced blood oxygenation and exercise. J Physiol, 551: 635-647. 193915

Kizakevich PN; McCartney ML; Hazucha MJ; Sleet LH; Jochem WJ; Hackney AC; Bolick K (2000). Noninvasive ambulatory assessment of cardiac function in healthy men exposed to carbon monoxide during upper and lower body exercise. Eur J Appl Physiol, 83: 7-16. 052691

Mayr FB; Spiel A; Leitner J; Marsik C; Germann P; Ullrich R; Wagner O; Jilma B (2005). Effects of carbon monoxide inhalation during experimental endotoxemia in humans. Am J Respir Crit Care Med, 171: 354-360. 193984

Morse CI; Pritchard LJ; Wust RC; Jones DA; Degens H (2008). Carbon monoxide inhalation reduces skeletal muscle fatigue resistance. Eur Phys J A, 192: 397-401. 097980

Ren X; Dorrington KL; Robbins PA (2001). Respiratory control in humans after 8 h of lowered arterial PO2, hemodilution, or carboxyhemoglobinemia. J Appl Physiol, 90: 1189-1195. 193850

Resch H; Zawinka C; Weigert G; Schmetterer L; Garhofer G (2005). Inhaled carbon monoxide increases retinal and choroidal blood flow in healthy humans. Invest Ophthalmol Vis Sci, 46: 4275-4280. 193853

Vesely AE; Somogyi RB; Sasano H; Sasano N; Fisher JA; Duffin J (2004). The effects of carbon monoxide on respiratory chemoreflexes in humans. Environ Res, 94: 227-233. 194000

Zevin S; Saunders S; Gourlay SG; Jacob P III; Benowitz NL (2001). Cardiovascular effects of carbon monoxide and cigarette smoking. J Am Coll Cardiol, 38: 1633-1638. 021120

Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at http://epa.gov/hero. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISAs) and the Integrated Risk Information System (IRIS).

Annex E. Toxicological Studies

Table E-1. Human and animal studies.

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
Acevedo and Ahmed (1998, 016003)	Human pregnant myometrium			HO-1 and HO-2 (mRNA and protein) were upregulated in pregnant myometrium when compared to nonpregnant myometrium. The HO activator hemin inhibited spontaneous and oxytocin-induced contractility of the myometrium. Progesterone induced HO-1 and HO-2 mRNA expression.
Achouha et al. (2008, 179918)	Human arteries	Until equilibrium	Approximately 30 µM	CO induced endothelium- and NO-independent relaxation of precontracted human ITA and RA graft by partially stimulating cGMP production. The mechanism and extent of relaxation depended upon the tissue.
Ahmed et al. (2000, 193863)	Human placenta			Placental HO-1 was significantly higher at term. HO-1 significantly attenuated TNFα-dependent cellular damage in placental explants. HO-1 was significantly attenuated in pre-eclampsia pregnancies vs non-pre-eclamptic pregnancies. Placental arteries exposed to the HO activator hemin demonstrated reduced vascular tension (i.e., placental blood vessel relaxation).
Ahmed et al. (2005, 193865)	Human placental cotyledons			The source of CO in term human placental chorionic villi was found to be the catalysis of heme by HO and not endogenous lipid peroxidation.
Alexander et al. (2007, 193869)	Rat Sprague Dawley Adult female		.	Modulation of the HO/CO system in the anterior pituitary of the female rat led to altered secretion of gonadotropins and prolactin.
Alexandreanu et al. (2002, 192373)	Rat Sprague Dawley Female			The role of the HO/CO system in estrous cyclicity, pregnancy and lactation was evaluated using HO inhibitors and substrates. The HO inhibitor CrMP decreased time in estrous. Administering HO-inhibitors to pregnant rodents induced total litter loss. CrMP induced decreased litter weight gain during lactation, which the authors attribute to maternal milk production or ejection problems as cross-fostered pups regained weight lost during nursing on CrMP dams.
Alexandreanu and Lawson ((2003, 193871)	Rat Sprague Dawley Adult female			Modulation of the HO/CO system in the anterior pituitary of the female rat led to altered secretion of gonadotropins and prolactin.
Alexandreanu and Lawson (2003, 193876)	Rat Sprague Dawley Adult female ovary			HO-1 and HO-2 were localized in the ovaries in rats, and treatment of rat ovaries in vitro with CrMP, an inhibitor of HO, or with hemin, a substrate for HO induced steroidogenic changes in the ovaries.
Alonso et al. (2003, 193882)	Human muscle tissue mitochondria	5 min	50-500 ppm	CO significantly reduced muscle mitochondrial cytochrome *c* oxidase activity by 20%, 42%, and 55% after treatment with 50, 100, and 500 ppm CO respectively but did not change the activity of 3 other electron transport proteins.
Andersen et al. (2006, 180449)	Rat Long Evans Male Mouse C57BL/6J Male Cerebral vessels		1-100 µM	CO did not dilate rat or mouse cerebral arteries until 100 µM, which is not a physiological concentration. Also, the HO inhibitors constricted vessels in a nonspecific manner.

Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at http://epa.gov/hero. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISAs) and the Integrated Risk Information System (IRIS).

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
Antonelli et al. (2006, 194960)	Rat Wistar	GD5-GD20	75 ppm	Pups exposed to CO in utero had significant impairment of cortical neuronal glutamanergic transmission at PND1 in both neurons at rest and in neurons stimulated with depolarization.
Appleton and Marks (2002, 193935)	Human placenta			Endogenous CO production by HO in the human placenta was regulated by O_2 availability. Placental HO activity was directly dependent on O_2 availability; this does not vary between pre-eclamptic and normotensive placentas.
Ashfaq et al. (2003, 194002)	Human placenta			Placentas were collected from smokers and nonsmokers who gave birth to male infants. Premature aging and a statistically significant increase in apoptotic cells were seen in placentas from smokers vs nonsmokers.
Astrup et al. (1972, 011121)	Rabbit (strain not identified)	Continuous CO exposure over gestation	90 or 180 ppm	Skeletal abnormalities: Three pups (from n = 123) in the 180 ppm CO group had deformities in their extremities at birth, whereas no control and no 90 ppm CO-exposed animals manifested with this malformation.
Bainbridge et al. (2002, 043161)	Human placenta		72–3369 nM	Isolated human placenta exposed to solutions containing CO demonstrated a concentration-dependent decrease in perfusion pressure further demonstrating the role of CO in maintaining basal vasculature tone.
Bainbridge et al. (2006, 193949)	Human placenta	6 h	Starting concentrations of CO: 3.9 µM CO in cell culture media (control) and CO-exposed groups: 116 µM, 145 µM, 181 µM. After 3 h, the CO in the culture media was 3.7 µM (control), and CO-exposed cells 10.2, 12, and 15.9 µM.	C-section placentas were collected from healthy term pregnancies. Villous explants of placentas were cultured under hypoxia followed by reoxygenation (H/R). H/R- and CO-exposed placental tissue had decreased apoptosis and decreased PARP (a protein marker of apoptosis) vs control H/R-exposed cells. Secondary necrosis of the placental tissue post H/R was inhibited by CO treatment.
Bainbridge and Smith (2005, 193946)	Human placenta			The role of HO in the placenta and during pregnancy is reviewed in this article. The conflicting data on the activity, localization and expression of HO in the placentas of pre-eclamptic women are presented.
Bamberger et al. (2001, 016271)	Human placenta			Expression and tissue localization of soluble guanylyl cyclase in human placenta using antibody localization were characterized. These tools can be used in future studies to elucidate the NO/CO/cGMP pathway.
Barber et al. (1999, 193953)	Human myometrium			HO and NOS did not maintain human uterine quiescence during pregnancy.
Barber et al. (2001, 193891)	Human placenta			Women who had pregnancies with fetal growth restrictions (FGR) produced term placenta with significant decreases in HO-2 vs healthy pregnancies.
Baum et al. (2000, 016435)	Human			End-tidal CO measurements in women with pregnancy-induced hypertension and pre-eclampsia were significantly lower than in normotensive pregnant women.
Benagiano et al. (2005, 180445)	Rat Wistar Female	GD0-GD20	75 ppm	CO caused a significant reduction in glutamic acid decarboxylase and GABA immunoreactivities in the cerebellar cortex of adult rats prenatally exposed to CO (number of positive neuronal bodies and axon terminals and the area they covered). No difference was found in the microscopic structure of the cerebellar cortex or distribution patterns of GAD or GABA.
Benagiano (2007, 193892)	Rat Wistar Female	GD5-GD20	75 ppm	Prenatal CO reduced GAD and GABA immunoreactivities. There were no structural alterations of the cerebellar cortex.
Bergeron et al. (1998, 193967)	Rat Brain			To address the developmental changes of HO staining in the brain, immunohistochemical staining for HO-1 was performed on the developing rat brain at PND7, PND14, and PND21. HO-1 staining was most intense at PND7, and by PND21 reached its adult pattern of staining localizing to the hippocampus, thalamic and hypothalamic nuclei, with virtually no staining of endothelium, white matter and cortex. HO-2 is the dominant HO isoform in the brain.

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
Bing et al. (1995, 079418)	Rodent		.	Spatial learning in the Morris water maze was enhanced in rodents exposed to the HO inhibitor tin protoporphyrin (Sn-PP).
Burmester et al. (2000, 099998)	Human Mouse			Nb had a high oxygen affinity similar to Mb, and thus may increase the availability of O_2 to brain tissue.
Bye et al. (2008, 193777)	Rat Wistar Female	100 h/wk for 18 mo	200 ppm	CO-exposed (11-14.7% COHb) rats experienced a 24% decrease in aerobic capacity evidenced by VO_2 max deficits. Left ventricular cardiomyocytes were longer and wider, had increased expression of growth-related proteins, and had impaired contraction-relaxation cycles. CO increased cGMP and impaired cardiomyocyte Ca^{2+} handling. No change in BP was observed.
Cagiano et al. (1998, 087170)	Rat Wistar Female	GD0-GD20	75 or 150 ppm	At 5 mo of age, CO-exposed male offspring showed decrements in sexual behavior, including an increase in mount- to-intromission latency, a decrease in mount-to-intromission frequency, and a decrease in ejaculation frequency. Basal extracellular dopamine concentration in the nucleus accumbens was unchanged after CO-exposure. However, when stimulated with amphetamine administration, control rats had increased release of dopamine that is absent in CO-exposed rats.
Carmines and Rajendran (2008, 188440)	Rat Sprague Dawley	GD6-GD19 of gestation for 2 h/day	600 ppm	Significant decreases in birth weight were reported after CO exposure. Maternal body weight was unchanged during gestation, but corrected terminal body weight (body weight minus uterine weight) was significantly elevated in CO-exposed dams at term.
Carratu et al. (1993, 013812)	Rat Wistar Male pups	GD0-GD20	75 or 150 ppm	Prenatal CO exposure slowed the inactivation kinetics of transient sodium current in the sciatic nerve fibers of 40-day-old male rats. The maximum number of activatable Na channels at normal resting potential was increased in CO exposed rats, and the voltage-current relationship showed a negative shift of sodium equilibrium potential.
Carratu et al. (1995, 079427)	Rat Wistar		150 ppm	Sphingolipid homeostasis was disrupted in male offspring of prenatally exposed rats, without a disruption in motor function.
Carratu et al. (2000, 015935)	Rat Wistar	GD0-GD20	150 ppm	Maternal COHb (mean % ± SEM) was 1.9 ± 0.04 and 16.02 ± 0.98 in control and 150 ppm CO-exposed animals, respectively. Prenatal CO exposure had no effect on brain sphinganine (SA) or sphingosine (SO) levels in male offspring at 90 days of age. However, the sciatic nerve had significant increases in SO after CO exposure, and no changes in SA at 90 days of age. Motor activity, which could be affected by changes in myelination, showed no differences between CO and control animals at 90 days of age.
Carratu et al. (2000, 015839)	Rat Wistar	GD0-GD20	75 or 100 ppm	The myelin sheath thickness of the nerve fibers was significantly decreased in CO-exposed animals (75 and 150 ppm). Axon diameter was not affected by CO exposure. Even though CO affected myelination, it did not significantly affect motor activity of CO-exposed rats at 40 and 90 days.
Carraway et al. (2002, 026018)	Rat model of hypoxic pulmonary vascular remodeling (Strain of rat not stated)	3 wk	Hypobaric hypoxia ± 50 ppm	CO promoted remodeling and increased pulmonary vascular resistance in response to HH. The number of small muscular vessels was increased compared with HH alone. Changes in cell proliferation, apoptosis, actin and HO-1 gene and protein expression correlated with structural changes. COHb levels were <0.5% in controls, 1.5-2.8% in the HH treatment group, and 3.5-3.9% in the HH + CO treatment group.
Cella et al. (2006, 193240)	Rat Sprague Dawley			HO-1 production and HO concentration were shown to be regulated by estrogen in the rat uterus.
Chen (2001, 193985)	Rat Long Evans Male 2 mo	3.5 h	1201 ± 18 ppm	CO potentiates-noise induced hearing loss. The NMDA inhibitor (+)-MK-801 did not block the potentiation of the NIHL by CO.
Cheng et al. (2009, 193775)	Human atherectomy biopsy (clinical carotid artery disease) Mouse model of vulnerable plaque ApoE-/- mouse			HO-1 expression correlated with features of vulnerable human atheromatous plaque.HO-1 expression was upregulated in vulnerable lesions in the mouse model. Induction of HO-1 in the mouse impeded lesion progression into vulnerable plaques. Inhibition of HO-1 augmented plaque vulnerability. Overexpression of HO-1 resulted in plaque stabilization. It was concluded that HO-1 induction was atheroprotective.

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
Chung et al. (2006, 193987)	Rat Sprague Dawley Male		3-6%	CO inactivation of Mb did not induce any change in the respiration rate, contractile function or high-energy phosphate levels in perfused rat hearts.
Cronje et al. (2004, 180440)	Rat Sprague Dawley Male 240-325 g	45 min	2,500 ppm	Results indicate that tissue and blood (CO) (66-72% COHb) dissociate during CO inhalation, but tissue (CO) does not follow blood (CO) or $1/pO_2$ as in the Warburg theory during intake or elimination. Tissue (CO) increases later during the resolution period and varies significantly among animals and tissues. The deviation from the predicted values in the brain is likely due to the release of heme and increase in NADPH stimulating endogenous CO production by HO. Immediately following exposure, tissue CO concentrations were found to be: Blood: 27,500 (800) pmol/mg Heart: 800 (300) pmol/mg Muscle: 90 (80) pmol/mg Brain: 60 (40) pmol/mg These values are estimates taken from a graph, with control levels in parentheses A later report stated that these tissue CO values were too high due to a computational error (Piantadosi et al., 2006, 180424)
Cudmore et al. (2007, 193991)	Human placenta Human (HUVEC) Mouse (HO-1 deficient mouse on 129/SV × C57BL/6 background) Pig (Porcine aortic endothelial cells)			HUVEC cells, porcine aortic endothelial cells, HO-1 null mice and placental villous explants (normotensive and pre-eclamptic pregnancies) were used in this study. The HO-1/CO system inhibited sFlt-1 and sEng release, two factors upregulated in pre-eclampsia.
D'Amico et al. (2006, 193992)	Human embryonic kidney (HEK293) cells	0-30 min	20 µM	Exogenous CO inhibited respiration in HEK293 cells under ambient O_2 concentration (21%). Inhibition was enhanced under hypoxic conditions. Increased endogenous CO resulting from HO-1 overexpression inhibited respiration by 12% and cytochrome c oxidase activity by 23%. This effect was enhanced under hypoxic conditions.
Dani et al. (2007, 193994)	Human (neonatal blood)			CO was lower at birth and 48-72 h postpartum in infants born by elective C-section and higher in vaginally born infants.
De Luca et al. (1996, 080911)	Rat Wistar Female Male pups	GD0-GD20	75 or 150 ppm	Prenatal CO (150 ppm) delayed development of the ion channels responsible for passive and active membrane electrical properties of skeletal muscle. CO-induced lower values of resting chloride conductance was reversed at PND80. CO-induced delayed developmental reduction of resting potassium conductance was reversed at PND60.
De Salvia et al. (1995, 079441)	Rat Wistar	GD0-GD20	75 or 150 ppm	Animals exposed to the higher dose of CO (150 ppm) in utero had significantly impaired acquisition (at 3 and 18 mo) and reacquisition (at 18 mo) of conditioned avoidance behavior.
Denschlag et al. (2004, 193894)	Human			Genetic polymorphisms in human HO-1 are linked to idiopathic recurrent miscarriages.
Dewilde et al. (2001, 019318)				Nb exists as a reversibly hexacoordinated Hb type with a His-Fe^{2+}-His binding scheme. Dissociation of the internal ligand by O_2 or CO is the rate limiting step.
Di Giovanni et al. (1993, 013822)	Rat Wistar Female	GD0-GD20	75 and 150 ppm	CO (150 ppm) reduced the minimum frequency of ultrasonic calls as well as decreased responsiveness to a challenge dose of diazepam. There was no change in locomotion; however CO impaired learning in a two-way active avoidance task.
Dubois et al. (2002, 193911)	Rat Wistar Adult female 250 g	3 wk	530 ppm	Intrapulmonary resistance artery smooth muscle cells were isolated from control and exposed rats. Electrophysiological recordings provided evidence of increased Ca^{2+}-activated K^+ current consequent to chronic CO exposure. The authors speculated that this could in part explain the vasodilatory effect of CO in the pulmonary circulation.

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
Dubois et al. (2005, 180435)	Rat Wistar Male	21 days	50 ppm	CO attenuated PAHT by activating BK_{ca} channels in PA myocytes and reduced hemodynamic changes of PAHT.
Dubois et al. (2003, 180439)	Rat Wistar Male	21 days	50 ppm	CO induced relaxation of pulmonary artery rings in normoxic, hypoxic, and hypoxic-CO rats, and it was not endothelium dependent. Chronic hypoxia decreased acute CO sensitivity, while CO-hypoxia increased it. K^+ channel blocker reduced this effect while sGC blocker did not.
Durante et al. (2006, 193778)				Reviews the role of CO in cardiovascular function.
Favory et al. (2006, 184462)	Rat 250-300 g (Strain not stated)	90 min	250 ppm	CO inhibited myocardial permeabilized fiber respiration (complex IV), increased coronary perfusion pressure and left ventricular developed pressure (LVDP) first derivative and decreased the cGMP/cAMP ratio in the heart. These changes were maintained over 24-48 h of recovery in air. Cardiac function and vasodilatory responses were evaluated at 3-h recovery in air. β-adrenergic blockade had no effect on coronary perfusion pressure or LVDP first derivative. Total inhibition of vasodilator response to acetylcholine and partial inhibition of vasodilator response to nitroprusside were observed. An increase in myofilament calcium sensitivity was also observed. Thus CO promotes abnormalities in mitochondrial respiration, coronary vascular relaxation and myocardial contractility. The authors speculated that CO may have a detrimental effect on heart O_2 supply-to-utilization which could potentially lead to myocardial hypoxia because of the increased O_2 demand resulting from increased contractility, the inhibited mitochondrial respiration and the reduced coronary blood-flow reserve resulting from the decreased vasodilatory capacity. COHb was found to be 11% immediately after exposure. COHb levels gradually returned to baseline (1.5%) over the next 96 h.
Fechter and Annau (1977, 010688)	Rat Long Evans	Continuous CO exposure throughout pregnancy	150 ppm CO	The authors found a 5% significantly decreased birth weights at PND1 in gestationally CO-exposed pups vs control animals with weight decrements persisting to weaning; lactational cross fostering did not ameliorate the CO-dependent reduced growth rates. Dams exposed to CO during gestation had COHb over gestation of 15% with control dams having less than 1%. Decreased birth weight and pre-weaning weight were seen in CO-exposed pups despite a lack of weight decrement in CO-exposed dams vs air-exposed control dams.
Fechter et al. (1980, 011294)	Rat Long Evans	Continuous CO exposure throughout pregnancy	150 ppm	CO-exposed animals had cardiomegaly at birth (wet heart weight) that dissipated by PND4.
Fechter and Annau (1980, 011295)	Rat Long Evans	Continuous CO exposure throughout pregnancy	150 ppm	CO-exposed animals had decreased birth weight, impaired righting reflexes, impaired negative geotaxis, and delayed homing behavior.
Fechter et al. (1987, 012194)	Rat Long-Evans Male		1-4 mL/100 g BW (ip)	High-dose CO led to dose-dependent, reversible loss of the compound action potential sensitivity for high frequency tone bursts. Also, CO produced a dose-dependent elevation in the cochlear blood flow.
Fechter et al.(1987, 012259)	Rat Long Evans Male	Continuous CO exposure throughout pregnancy or from GD0 to PND10	75, 150, or 300 ppm	The neostriatum of each PND21 rat brains was collected and showed disrupted development following CO exposure (GD0-PND10 group, 300 ppm CO). Dopamine levels were also significantly elevated in CO-exposed animals (GD0-PND10, 150 and 300 ppm CO).
Fechter et al. (1997, 081322)	Guinea pigs		35 ml/kg gas (ip) 40% COHb	CO impairs high-frequency auditory sensitivity, shown by increased compound action potential threshold at higher test frequencies. Free radical inhibitors blocked this response.
Fechter et al. (1986, 012030)				Reviews the effects of carbon monoxide on brain development.

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
Garofolo et al. (2002, 193930)	Human infants Rat	Rat: PND2-PND5		Human infants who die from SIDS showed decreased brainstem muscarinic receptor binding vs infants dying from other causes. ß-adrenergic modulation of muscarinic receptors in developing heart was observed. Rodent ß-adrenergic agonists at PND2-PND5 induced muscarinic receptor decrement in adenylyl cyclase.
Gautier et al. (2007, 096471)	Rat Wistar Adult male Model of right ventricular hypertrophy secondary to chronic hypoxia	3 wk of HH ± CO in final wk Or 1 wk of CO	50 ppm	CO altered the right ventricular adaptive response to pulmonary hypertension which occurs secondarily to chronic hypoxia. Right ventricular end-systolic pressure (RVESP) and right ventricular shortening fraction (RVSF) were smaller in rats treated with CO+HH compared with rats treated with HH alone. CO alone had no effect on these measures. Hypobaric hypoxia had no effect on left ventricular function while CO+ HH led to an increased left ventricular shortening fraction (LVSF). CO alone led to a decrease in LVSF and the mitral E-to-A ratio, indicative of an LV-filling impairment. Hypobaric hypoxia decreased the relative RV perfusion and increased the relative LV perfusion. These effects were prevented with concomitant exposure to CO, although exposure to CO alone had no effects on myocardial perfusion. Morphologic and histologic analysis demonstrated RV hypertrophy in both the HH group and the CO+HH group and fibrotic lesions in the CO+HH group. The authors concluded that the 1-wk exposure to 50 ppm CO had a deleterious effect on RV myocardial perfusion adaptation to chronic hypoxia and pressure overload. Although the reduced RV pressure overload was beneficial, it was counterbalanced by impaired RV perfusion and redistribution of perfusion toward the LV.
Gaworski et al. (2004, 193933)	Rat Sprague Dawley	2 h/day, 7 days/wk by nose-only inhalation Males: 4 wk prior to and during mating; and Females: 2 wk prior to mating; during mating; and through weaning to PND21	Cigarette smoke: 150, 300, or 600 mg/m^3 Total Particulate Matter (TPM)	Maternal exposure to high concentrations of cigarette smoke during gestation and lactation reduced pup birth weight and retarded neonatal pup growth. Developmental and neurobehavioral testing of neonates did not show any behavioral effects following parental smoke exposure.
Ghio et al. (2008, 096321)	Rat Sprague Dawley Adult male	24 h	50 ppm	Mild neutrophil accumulation was observed in BALF, accompanied by increases in BALF MIP-2, protein and LDH. Iron status was altered since CO exposure led to an increase in BALF iron and ferritin, a decrease in lung non-heme iron and an increase in liver non-heme iron.
	Human bronchial epithelial cells (BEAS-2B)	2-24 h	10-100 ppm	CO exposure for 24 h led to a dose-dependent decrease in cellular non-heme iron, with the effect at 10 ppm statistically significant and the effect at 50 ppm maximal. This effect was reversible since removing the cells after 2 h of CO and incubating them in air restored non-heme iron concentrations at 24 h. A dose-dependent decrease in cellular ferritin was observed following exposure for 24 h to 50-500 ppm CO. In addition, exposure to 50 ppm CO for 20 h blocked iron uptake by cells, while exposure to 50 ppm CO for 2 h increased iron release from cells. Increased protein expression of the iron transporter DMT-1 was also noted after 24 h exposure to 50 ppm CO. Oxidative stress, mediator release and cell proliferation were also decreased by exposure to 50 ppm for 24 h. This effect was also reversible upon removal to air. Effects of CO on cell proliferation indices were mimicked by with the iron-depleting agent deferoxamine. The authors concluded that CO exposure altered lung iron homeostasis possibly by initially causing heme release from proteins.
Giustino et al. (1999, 011538)	Rat Wistar Male and pregnant female	GD0-GD20	75 or 150 ppm	This study showed that CO- exposed (75 and 150 ppm) male animals at 40 days of age had a significantly decreased time of exploration of novel objects. The 150 ppm CO group showed a lack of habituation after the second exposure to a previously viewed object. Blood COHb concentrations (mean % ± SEM) on GD20 were reported (0 ppm: 1.6 ± 0.1; CO 75 ppm: 7.36 ± 0.2; CO 150 ppm: 16.1 ± 0.9).

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
Giustino et al. (1993, 013833)	Rat Wistar	GD0-GD20	75 or 150 ppm	CO exposure in utero led to a reversible and dose-dependent loss of function of splenic macrophages, with decreased killing ability, decreased phagocytosis, and decreased ROS production during the macrophage respiratory burst.
Giustino et al. (1994, 076343)	Rat Wistar Male pups	GD0-GD20	75 or 150 ppm	CO (150 ppm) decreased the number of leukocyte common antigen (LCA+) cells at PND21. This was reversed by PND540. CO (75 ppm), and other measures of immunological changes showed trends toward reduction (macrophages, T cells, B cells, and MHC II cells).
Glabe et al. (1998, 086704)	Rat Sprague Dawley Male, Myocardium		pCO = 0-107 Torr	Increased pCO and increased COMb saturation did not alter high-energy phosphate signals (ATP, phosphocreatine, P_i). MVO_2 began to decline at 87.6% COMb and is likely not due to cytochrome c oxidase inhibition.
Grover et al. (2000, 010465)	Fetal lamb (mixed breed)	10 min	500 ppm	Fetal methoxyhemoglobin (COHb%) ranged from 3.8 ± 0.2 to 8.1 ± 2.0 at 0 and 500 ppm CO, respectively. Inhaled 0-500 ppm CO administered to near-term fetal lambs did not induce pulmonary vasodilation (main pulmonary artery, left pulmonary artery, aorta and left atrium), and the HO inhibitor zinc protoporphyrin IX failed to affect baseline vascular tone.
Hara et al. (2002, 037497)	Rat Sprague Dawley Male	40 min	1,000-3,000 ppm	CO exposure increased extracellular dopamine levels and decreased its major metabolites in a Na^+-dependent pathway. CO withdrawal and reoxygenation caused levels to return to control or overshoot, which may suggest an increase in oxidative metabolism of CO, mediated by MAO-A.
Harada et al. (2004, 193920)	Pig Granulosa cells			In this porcine model, HO was able to augment granulosa cell apoptosis allowing for proper follicular maturation.
Hendler and Baum (2004, 193925)	Human			End-tidal breath CO measurements in pregnant women with contractions (term and pre-term) were lower than those measurements in noncontracting women.
Hofmann and Brittain (1998, 052019)	Human			Partitioning of O_2 and CO in the human embryonic Hb is discussed.
Iheagwara et al. (2007, 193861)	Mouse C57BL/6 Male	3 h	1,000 ppm	CO significantly reduced cytochrome c oxidase activity and V_{max} but not K_m in myocardial mitochondria. Cytochrome c oxidase protein levels and heme content were significantly decreased. The average COHb level was 61%, but no tissue hypoxia was observed in the heart.
Imai et al. (2001, 193864)	HO-1 transgenic mice which specifically over-express HO-1 in smooth muscle			Transgenic mice had a significant increase in arterial pressure and impaired nitrovasodilatory aortic responses. The mice had enhanced NO production and impaired sGC activity. The authors speculated that the effect of HO-1 overexpression was to suppress vasodilatory responses to NO in vascular smooth muscle.
Ischiropoulos et al. (1996, 079491)	Rat Wistar Male 200-290 g	60 min 40-60 min	1,000-3,000 ppm 1,000 ppm	CO poisoning resulted in free NO in brains as measured by electron paramagnetic resonance spectroscopy and in a 10-fold increase in nitrotyrosine as measured by immunohistochemical staining. These responses were blocked by pretreatment with a NOS inhibitor but not by neutrophil depletion. Brain nitrotyrosine formation was blocked by platelet depletion following 40-min but not 60-min exposure to 1,000 ppm CO. Following CO poisoning, myeloperoxidase activity, a measure of leukocyte sequestration, was increased in brain microvessels. This response was blocked by NOS inhibition but not by platelet depletion. Similar effects were noted for xanthine oxidase activation. The authors concluded that perivascular reactions mediated by peroxynitrite are key to CO poisoning effects in brain.
Johnson and Johnson (2003, 053611)	Rat Sprague Dawley Male 250-300 g		0-100 µM	CO produced a concentration-dependent, endothelium-dependent vasoconstriction in isolated gracilis muscle arterioles, evident at 1 µM CO. Pretreatment with a NOS substrate prevented this response, while pretreatment with a NOS inhibitor converted this response to a vasodilation. The authors concluded that exogenous CO was acting through NOS inhibition.

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
Johnson et al. (2003, 193868)	Rat Dahl/Rapp salt-resistant and salt-sensitive model Male			High-salt diet increased COHb, BP, and aortic HO-1 protein levels in salt-sensitive Dahl rats. Enhanced immunostaining was observed for HO-1 but not HO-2 in isolated gracilis muscle arterioles. Compared with the low-salt diet, the high-salt diet resulted in a smaller vasoconstrictor response when NOS was inhibited. Vasoconstriction was exacerbated in arterioles from both low-salt- and high-salt-treated rats using both NOS and HO inhibitors. Acetylcholine-induced vasodilation was diminished in the high-salt diet group compared with the low-salt diet group. This effect was not seen using the HO inhibitor. The high-salt diet did not alter endothelium-independent vasodilation. The authors concluded that HO-derived CO caused dysfunction of the $NO^{\bullet}$ system in salt-sensitive rats treated with a high-salt diet.
Johnson et al. (2004, 193870)	Rat Sprague Dawley Male Deoxycorticosterone acetate (DOCA)-salt hypertension model Rats WKY Rats Spontaneously hypertensive (SHR)			Salt-sensitive DOCA rats, but not SHR, had elevated aortic HO-1 expression and blood COHb levels. Both had elevated mean arterial BP compared with controls. Acetylcholine-mediated vasodilation of isolated gracilis muscle arterioles was attenuated in DOCA rats but not SHR. Pretreatment with an HO inhibitor restored the response in DOCA rats. The authors concluded that HO-1-derived CO contributes to endothelial dysfunction in DOCA but not SHR.
Johnson et al. (2006, 193874)	Rat Zucker Lean and obese Male		100 µM CO	The obese rats had increased CO expiration and mean arterial pressure, which was decreased by pretreatment with a HO inhibitor. No difference was observed in HO-1 protein between lean and obese rats. Acetylcholine- and flow-mediated vasodilation of isolated gracilis muscle arterioles was attenuated in obese but not lean rats. Pretreatment with a HO inhibitor restored the response in obese rats. Exogenous CO prevented the restoration of flow-induced dilation by the HO inhibitor. The authors concluded that HO-derived CO contributes to endothelial dysfunction in this model of metabolic syndrome.
Katoue et al. (2005, 193896)	Rat Wistar			HO activity in the aorta is significantly increased during pregnancy, but aortic AVP-dependent vasoconstriction appears to be HO/CO independent.
Katoue et al. (2006, 193954)	Rat Wistar			Pregnancy-induced modulation of calcium mobilization and downregulation of Rho-kinase expression contributed to attenuated vasopressin-induced contraction of the rat aorta.
Khan et al. (2006, 193955)	Nb overexpressing BDF × CD1 mice			Cerebral and myocardial infarcts were decreased in neuroglobin overexpressing mice, decreasing ischemic injury.
Kim et al. (2005, 193959)	Primary rat pulmonary artery smooth muscle cells Rat Inbred LEW Sprague Dawley 200-250 g	24 h or pretreatment for 1-2 h followed by 24 h post-treatment	250 ppm	Exposure of cells in culture to 250 ppm CO for 24 h inhibited serum-stimulated cell proliferation, increased expression of p21Waf1/Cip1, and decreased expression of cyclin A. CO also inhibited PDGF-stimulated cell proliferation and reversed the inhibitory effect of PDGF on caveolin-1 expression. Genetic silencing of caveolin-1 using siRNA, prevented the antiproliferative effect of CO. Endogenous CO, derived from HO-1 in an overexpression system, was found to upregulate caveolin-1 expression. Effects of CO on caveolin-1 were found to be mediated by p38 MAPK and cGMP. Experiments in fibroblasts deficient in p38 confirmed a role for p38 in CO-mediated inhibition of cellular proliferation via effects on p21Waf1/Cip1, cyclin A and caveolin-1. Experiments in fibroblasts deficient in caveolin-1 confirmed the role of caveolin-1 in the anti-proliferative effects of CO. In a model of neointimal injuries induced by balloon injuries in intact animals, exposure to CO inhibited neointimal formation and increased caveolin-1 expression in the intima and media.

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
Kim et al. (2008, 193961)	Primary rat hepatocytes Primary mouse hepatocytes Respiration-deficient human Hep3B cells	10-60 min	250 ppm	Exposure of cells in culture to 250 CO for 1 h twice a day prevented spontaneous hepatocyte death over 6 days in culture. CO also decreased caspase-3 activity. Cell death was determined to be partly due to apoptosis. CO also increased ROS as measured by dichlorofluorescein fluorescence in rat hepatocytes, mouse hepatocytes, and Hep3B cells but not in respiration-deficient Hep3B cells, indicating that ROS were mitochondrial in origin. An increase in mitochondrial oxidized glutathione was noted in rat hepatocytes treated with CO for 30 min. Increased Akt phosphorylation occurred following 10-30 min CO and was diminished by treatment with antioxidants. CO was found to activate NFκB through a PI3K and oxidant-dependent pathway. CO mediated spontaneous cell death was found to be dependent on ROS and Akt phosphorylation. The authors concluded that CO prevents hepatocyte apoptosis through redox mechanisms, leading to cytoprotection.
Kinobe et al. (2006, 188447)	Sheep Gravid and nongravid sheep and their near-term fetuses			There were no significant differences in hypoxic adult and hypoxic fetal sheep when compared to their normoxic controls.
Knuckles et al. (2008, 191987)	Mouse	4 h	Diesel emissions: 350 µg/m^3	Diesel exhaust enhanced vasoconstriction in veins but not arteries. It were suggested that this is through the uncoupling of eNOS.
Korres et al. (2007, 190908)	Human			Transient evoked otoacoustic emissions response and amplitude at 4,000 Hz was lower in neonates with prenatal exposure to cigarette smoke. There was no dose-dependent change in response depending on the amount cigarettes per day that was smoked.
Kreiser et al. (2004, 193948)	Human			End-tidal CO concentrations were lower in pregnant women with gestational hypertension and pre-eclampsia than normotensive women.
Lash et al. (2003, 193849)	Human Term placental chroionic villi from healthy or pre-eclamptic placentas			Infarcted areas of placenta had decreased HO expression (in pre-eclamptic placenta only).
Li et al. (2008, 187003)	Mouse ICR (CD-1) Pregnant			The effect of maternal LPS exposure on fetal liver HO was measured. HO-1 was upregulated in fetal livers post-LPS exposure, and this HO-1 upregulation was attenuated with the spin trap agent PBN, pointing to a ROS-dependent HO-1 upregulation post-maternal LPS treatment.
Liu and Fechter (1995, 076524)	Guinea pig Male		35 mL/kg (ip)	CO increased the compound action potential threshold at high frequencies. This could be blocked by inhibition of the glutamate receptor.
Loennechen et al. (1999, 011549)	Rat Sprague Dawley Female 220-240g	1 wk 1 wk 100 ppm and 1 wk 200 pm	100 ppm 100-200 ppm	Endothelin-1 expression increased by 53% and 54% in the left and right ventricle, respectively, during the 2-wk exposure, and by 43% and 12% in the left and right ventricle, respectively, during the 1-wk exposure. Right ventricular to body weight ratio was increased by 18% and 16% in the 2-wk and 1-wk exposure groups, respectively. COHb levels were 23% and 12% in the 2-wk and 1-wk exposure groups, respectively.
Longo et al. (1999, 011548)	Rat uterine tissue and tail artery rings Sprague Dawley Human uterine biopsies		10^{-4} M	The addition of exogenous CO to isolated human and rat uterine tissue failed to induce relaxation of uterine tissue. Isolated rat aortic rings and tail artery rings from pregnant dams can be relaxed by submersion in exogenous CO solutions.

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
Lopez et al. (2008, 097343)	Rat Sprague Dawley	Pregnant rats exposed to CO GD5-GD20 (Group A) or GD5-GD20 plus PND5-PND20 (Group B); Group C (control air exposure). 10-18 h/day	25 ppm	CO exposure induced damage to the spiral ganglia neurons and inner hair cells, with oxidative stress seen in cochlear blood vessels. At PND20 groups A and B showed vacuolization of afferent terminals at the base of the cochlea. At PND3, group A showed decreased synapsin-1 staining of the efferent nerve terminals. At PND20, groups A and B showed decreased neurofilament-IR (staining) in type I spiral ganglia neurons and afferent nerve fibers. At PND12 and PND20, group B showed increased HO-1 and SOD-1-IR in blood vessels of the stria vasularis; group A was similar to controls. From PND3-PND20, there was increased iNOS and increased nitrotyrosine-IR in blood vessels of the cochlea.
Lopez et al. (2003, 193901)	Rat Sprague Dawley	PND6 to weaning (PND19-PND20)	12 or 25 ppm	In the cochlea, atrophy or vacuolization of the nerve cells that innervate the inner (not outer) hair cells was seen. Fibers of the 8th cranial nerve (internal auditory canal of the ARCO animals, 25 ppm) had distorted myelination and vacuolization of the axoplasm. In the organ of corti and spiral ganglion neurons, cytochrome c oxidase and NADH-TR were significantly decreased in 25 ppm exposure group vs control. Expression of the calcium-mediated myosin ATPase in the organ of corti and spiral ganglion neurons was significantly decreased in the 25 ppm CO exposure group vs controls.
Lund et al. (2007, 125741)	Mouse ApoE$^{-/-}$ Male High-fat diet	6 h/day, 7days/wk, 7 wk	8, 40, or 60 µg/m^3 PM whole-gasoline exhaust; or filtered exhaust with gases matching the 60 µg/m^3 concentration. CO concentrations were 9, 50, and 80 ppm, corresponding to the 8, 40, and 60 µg/m^3 PM whole-exhaust exposures	Both whole-gasoline and filtered-gasoline exhaust increased aortic mRNA expression of matrix metalloproteinase-3 (MMP-3), MMP-7, and MMP-9, tissue inhibitor of metalloproteinases-2, endothelin-1 and HO-1 at 60 µg/m^3. Aortas also showed increased immunostaining for MMP-9 and nitrotyrosine in 60 µg/m^3 PM whole exhaust and PM-filtered exhaust exposed groups. Aortic TBARS, a measure of lipid peroxidation, was also increased in all treatment groups.
Lund et al. (2009, 180257)	Mouse ApoE$^{-/-}$ Male High-fat diet	6 h/day, 1 or 7 days	Gasoline engine exhaust containing 60 µg/m^3 PM and 80 ppm CO	Gasoline exhaust exposure increased aortic MMP-2/9 activity at 1 and 7 days. Protein levels of aortic MMP-9, MMP-2, TMP-2 and plasma MMP-9 were also increased after 7 days. Lipid peroxidation in aorta, resulting from gasoline exhaust exposure, was inhibited by treatment with the antioxidant Tempol, while increases in mRNA for ET-1 and MMP-9 in aortas were inhibited by treatment with BQ-123, an antagonist of ETA receptor. Treatment with BQ-123 also reduced aortic MMP-2/9 activity in aortas following gasoline exhaust exposure. The authors concluded that ETA receptor pathway is a key mediator of gasoline engine exhaust effects in the vasculature.
Lyall and Myatt (2002, 193971)	Human			Women with pre-eclampsia produced term placenta with significant decreases in HO-2 vs women with healthy pregnancies.
Lyall et al. (2000, 193902)	Human (placentas from 8-to19-wk pregnancy and term placentas)			The use of a HO inhibitor ZnPP increased placental perfusion pressure. HO-1 and HO-2 were expressed in the placenta and placental bed and vary in expression over the course of pregnancy. HO may thus be involved in trophoblast invasion, placental function, and perfusion pressure.
Mactutus and Fechter (1984, 011355)	Rat Long Evans	Continuous exposure to CO over gestation	150 ppm	Acquisition as measured in a two-way conditioned avoidance (flashing light warnings followed by mild footshock) test failed to improve with age of in utero CO-exposed (150 ppm, dam COHb 15%) rats (male and female offspring) in contrast to air-exposed controls who improved with age/maturation, indicating a failure in the associative process of learning. The authors also found impairments in reacquisition performance, an index of retention, in PND31 rats that had received continuous in utero CO exposure. Prenatal CO exposure induced learning and memory deficits in male and female offspring.
McGregor et al. (1998, 085342)	Guinea pig	GD23-GD25 until term (approximately 68 days) 10 h/day	200 ppm	Aberrant respiratory responses (to asphyxia and CO_2) of offspring with prenatal CO exposure. The authors hypothesized that this may be related to changes in the brainstem. COHb was measuerd in maternal (8.53 ± 0.6% vs 0.25 ± 0.1%) and fetal blood (13.0 ± 0.4% vs 1.6 ± 0.1%) from CO-treated vs controls.

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
McLaughlin et al. (2001, 193823)	Human placenta			Various pathologies of pregnancy including IUGR and pre-eclampsia are associated with significant decreases in placental HO activity. The endogenous generation of CO in the placenta has been demonstrated in chroionic villi of term placenta.
McLaughlin et al. (2000, 015815)	Human placenta			Placental regional localization of HO was explored. The chorionic plate, chorionic villi, basal plate, and choorio-decidua had significantly higher HO activity than the amnion.
McLaughlin et al. (2003, 193827)	Human placenta			HO expression in various regions of term placentas was explored. Microsomal HO-2 protein content was not different between normotensive and milk pre-eclamptic pregnancies. There was increased expression of microsomal HO-1 protein in chorionic villi and fetal membranes from pre-eclamptic pregnancies vs normotensive pregnancies.
McLean et al. (2000, 016269)	Human placenta			HO activity was highest in the placenta near term.
Melin et al. (2002, 037502)	Rat Dark Agouti Male Model of right ventricle hypertrophy secondary to chronic hypoxia (HH 10 wk)	10 wk	50 ppm alone or concomitant with HH	Hb and hematocrit levels were increased above controls in HH rats, CO rats and HH+CO rats, with the increase due to the combined treatment significantly higher than the increase due to HH. COHb levels were 1.1% in controls, 1.3% in HH rats, 4.7% in CO rats and 9.1% in HH plus CO rats. HH treatment significantly increased right ventricular (RV) heart weight above controls while CO treatment had no effect on any postmortem heart weights. Combined treatment with HH+CO resulted in a significant increase in left ventricular plus septum (LV+S) weight and RV weight compared with HH treatment alone. Echocardiographic left ventricular morphology and mass also showed the greatest changes in the HH+CO group. Hemodynamic measurements of LV function demonstrated significant effects in the HH+CO group for left ventricular end diastolic pressure (LVESP), left ventricular maximal first derived pressure (+dP/dtLV), and left ventricular work (LVW) compared with controls. Hemodynamic measurements of RV function demonstrated significant effects in the HH group for right ventricular end systolic and diastolic pressure (RVESP, RVEDP), right ventricular maximal and minimal first derived pressure (+dP/dtRV, -dP/dtRV) and right ventricular work (RVW). CO significantly enhanced the effects of HH on RVEDP and significantly diminished the effects of HH on dP/dtRV and RVW. The authors concluded that CO intensified the HH-induce RV hypertrophy, increased LV weight, and induced severe hematological responses that could hamper adaptation.
Melin et al. (2005, 193833)	Rat Dark Agouti Male and female Model of right ventricle hypertrophy secondary to chronic hypoxia (HH, 10 wk) Half of the animals were exercise trained to induce LV hypertrophy	10 wk	50 ppm alone or concomitant with HH	In untrained animals, combined treatment with HH+CO led to increased LV+S and RV weights compared with HH treatment alone. HH+CO led to several changes in measured echocardiographic parameters, including increased anterior and posterior wall thickness in diastole (AWTd, PWTd), and to increased fraction of shortening. These effects were not seen with HH alone. In addition, RVEDP was enhanced in HH+CO compared with HH alone. HRV components were altered by HH+CO but not by CO alone.
Mereu et al (2000, 193838)	Rat Wistar	GD0-GD20 continuous CO exposure	150 ppm	In utero exposure to CO disrupted hippocampal LTP with concomitant HO-2 and nNOS reductions. The authors surmised that these changes may be related to the memory deficits seen in animals exposed to CO in utero.
Middendorff et al. (2000, 015842)	Human Adult males aged 65-75 yr Testicular tissue from orchiectomy			Zn protoporphryin (ZnPP) and Hb both significantly reduced seminiferous tubular cGMP generation, suggesting a role for CO in human testicular tissue.
Montagnani et al. (1996, 080902)	Rat Wistar Male pups	GD0-GD20	75 or 150 ppm	CO caused an increase in tetrodotoxin-induced inhibition of perivascular nerve stimulation PNS-evoked vasoconstriction, increased the time to NO-related relaxant effect by ACh, and decreased the contractile response evoked by ACh on resting tone.

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
Naik and Walker (2003, 193852)	Rat Sprague Dawley Male		210 µL of CO/100 mL of physiological saline solution	Endogenous CO-mediated vasorelaxation involved cGMP-independent activation of vascular smooth muscle large-conductance Ca^{2+}-activated K^+ channels. However, exogenous CO vasodilation was cGMP dependent.
Ndisang et al. (2004, 180425)				Review of CO and hypertension. CO is a vasorelaxant due to activation of the big conductance calcium-activated potassium channels and soluble guanylate cyclase/cGMP pathway. Developmental stage and tissue type will determine which of these pathways plays more of a role in vasorelaxation.
Neggers and Singh (2006, 193964)	Mouse CD-1	GD8-GD18	500 ppm	Developmental toxicitiy of CO was attenuated by protein supplementation, i.e., protein supplemented animals (27%) showed a significantly lower incidence of fetal mortality vs 8% and 16% protein groups. Further, dietary restriction of both protein and zinc with CO exposure to during gestation increased the incidence of pup mortality and malformations including gastroschisis. Zinc supplementation to a protein-deficient diet in CO-exposed mice decreased fetal mortality and malformation.
Newby et al. (2005, 193966)	Human placental cells in culture			Term human placental cells were grown in cell culture under basal and hypoxic conditions to explore changes in HO expression. HO-1 was unchanged in cytotrophoblasts under hypoxia, but HO-1 was significantly decreased in hypoxic syncytiotrophoblasts. HO-2 was unchanged in either cell type with hypoxia. These cell culture data can give insight into what cell types might be responsive to hypoxia through the HO/CO system in the human placenta.
Odrcich et al. (1998, 193958)	Guinea pig			Immunohistochemical localization of HO in guinea pig placentae showed that HO-1 staining was highest near term (PND62) and lesser at term or earlier in pregnancy. HO-1 was localized in the advential layer of fetal blood vessels.
Ozawa et al. (2002, 193841)	Rat Wistar Adult male			The role of HO-1 in spermatogenesis was explored. $CdCl_2$ induced testicular HO-1 and reduced HO-2 protein in rats. Pretreatment with ZnPPIX attenuated $CdCl_2$-dependent apoptosis. Leydig cells use HO-1-derived CO to trigger apoptosis of pre-meiotic germ cells and modulate spermatogenesis under $CdCl_2$ dependent oxidative stress.
Patel et al. (2003, 043155)	Rat Sprague Dawley Male 262 ± 30 g Isolated hearts	30 min	Buffer saturated with 0.01 and 0.05% CO	The ventricular glutathione content, both reduced and oxidized, decreased by 76% and 84% 90 min post-exposure to 0.01% and 0.05% CO, respectively. Treatment with antioxidants partially blocked the decreases in glutathione. Increased creatine kinase activity was observed in heart perfusate during and after treatment.
Penney et al. (1983, 011385)	Rat (strain not reported)	GD17-GD22	157, 166 or 200 ppm	In utero CO exposure induced decreased fetal body weight, decreased placental weight, increased wet heart weight at birth, and altered cardiac enzymes at birth.
Penney et al. (1982, 011387)	Rat COBS	GD0-GD32	350 ppm PND1-PND3, then 425 ppm PND4-PND7, then 500 ppm PND8-PND32	Postnatal CO exposure decreased body weight, to a greater extent in male pups. The heart to body weight ratio and left ventricle plus interventricular septum and right ventricle weight increased after birth in CO exposed pups. This persistent cardiomegaly was not explained by increasing in DNA or hydroxyproline.
Piantadosi (2002, 037463)				Reviews the biochemical activities of CO, including various heme protein binding. The review stresses the importance of the CO/O_2 ratio in determining the physiological effects of CO.
Piantadosi (2008, 180423)				Reviews the physiologic responses to exogenous and endogenous CO and biochemical effects, including the binding to heme proteins, the generation of reactive O_2 species, and activation-related signaling pathways.

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
Piantadosi et al. (2006, 180424)	Rat Sprague Dawley Adult male	1, 3, or 7 days	50 ppm or HH	COHb produced COHb levels of 4-5% (controls approximately 1%) and liver CO concentration of 30-40 pmol/mg wet weight (controls approximately 10 pmol/mg wet weight). Both CO and HH led to increased expression of hypoxia-sensitive proteins HO-1 and HIF-1α and mitochondrial antioxidant protein SOD-2. CO caused a greater change in mitochondrial GSH/GSSG than HH. Only CO increased mitochondrial 3-nitrotyrosine and protein mixed disulfides. Mitochondria isolated from CO-exposed rats, but not from HH-exposed rats, showed an increase in the calcium sensitivity of the mitochondrial permeability transition (MPT). Exposure to CO or HH resulted in a loss of the ability of adenine nucleotides to protect mitochondria from MPT. This effect was restored in the presence of a strong reductant. The authors concluded that CO caused mitochondrial pore stress independently of its hypoxic effects
Prigge and Hochrainer (1977, 012326)	Rat Wistar, SPF	GD0-GD20	60, 100, 250, 500 ppm	Fetuses were collected by C-section after 21-days exposure. Significant increases in fetal heart weight were seen in fetuses exposed to CO in all dose groups. Fetal body weight was signifi-cantly decreased (NOAEL 125 ppm CO).
(Raub and Benignus, 2002, 041616)				Reviews the physiology of CO and the effects on the nervous system. It is estimated that COHb would have to rise to 15-20% before a 10% reduction in any behavioral or visual measurement could be observed.
Richardson et al. (2002, 037513)	Human Male		20% COHb	20% COHb did not influence O_2Mb binding indicated by unaltered deoxy-myoglobin signal. Resting skeletal muscle metabolic rate was unaffected by 20% COHb. VO_2 max was decreased. No decrement in intracellular PO_2 was found. 20% COHb altered exercising bioenergetics, pH, PCr, and ATP levels.
Ryter et al. (2006, 193765)				Reviews the basic science of exogenous and endogenous CO including HO-1 regulation. It also reviews some therapeutic applications for CO.
Sartiani et al. (2004, 190898)	Rat Wistar	In utero inhalation exposure	150 ppm	At 4 wk of age, the action potential duration APD of isolated cardiac myocytes from CO-exposed animals failed to shorten or mature as did the APD of control animals. Further, the two ion conduction channels Ito (transient outward current, K^+-mediated) and ICa,L (L-type Ca^{2+} current), which largely control the rat APD, were significantly different from control animals after CO exposure at 4 wk of age. All of these CO-dependent changes were no longer different from controls at 8 wk of age, showing a delayed maturation.
Schwetz et al. (1979, 011855)	Mouse CF-1 Rabbit New Zealand	7 or 24-h/day GD6-GD15 (Mice) GD6-GD18 (Rabbits)	250 ppm	In mice there was a significant increase in number of skeletal abnormalities in CO-exposed mice. Decreased birth weight in mice exposed to 24 h/day CO vs control. Increased birth weight in mice exposed to 7 h/day CO vs controls. No similar effects were seen in rabbits.
Singh et al. (1992, 013759)	Mouse CD-1	GD8-GD18	65, 125, or 250 ppm	CO exposure concomitant with a low-protein diet exacerbated the percent of skeletal malformations in offspring. The percent of dead, resorbed, or grossly malformed fetuses was directly related to CO concentration and inversely related to maternal dietary protein levels. CO and maternal dietary protein restriction had a synergistic effect on offspring survival and an additive effect on malformations.
Singh (2006, 190512)	Mouse CD-1	6 h/day during the first 2nd wk of pregnancy	65 or 125 ppm	Modulating dam protein intake during in utero CO exposure altered pup mortality.
Singh et al. (1993, 013892)	Mouse Albino CD-1	GD8-GD18	65, 125, 250, or 500 ppm	Mice were given various protein diets (4, 8, 16, or 27% protein) during pregnancy, along with CO exposure. All concentrations of CO exposure within each maternal dietary protein level significantly increased the percentage of litters with malformations in a dose-dependent manner. CO exposure concomitant with a low protein diet exacerbated the percent of skeletal malformations in offspring. The percent of dead, resorbed, or grossly malformed fetuses was directly related to CO concentration and inversely related to maternal dietary protein levels. CO and maternal dietary protein restriction had a synergistic effect on mouse offspring mortality and an additive effect on malformations.

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
Singh (2003, 053624)	Mouse Albino CD-1	GD8-GD18	500 ppm	CO decreased the mean implants per litter and increased the incidence of fetal mortality. Under low protein conditions, CO exposure increased the incidence of malformations (9.4% vs 0%) when Zn levels were normal and increased the incidence of gastroschisis (5% vs 0%) when Zn levels were low.
Singh and Scott (1984, 011409)	Mouse Albino CD-1	GD7-GD18	65, 125, 250, or 500 ppm	All concentration of CO decreased fetal weight in mouse pups. Near-term fetal body weight was decreased at GD18 in mice exposed from GD7-GD18 to 125, 250, and 500 ppm CO but not at 65 ppm CO.
Singh (1986, 012827)	Mouse Albino CD-1	GD7-GD18	65 or 125 ppm	Impaired aerial righting score at PND14 (65 and 125 ppm), impaired negative geotaxis at PND10 and righting reflex on PND1 (125 ppm)
Sitdikova et al. (2007, 180417)	Frog neuro-muscular junctions	20 min	96 µM	CO-induced acetylcholine release, without effects on the pre-synaptic action potential or functional properties of post-synaptic receptors in frog neuro-muscular preparations.
Song et al. (2002, 037531)	Human Primary human airway smooth muscle cells	0-48 h	10-250 ppm	CO inhibited SMC proliferation at concentrations from 50-500 ppm. The cell cycle arrest occurred at the G0/G1 phase of the cell cycle. CO increased expression of the cell cycle inhibitor p21Cip1 at 1 h and decreased expression of cyclin D1 over 24-48 h. The antiproliferative actions of CO were found to be independent of sGC, but instead exerted through the inhibition of ERK MAPK activation since 15 min exposure to 250 ppm CO blocked serum-mediated ERK phosphorylation.
Sorhaug et al. (2006, 180414)	Rat Wistar Female 169 ± 4.5 g	20 h/day, x 5 days/wk, x 72 wk	200 ppm	COHb was 14.7% in CO-exposed animals and 0.3% in controls. Total Hb was also increased in following CO exposure. CO caused no changes in lung morphology or pulmonary hypertenstion. No atherosclerotic lesions were found in aorta or femoral artery. Weight increases of 20% and 14% were observed in the right ventricle and left ventricle plus septum, respectively, indicative of ventricular hypertrophy following chronic CO exposure.
Stevens and Wang (1993, 188458)	Mouse C57/Bl-6J Rat Sprague Dawley Hippocampal brain slices			HO inhibition blocked long-term potentiation but not long-term depression.
Stockard-Sullivan et al. (2003, 190947)	Rat Sprague Dawley	22 h/day, PND6-PND22	12, 25, 50, or 100 ppm	Using functional OAE testing and ABR showed that with perinatal CO exposure (50 and 100 ppm CO) there were significant decrements in OAE in CO-exposed animals. ABR showed no functional deficits with CO exposure. Using another otoacoustic test revealed significant attenuation of the AP of the 8th cranial nerve with CO exposure (12, 25, and 50 ppm CO) vs controls at PND22.
Storm and Fechter (1985, 011653)	Rat Long Evans	GD0-parturition	150 ppm	Prenatal CO exposure increased mean and total cerebellar norepinephrine concentration from PND14-PND42 but not in the cortex.
Storm and Fechter (1985, 011652)	Rat Long Evans	GD0-GD20	75, 150, and 300 ppm	CO transiently decreased 5HT and NE in the pons/medulla and increased NE in the cortex and hippocampus at PND42. CO dose-dependently reduced cerebellum wet weight. Maternal COHb: 2.5%, 11.5%, 18.5%, and 26.8% (0, 75, 150, and 300 ppm, respectively).
Storm et al. (1986, 012136)	Rat Long Evans	GD0-PND10	75, 150, and 300 ppm	CO decreased cerebellar weight (150-300 ppm at PND10, 75-300 ppm at PND21) and decreased total cerebellar GABA (150-300 ppm at PND10 and PND21). CO- exposed (300 ppm) cerebella had fewer fissures.
Styka and Penney (1978, 011166)	Rat Charles River Male	6 wk	400 ppm or gradual increase from 500 to 1,100 ppm	CO caused increased heart weight to body weight that regressed within a couple of mo after CO exposure. COHb: 400 ppm – 35%; 1,100 ppm – 58%

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
Suliman et al. (2007, 193768)	Mouse C57BL/6 Wild-type and eNOS deficient Male Rat Embryonic cardiomyocytes H9c2 cells	1 h	50-1,250 ppm Or HH Or 100 mM dichloromethane	One-h exposure of mice to 1,250 ppm CO increased cardiac mitochondrial content of all 5 respiratory complexes 24 h later. The volume density of interfibrillar mitochondria was increased by 30% after 24 h demonstrating that CO caused cardiac mitochondrial biogenesis. The CO concentration in heart increased from 9 pmol/mg to 50-150 pmol/mg in mice exposed to 50-1,250 ppm CO for 1 h. These levels declined to baseline by 6 h. Peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1α) expression was increased 6 h following exposure to 50-1,250 ppm CO. Expression of DNA polymerase and mitochondrial transcription factor A (TFAM) was increased 6 and 24 h after exposure, while mitochondrial DNA was increased two- to threefold 24 h after exposure. CO activated gene expression of these proteins involved in cardiac mitochondrial biogenesis beginning at 2 h postexposure for PGC-1α, nuclear respiratory factors 1 and 2 (NRF-1 and -2) and at 6 h postexposure for TFAM. These effects were independent of NOS and not seen with HH. CO exposure resulted in phosphorylation of p38 MAPK and Akt at 2 and 6 h postexposure to 1,250 ppm CO for 1 h. Inhibition of p38 activation failed to inhibit the CO-mediated increase in cardiac mitochondrial biogenesis. In cell culture experiments, CO derived from dichloromethane metabolism resulted in increased cGMP, protein levels of SOD2, TFAM, NRF-1, NRF-2, PGC-1,mitochondrial ROS, Akt phosphorylation, and mitochondrial DNA. Inhibition of GC or PI3K/Akt but not p38 blocked the responses to CO. A role for mitochondrial H_2O_2 in Akt regulation was demonstrated. Mitochondrial H_2O_2 and the PI3K/Akt pathway were important mediators of TFAM expression. The authors concluded that CO exposure increased mitochondrial ROS, which promoted mitochondrial biogenesis in the heart.
Sun et al. (2001, 026022)	Mouse Neuronal cultures prepared from the cerebral hemispheres of 16-day Charles River CD1 mouse embryos			Nb expression was increased by neuronal hypoxia in vitro and focal cerebral ischemia in vivo. Inhibiting Nb reduced neuronal survival after hypoxia whereas Nb overexpression enhanced neuronal survival.
Tattoli et al. (1999, 011557)	Rat Wistar Male and pregnant female	PND1-PND10	75 and 150 ppm	Cognitive function was assessed in rats after postnatal CO exposure at 3 and 18 mo of age. Postnatal CO exposure did not affect the acquisition and reacquisition of an active avoidance task. This is different from previous findings by the same laboratory, indicating that in utero exposure to CO (75 and 150 ppm) induced long-lasting learning and memory deficits.
Telfer et al. (2001, 193769)	Human Myometrium tissue obtained from gravid (pre-term [25- to 34 wk gestation], term not in labor or term in labor) and non-gravid women			cGMP was monitored in various myometrial tissues. cGMP was significantly higher than that from nonpregnant tissue and decreased at term, especially in tissue from laboring women.
Teran et al. (2005, 193770)	Rat Dahl/Rapp salt-sensitive rats Male		100 µM	A high-salt diet for 1-4 wk resulted in increased aortic HO-1 protein expression, an increase in mean arterial pressure, and time-dependent inhibition of flow- and acetylcholine-mediated vasodilation in isolated gracilis muscle arterioles. A smaller degree of inhibition of acetylcholine-mediated vasodilation was observed with a low-salt diet for 1-4 wk. Pretreatment with a HO inhibitor restored these responses, but this effect was reversed in the presence of exogenous CO. Mean arterial pressure was decreased in intact animals fed a high-salt diet for 4 wk and then treated with a HO inhibitor. The authors concluded that the HO-derived CO contributed to the development of hypertension and the impairment of endothelium-dependent vasodilator responses in this model.

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
Thom et al. (1994, 076459)	Rat Wistar Male Isolated blood cells	1 h Or >1 h 30 min	1,000 ppm Or 1,000-3,000 and higher ppm 0.5 mL of pure CO	CO poisoning inhibited B_2 integrin-dependent PMN adherence in heparinized blood obtained from rats immediately after exposure. Adherence was restored when platelet number was decreased. Adherence was also decreased when PMN from control animals were incubated with platelets from poisoned animals. Adherence of activated PMN was reduced in the presence of SOD and enhanced by NOS inhibition. Platelet production of NO was significantly greater while platelet NOS activity was significantly inhibited after poisoning. When whole blood or platelet-rich plasma was incubated with CO, PMN adherence was inhibited. The authors concluded that PMN B_2 integrin activity was inhibited by CO-dependent release of NO from the platelets into the blood.
Thom and Ischiropoulos (1997, 085644)	Ra Wistar Male 200-290 g Platelet-rich plasma from rats was used as the source of platelets Bovine pulmonary artery endothelial cells	1 h 30 min or 2 h 1 h	20-1,000 ppm 10-20 ppm 10-100 ppm	Platelets isolated from rats exposed to 20-1,000 ppm CO for 1-h released NO in a dose-dependent manner. COHb levels were 0.7% in controls and 3.2%, 7.8% and 51.0% in 20, 100 and 1,000 ppm exposure groups, respectively. Isolated platelets released NO when incubated for 30 min with 20-100 ppm CO. NOS activity was not enhanced by 100 ppm CO. Platelets released NO in response to 10-100 ppm CO after 30-min pretreatment with a NOS inhibitor, suggesting that CO displaces NO from heme-binding sites. Longer incubations (2 h) with the NOS inhibitor led to a diminished response to 100 ppm CO. There appears to be a discrepancy in the results, depending on howNOwas measured (electrode vs Greiss reaction). Endothelial cells released NO in response to 20-100 ppm CO. NOS inhibition blocked the response to 100 ppm CO. CO was found not to affect arginine transport or NOS activity in endothelial cells. Exposure to 40-100 ppm CO resulted in the release of short-lived oxidants. This response was blocked by NOS inhibition. Lysates from cells exposed to 50 and 100 ppm CO had increased nitrotyrosine content. This response was blocked by NOS inhibition. Cellular reduced sulfhydryls were not decreased by 100 ppm CO. Dihydrorhodamine 123 oxidation, a measure of peroxynitrite formation, was increased by exposure to 100 ppm CO. This effect was blocked by NOS inhibition. Cytotoxicity of CO was evaluated by the release of ^{51}chromium. Cytotoxicity was evident 4 h following a 2-h incubation with 100 ppm CO but not immediately after exposure. This response was not blocked by NOS inhibition, although NOS inhibition had protective effects under conditions of continuous CO exposure of 4 h. Exposure to 20 and 100 ppm CO for 2 h led to the loss of membrane integrity (measured by ethidium homodimer-1 staining) 18 h later. Results demonstrate that 10-20 ppm CO released NO from platelets and endothelial cells in vitro. Platelets from rats that inhaled 20 ppm CO also released NO in vitro. The authors suggested that CO-mediated NO release from platelets and endothelial cells resulted from disrupted intracellular scavenging for NO. They also suggested that peroxynitrite may have been generated in response to CO.

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
Thom et al. (1997, 084337)	Bovine pulmonary artery endothelial cells	30 min-4 h	10-100 ppm (11-110 nM)	One-h exposure to 111-110 nM CO led to a dose-dependent increase in NO release, as measured by nitrite+nitrate. Significance was achieved at 22 nM (corresponding to an interstitial partial pressure of 20 ppm and a blood COHb level of 7%). NOS inhibition blocked the response to 110 nM CO. A dose-dependent increase in cellular nitrotyrosine was also observed following a 2-h exposure to CO, with significance achieved at 55 nM CO. NOS inhibition blocked the response to 110 nM. CO exposure failed to decrease the concentration of reduced sulfhydryls but did result in the extracellular release of a short-lived oxidant species, which was blocked by NOS inhibition. Dihydrorhodamine oxidation, a measure of peroxynitrite formation, occurred in response to 110 nM CO, an effect which was blocked by NOS inhibition. Cytotoxicity of CO was evaluated by the release of ^{51} chromium. Cytotoxicity was evident 4 h following a 2-h incubation with 110 nM CO but not immediately after exposure. This response was not blocked by NOS inhibition, although NOS inhibition had protective effects under conditions of continuous CO exposure of 4 h. Exposure to 110 nM CO for 2 h led to the loss of membrane integrity (measured by ethidium homodimer-1 staining) 18 h later. This response was blocked by NOS inhibition. Exposure to 110 nM CO had no effect on O_2 consumption, production of intracellular $H2O_2$ or cellular redox activity. Exposure to 110 nM did not alter arginine transport or NOS activity. NO release from cells which had been pretreated with a NOS inhibitor and then exposed briefly to 5% CO was measured using a NO-selective electrode, suggesting that CO competed with intracellular binding sites of NO. The authors concluded that endothelial cells release NO and NO-derived oxidants in response to CO. A delayed cell death occurred following exposures to 22 nM and higher concentrations of CO.
Thom et al. (1999, 016753)	Rat Wistar Male 200-290 g Some rats were fed a high cholesterol diet	1 h	50-1,000 ppm	Nitrotyrosine immunoreactivity was found in aortic intima in rats exposed to CO for 1 h but not in controls. Nitrotyrosine content was quantitated and found to be increased in a dose-dependent manner following 1-h exposure to 50-1,000 ppm CO. The effect was significant at 50 ppm but the COHb content measured immediately after exposure was not different than controls. Platelet and neutrophil depletion did not alter nitrotyrosine content following CO exposure. Leukocyte adherence to the aorta occurred 18 h but not immediately after a 1-h exposure to 100 ppm CO. This effect was blocked by NOS inhibition. The influx of albumin from the microvasculature into skeletal muscle increased during the 3 h after exposure to 100 ppm CO but was not seen 18 h later. This effect was blocked by NOS inhibition. Rats fed a high-cholesterol diet and exposed to 100 ppm CO for 1 h had increased aortic nitrotyrosine content, which was not different than that in CO-exposed rats fed the standard diet. However, rats on the high-cholesterol diet had a six-fold increase in LDL oxidation immediately after 1-h exposure to 100 ppm CO. This effect was not blocked by NOS inhibition. The authors concluded that CO can alter vascular status by several mechanisms linked to NO-derived oxidants.

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
Thom et al. (1999, 016757)	Rat Wistar Male 200-290 g	1 h	50-1,000 ppm	Leakage of albumin into lung parenchyma occurred 18 h after rats were exposed to 100 ppm CO for 1 h. This response was not observed at earlier timepoints following CO exposure. This response was also observed using 50 and 1,000 ppm but not 20 ppm CO. Leakage resolved by 48 h. Furthermore, no leakage occurred when rats which were exposed to 100 ppm CO were pretreated with a NOS inhibitor. COHb levels were 0.9% in controls and 4.8%, 10.6% and 53.7% following 1-h exposure to 50, 100 and 1,000 ppm CO, respectively. Elevated free NO (determined by EPR) was observed in lungs of rats exposed to 100 ppm CO for 1 h. This effect was blocked when rats were pretreated with a NOS inhibitor. Lung H_2O_2 was elevated by exposure to 100 ppm CO for 1 h, and this effect was blocked when rats were pretreated with a NOS inhibitor. Elevated nitrotyrosine content was observed in lung homogenates 2-4 h following 1-h exposure of rats to 100 ppm CO. This effect was also blocked by pretreatment with a NOS inhibitor. No leukocyte sequestration was observed in lungs 18 h following exposure to 100 ppm CO. CO-induced lung leak was not affected by neutrophil depletion. The authors concluded that CO causes lung vascular injury which is dependent on NO.
Thom et al. (2000, 011574)	Bovine pulmonary artery endothelial cells	40 min-2 h	11-110 nM (10-100 ppm)	Increased uptake of ethidium homodimer-1, a measure of decreased membrane integrity and cell death, was observed in endothelial cells 18 h after exposure to 110 nM for 60-120 min. Exposures of 20-40 nM were ineffective in this regard. Ethidium uptake was also increased by 2-h exposure to 88 nM CO. Preincubation for 2 h with an inhibitor of eNOS, an antioxidant, and an inhibitor of peroxynitrite reactions blocked the CO-mediated cell death. Morphological changes in cells were observed 2 h following a 2-h exposure to 110 nM CO. Cell death induced by 110 nM CO was also blocked by inhibition of protein synthesis and inhibition of caspase-1 but of caspase-3. Caspase-1 activity was increased following 2-h exposure to 110 nM CO; this effect was blocked by inhibiting eNOS. Pre-exposure of cells to 11 nM CO for 40 min followed by a 3-h incubation period resulted in an increased level of MnSOD and protection against cell death 18 h following a 2-h exposure to 110 nM CO. The authors concluded that exposure to 11 nM CO led to an adaptive response which protected cells from injury and apoptosis resulting from NO-derived oxidants.
Thom et al. (2001, 193779)	Rat	Until lost consciousness	1,000-3,000 ppm	Neutrophils sequestration was observed in the brain vessels of rats exposed to high-dose CO. CO also led to increased nitrotyrosine formation in the brain vessels. These events were blocked by pretreatment with a peroxynitrite scavenger or a PAF receptor antagonist.
Thom et al. (2006, 098418)	Human Rat Wistar Male Mouse C57B6J MPO-deficient Blood samples and brain tissue	1 h	Humans: Acute CO poisoning Rats and mice: 1,000-3,000 ppm	In humans, COHb was 20-30.5%. Increased cell surface expression of CD18 and PAC1 was observed in neutrophils from people with CO poisoning. Increased surface-bound myeloperoxidase (MPO, indicative of neutrophil degranulation), increased plasma MPO, and more numerous platelet-neutrophil aggregates were also observed. Similar changes were observed in blood of CO-poisoned rats. Platelet depletion, inhibition of NOS, and inhibition of platelet integrin-dependent adhesion blocked these responses. Brains from poisoned rats had significant elevations in MPO, which could reflect either an increase number of neutrophils or an increase in neutrophil degranulation. Perivascular MPO and nitrotyrosine were CO-localized in brain. CO poisoning also resulted in altered brain myelin basic protein. Similar changes were observed in blood of CO-poisoned mice. MPO deficiency blocked the CO-mediated alteration in brain myelin basic protein. The authors concluded that exposure to CO triggers intravascular interactions between platelets and neutrophils that lead to neutrophil degranulation in experimental animals and people with CO poisoning.

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
Thorup et al. (1999, 193782)	Rat Sprague Dawley Male 200-250 g		0.01-10 µM	Perfusion of isolated rat renal resistance arteries with CO-containing buffer (0.001-10 µM) led to the biphasic release of NO, peaking at 100 nM and declining to undetectable responses at 10 µM. Sequential pulses of 100 nM resulted in a blunting of NO release with consecutive pulses, consistent with a depletion of intracellular NO stores. NO release was dependent on arginine concentrations and was inhibited by pretreatment with a NOS inhibitor. Perfusion with 100 nM CO blocked carbachol-dependent NO release from vessels. Rats were treated with a HO-1 inducer, and renal resistance arteries were isolated 12 h later. Carbachol-induced NO release was smaller in the HO-1-induced rats compared with controls, suggesting that endogenous CO has a similar effect as 100 nM exogenous CO. This effect was reversed in the presence of excess arginine. Vasodilation was measured in blood-perfused afferent arterioles perfused with CO in solution. A biphasic vasodilatory response was observed as well as a blunted muscarinic vasorelaxation. CO (0.1-10 µM) suppressed the release of NO from purified recombinant eNOS in solution. The authors concluded that low levels of CO may release NO and elicit vasorelaxation and modulate basal vascular tone, while higher levels of CO may inhibit eNOS and NO generation.
Tolcos et al. (2000, 015997)	Guinea pig	10 h/day over the last 60% of gestation	200 ppm	Fetal nd maternal COHb were 13% and 8.5%, respectively. Neurotransmitter systems were affected after CO exposure. The catecholaminergic system of the brainstem displayed significant decreases in immunoreactivity for tyrosine hydroxylase (TH), which was likely due to decreased cell number in specific medullar regions. The cholinergic system was also affected by prenatal CO exposure with significant increases in ChAT immunoreactivity of the medulla and no changes in muscarinic acetylcholine receptor.
Tolcos et al. (2000, 010468)	Guinea pig	10 h/day for the last 60% of gestation	200 ppm	Brains were collected at 1 and 8 wk of age. These data showed that CO exposure in utero sensitized the brain to hyperthermia at PND4 leading to generation of necrotic lesions in the brain and changes in neurotransmitter levels.
Toyada et al. (1996, 079945)				
Tschugguel et al. (2001, 193785)	Human HUVEC			CO was generated by primary endothelial cells from human umbilical veins and uterine arteries after exogenous 17-ß estradiol administration.
Vallone et al. (2004, 193993)	Mouse protein			The authors presented the X-ray structure of CO-bound ferrous murine Nb. When CO binds, the heme group slides deeper into the protein crevice.
Villamor et al. (2000, 015838)				
Vreman et al. (2000, 096915)	Human Umbilical cord (artery and vein) Rat Aorta, vena cavae, liver and heart			HO activity was quantified in human umbilical cord and in the rat vasculature (aorta and vena cavae). Human umbilical artery and vein HO activity were equal. The rat aorta and vena cavae produced equal amounts of HO activity (wet weight/g tissue) but generated 3 times greater HO than the heart and 0.2 times of the liver. HO activity in rat vasculature was 3 times that of the human cord tissues. Use of the HO inhibitor CrMP effectively blocked HO activity in the rat liver and heart but was less effective at blocking HO activity in the human umbilical cord or the rat vasculature (only 50% effective). The activity of HO in the umbilical vessels may provide a role for CO in control of vasculature tone during pregnancy.

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
Vreman et al. (2005, 193786)	Mouse BALB/c	30 min	500 ppm OR Heme arginate 30 µmol/kg body weight i.v.	Following CO exposure, COHb levels were 28%. Tissue concentrations of CO were as follows with control levels in parenthesis. Blood: 2648 ± 400 (45) pmol/mg Heart: 100 ±18 (6) pmol/mg Muscle: 14 ± 1 (10) pmol/mg Brain: 18 ± 4 (2) pmol/mg Kidney: 120 ± 12 (7) pmol/mg Spleen: 229 ± 55 (6) pmol/mg Liver: 115 ± 31 (5) pmol/mg Lung: 250 ± 2 (3) pmol/mg Intestine: 9 ± 7 (4) pmol/mg Testes: 6 ± 3 (2) pmol/mg CO concentration relative to 100% blood: Lung: 9.4%, Spleen: 8.6% Kidney: 4.5%, Liver: 4.3%, Heart: 3.8%, Brain: 0.7%, Muscle: 0.5%, Intestine: 0.3%, Testes: 0.2% Injection of heme arginate resulted in a threefold increase in CO excretion, reaching a maximum at 60 min. Animals were sacrificed at 90 min. COHb levels were 0.9%. Tissue concentrations of CO were as follows with control levels in parenthesis: Blood: 88 ±10 (45) pmol/mg Heart: 14 ± 3 (6) pmol/mg Muscle: 7 ± 1 (10) pmol/mg Brain: 2 ± 0 (2) pmol/mg Kidney: 7 ± 2 (7) pmol/mg Spleen: 11 ± 1 (6) pmol/mg Liver: 8 ± 3 (5) pmol/mg Lung: 8 ± 3 (3) pmol/mg Intestine: 3 ± 1 (4) pmol/mg Testes: 2 ± 0 (2) pmol/mg CO concentration relative to 100% blood: Heart: 16% Spleen: 13% Lung: 9% Liver: 9% Kidney: 8% Muscle: 8% Intestine: 3% Brain: 2% Testes: 2%
Weaver et al. (2007, 193939)	Human		Acute CO poisoning	Mean COHb in humans with acute CO poisoning was 35%. Hyperbaric O_2 reduces cognitive sequelae in a randomized clinical trial of CO-poisoned patients. Risk factors for cognitive sequelae without hyperbaric O_2 included older age and longer CO exposures. Patients with loss of consciousness or high initial COHb levels should also be treated with hyperbaric O_2.
Webber et al. (2003, 190515)	Rat (Strain not stated)	PND8-PND22	12.5, 25, or 50 ppm	Immunostaining of c-Fos, a marker of neuronal activation in the nervous system, was followed. C-Fos immunoreactivity in the central IC was significantly decreased in the CO-exposed animals at both PND27 and PND75-PND77 over all dose groups of CO; immnunostaining of other subregions of the IC were not affected by CO. These studies show exposure to CO during development can lead to permanent changes in the auditory system of rats that persist into adulthood.

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
Webber et al. (2005, 190514)	Rat (Strain not stated)	PND9-PND24	25 or 100 ppm	Neurofilament loss from the spiral ganglion neurons and somas after ARCO treatment was rescued (no detectable neurofilament loss) with low iron+CO (ARIDCO); ARID (low iron) treatment induced no change in neurofilaments. CuZn superoxide dismutase (SOD1) was significantly increased with CO exposure (ARCO) and rescued in ARIDCO animals; SOD1 was unchanged in low-iron-only animals (ARID). Low-iron treatment or CO exposure alone led to significant decreases in c-fos positive cell numbers of the central IC, but c-fos levels were unchanged after low-iron diet concomitant with CO exposure (ARIDCO).
Wellenius et al. (2004, 087874)	Rat Sprague Dawley 250 g Diazepam-sedated Model of acute MI induced by thermocoagulation	1 h, 12-18 h after surgery	35 ppm	CO exposure decreased ventricular premature beat frequency by 60.4% during the exposure period compared to controls. 1-h exposure to CAPs (318 $\mu g/m^3$) decreased ventricular premature beat frequency in specific subgroups. Neither CAPs nor CO had an effect on heart rate. There were no significant interactions between their effects when rats were exposed to both CO and CAPs.
Wellenius et al. (2006, 156152)	Rat Sprague Dawley 250 g Diazepam-sedated Model of acute MI induced by thermocoagulation	1 h, 12-18 h after surgery	35 ppm	Exposure to CO failed to increase the probability of observing supraventricular ectopic beats (SVEB). Exposure to CAPs (646 $\mu g/m^3$) for 1 h decreased the frequency of SVEB. There were no significant effects observed when rats were exposed to both CO and CAPs. Among a subset of rats with one or more SVEB at baseline, a significant decrease in number of SVEB during the exposure period was observed with either CO or CAPs exposure compared with controls.
Yoshiki et al.(2001, 193790)	Human			HO localization in human endometrium and its changes in expression over the menstrual cycle were explored in this study. HO-1 was constitutively expressed throughout the menstrual cycle, and HO-2 was greater in the secretory than the proliferative phase of the menstrual cycle. HO-1 was localized to the epithelial cells and macrophages. HO-2 was found in endothelial cells and smooth muscle cells of endometrial blood vessels.
Yu et al. (2008, 192384)	Guinea pig Allergic rhinitis model using nasal ovalbumin sensitization			Indicators of allergic rhinitis were enhanced by treatment with a HO-1 inducer and decreased by treatment with a HO-1 inhibitor. Immunoreactivity for HO-1 was shown in the lamina of mucosa of sensitized guinea pigs. Endogenous CO may play a role in the inflammation process of allergic rhinitis.
Zamudio et al. (1995, 193908)	Human			Women living at high altitude had an increased risk of adverse pregnancy outcomes vs women living at lower altitudes.
Zenclussen et al. (2006, 193873)	Mouse CBA/J x DBA/2J			To evaluate the role of HO-1 in spontaneous abortion, a mouse model that spontaneously undergoes abortion (CBA/J x DBA/2J mice) was used with and without HO adenovirus treatment to see if pregnancy outcome could be modulated by changing HO concentration. Pregnancy outcome was significantly better (abortion rate significantly decreased) in mice overexpressing HO due to adenovirus transfer.
Zhang et al. (2005, 184460)	Rat Pulmonary artery endothelial cells	8-28 h	15 ppm	Exposure to 15 ppm CO during anoxia resulted in decreased phosphorylation of STAT1 and increased phosphorylation of STAT3 at 8-24 h. Similar responses were observed when 24-h anoxia was followed by a period of reoxygenation (0.5-4 h). DNA binding of STAT1 was decreased while that of STAT3 was enhanced by CO treatment during anoxia/reoxygenation. Exposure to 15 ppm during 8-24-h anoxia or 24 h anoxia followed by 0.5-4 h reoxygenation resulted in increased phosphorylation of Akt and p38 MAPK. Inhibitor studies demonstrated that activation of the PI3K pathway by CO was upstream of p38 MAPK activation during anoxia/reoxygenation. Similarly, the PI3K and p38 MAPK pathways were found to be upstream of STAT modulation. The anti-apoptotic effects of 15 ppm CO during anoxia-reoxygenation involved decreased FAS expression and decreased caspase 3 acvitiry. These effects were dependent on activation of the PI3K, p38 MAPK and STAT3 pathways. The authors concluded that CO blocks anoxia-reoxygenation mediated apoptosis through modulation of PI3K/Akt/p38 MAPK and STAT1 and STAT3.

Reference	Species / Model	Exposure Duration	CO Concentration	Findings
Zhang et al. (2007, 193879)	Mouse			A single dose of LPS administered to pregnant mice induced up-regulation of HO-1 but not HO-2 in the mouse placenta 12-48 h postLPS treatment. Pretreatment of mice with the spin trap agent PBN or the TNF α inhibitor pentoxifylline prevented the LPS-dependent HO-1 upregulation. Thus ROS may mediate the LPS-dependent upregulation of HO-1.
Zhao et al. (2008, 193883)	Mouse FVB			With pregnancy, there was an increased blood volume without a concurrent increase in systemic BP; this was accomplished by a decrease in total vascular resistance, to which CO contributed as determined by using HO inhibitors.
Zhuo et al. (1993, 013905)	Guinea pig Adult male			Hippocampal LTP of brain sections is significantly affected by CO exposure with ZnPP IX, a HO inhibitor, blocking hippocampal LTP.
Zuckerbraun et al. (2007, 193884)	Macrophages RAW 264.7 THP-1 cells, wild-type and respiration-deficient	10 min-24 h	50-500 ppm	Exposure of RAW macrophages to 250 ppm CO for 10-60 min increased ROS generation, measured as dichlorofluorescein (DCF) fluorescence. ROS generation at 1 h was dose dependent with significant effects observed at 50, 250 and 500 ppm CO. This response was not blocked with a NOS inhibitor. A 1-h exposure to 250 ppm resulted in decreased intracellular glutathione levels. CO treatment was found to block TNFα production and to enhance p38 MAPK phosphorylation in LPS-stimulated cells. These effects were diminished by pretreatment with antioxidants. The source of CO-derived oxidants was determined to be mitochondrial since respiration-deficient THP-1 macrophages, unlike wild-type cells, failed to generate ROS in response to 250 ppm CO. Furthermore, treatment of RAW cells with the mitochondrial complex III inhibitor antimycin C, blocked ROS generation in response to 250 ppm CO. Exposure of RAW cells to 250 ppm CO for 1 h inhibited cytochrome c oxidase activity by 50%. Exposure to 250 ppm CO for 6 h had no effect on cellular ATP levels or mitochondrial membrane potential. Antimycin C treatment was found to reverse the effects of CO on LPS-mediated responses (TNFα and p38 MAPK), suggesting that mitochondrial-derived ROS mediated the effects of CO. The authors concluded that CO increased the generation of mitochondrial-derived ROS.

References

Acevedo CH; Ahmed A (1998). Hemeoxygenase-1 inhibits human myometrial contractility via carbon monoxide and is upregulated by progesterone during pregnancy. J Clin Invest, 101: 949-955. 016003

Achouh PE; Simonet S; Fabiani JN; Verbeuren TJ (2008). Carbon monoxide induces relaxation of human internal thoracic and radial arterial grafts. Interact Cardiovasc Thorac Surg, 7: 959-963. 179918

Ahmed A; Rahman M; Zhang X; Acevedo CH; Nijjar S; Rushton I; Bussolati B; St John J (2000). Induction of placental heme oxygenase-1 is protective against TNFalpha-induced cytotoxicity and promotes vessel relaxation. Mol Med, 6: 391-409. 193863

Ahmed H; McLaughlin BE; Soong J; Marks GS; Brien JF; Nakatsu K (2005). The source of endogenous carbon monoxide formation in human placental chorionic villi. Cell Mol Biol Incl Cyto Enzymol, 51: 447-451. 193865

Alexander PG; Chau L; Tuan RS (2007). Role of nitric oxide in chick embryonic organogenesis and dysmorphogenesis. Birth Defects Res A Clin Mol Teratol, 79: 581-594. 193869

Alexandreanu IC; Lawson DM (2002). Effects of chronic administration of a heme oxygenase substrate or inhibitor on progression of the estrous cycle, pregnancy and lactation of Sprague-Dawley rats. Life Sci, 72: 153-162. 192373

Alexandreanu IC; Lawson DM (2003). Heme oxygenase in the rat anterior pituitary: Immunohistochemical localization and possible role in gonadotropin and prolactin secretion. Exp Biol Med, 228: 64-69. 193871

Alexandreanu IC; Lawson DM (2003). Heme oxygenase in the rat ovary: Immunohistochemical localization and possible role in steroidogenesis. Exp Biol Med, 228: 59-63. 193876

Alonso JR; Cardellach F; Lopez S; Casademont J; Miro O (2003). Carbon monoxide specifically inhibits cytochrome c oxidase of human mitochondrial respiratory chain. Pharmacol Toxicol, 93: 142-146. 193882

Andresen JJ; Shafi NI; Durante W; Bryan RM Jr (2006). Effects of carbon monoxide and heme oxygenase inhibitors in cerebral vessels of rats and mice. Am J Physiol Heart Circ Physiol, 291: H223-H230. 180449

Antonelli T; Tomasini MC; Tattoli M; Cassano T; Finetti S; Mazzoni E; Trabace L; Carratu MR; Cuomo V; Tanganelli S; Ferraro L (2006). Prenatal exposure to the cannabinoid receptor agonist WIN 55,212-2 and carbon monoxide reduces extracellular glutamate levels in primary rat cerebral cortex cell cultures. Neurochem Int, 49: 568-76. 194960

Appleton SD; Marks GS; Nakatsu K; Brien JF; Smith GN; Graham CH (2002). Heme oxygenase activity in placenta: Direct dependence on oxygen availability. Am J Physiol Heart Circ Physiol, 282: 2055-2059. 193935

Ashfaq M; Janjua MZ; Nawaz M (2003). Effects of maternal smoking on placental morphology . JAMC, 15: 1-5. 194002

Astrup P; Olsen HM; Trolle D; Kjeldsen K (1972). Effect of moderate carbon-monoxide exposure on fetal development. Lancet, 7789: 1220-1222. 011121

Bainbridge SA; Belkacemi L; Dickinson M; Graham CH; Smith GN (2006). Carbon monoxide inhibits hypoxia/reoxygenation-induced apoptosis and secondary necrosis in syncytiotrophoblast. Am J Pathol, 169: 774-783. 193949

Bainbridge SA; Farley AE; McLaughlin BE; Graham CH; Marks GS; Nakatsu K; Brien JF; Smith GN (2002). Carbon monoxide decreases perfusion pressure in isolated human placenta. Placenta, 23: 563-569. 043161

Bainbridge SA; Smith GN (2005). HO in pregnancy. Free Radic Biol Med, 38: 979-988. 193946

Bamberger A-M; Koglin M; Kempfert J; Loning T; Scholz H; Behrends S (2001). Expression and tissue localization of soluble guanylyl cyclase in the human placenta using novel antibodies directed against the alpha2 subunit. J Clin Endocrinol Metab, 86: 909-912. 016271

Barber A; Robson SC; Lyall F (1999). Hemoxygenase and nitric oxide synthase do not maintain human uterine quiescence during pregnancy. Am J Pathol, 155: 831-840. 193953

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Barber A; Robson SC; Myatt L; Bulmer JN; Lyall F (2001). Heme oxygenase expression in human placenta and placental bed: reduced expression of placenta endothelial HO-2 in preeclampsia and fetal growth restriction. FASEB J, 15: 1158-68. 193891

Baum M; Schiff E; Kreiser D; Dennery PA; Stevenson DK; Rosenthal T; Seidman DS (2000). End-tidal carbon monoxide measurements in women with pregnancy-induced hypertension and preeclampsia. Am J Obstet Gynecol, 183: 900-903. 016435

Benagiano V; Lorusso L; Coluccia A; Tarullo A; Flace P; Girolamo F; Bosco L; Cagiano R; Ambrosi G (2005). Glutamic acid decarboxylase and GABA immunoreactivities in the cerebellar cortex of adult rat after prenatal exposure to a low concentration of carbon monoxide. Neuroscience, 135: 897-905. 180445

Benagiano V; Lorusso L; Flace P; Girolamo F; Rizzi A; Sabatini R; Auteri P; Bosco L; Cagiano R; Ambrosi G (2007). Effects of prenatal exposure to the CB-1 receptor agonist WIN 55212-2 or CO on the GABAergic neuronal systems of rat cerebellar cortex. Neuroscience, 149: 592-601. 193892

Bergeron M; Ferriero DM; Sharp FR (1998). Developmental expression of heme oxygenase-1 (HSP32) in rat brain: An immunocytochemical study. Dev Brain Res, 105: 181-194. 193967

Bing O; Grundemar L; Ny L; Moller C; Heilig M (1995). Modulation of carbon monoxide production and enhanced spatial learning by tin protoporphyrin. Neuroreport, 6: 1369-1372. 079418

Burmester T; Weich B; Reinhardt S; Hankeln T (2000). A vertebrate globin expressed in the brain. Nature, 407: 520-523. 099998

Bye A; Sørhaug S; Ceci M; Høydal MA; Stølen T; Heinrich G; Tjønna AE; Najjar SM; Nilsen OG; Catalucci D; Grimaldi S; Contu R; Steinshamn S; Condorelli G; Smith GL; Ellingsen O; Waldum H; Wisløff U (2008). Carbon monoxide levels experienced by heavy smokers impair aerobic capacity and cardiac contractility and induce pathological hypertrophy. Inhal Toxicol, 20: 635-646. 193777

Cagiano R; Ancona D; Cassano T; Tattoli M; Trabace L; Cuomo V (1998). Effects of prenatal exposure to low concentrations of carbon monoxide on sexual behaviour and mesolimbic dopaminergic function in rat offspring. Br J Pharmacol, 125: 909-915. 087170

Carmines E; Rajendran N (2008). Evidence for carbon monoxide as the major factor contributing to lower fetal weights in rats exposed to cigarette smoke. Toxicol Sci, 102: 383. 188440

Carratu MR; Cagiano R; De Salvia MA; Trabace L; Cuomo V (1995). Developmental neurotoxicity of carbon monoxide. Presented at In: Degen, G. H.; Seiler, J. P.; Bentley, P., eds. Toxicology in transition: proceedings of the 1994 EUROTOX congress; August 1994; Basel, Switzerland. Arch. Toxicol. Suppl. 17: 295-301. 079427

Carratu MR; Cagiano R; Desantis S; Labate M; Tattoli M; Trabace L; Cuomo V (2000). Prenatal exposure to low levels of carbon monoxide alters sciatic nerve myelination in rat offspring. Life Sci, 67: 1759-1772. 015839

Carratu MR; Cagiano R; Tattoli M; Trabace L; Borracci P; Cuomo V (2000). Prenatal exposure model simulating CO inhalation in human cigarette smokers: sphingomyelin alterations in the rat sciatic nerve. Toxicol Lett, 117: 101-106. 015935

Carratu MR; Renna G; Giustino A; De Salvia MA; Cuomo V (1993). Changes in peripheral nervous system activity produced in rats by prenatal exposure to carbon monoxide. Arch Toxicol, 67: 297-301. 013812

Carraway MS; Ghio AJ; Suliman HB; Carter JD; Whorton AR; Piantadosi CA (2002). Carbon monoxide promotes hypoxic pulmonary vascular remodeling. Am J Physiol, 282: L693-L702. 026018

Cella M; Farina MG; Sarmiento MIK; Chianelli M; Rosenstein RE; Franchi AM (2006). Heme oxygenase-carbon monoxide (HO-CO) system in rat uterus : Effect of sexual steroids and prostaglandins. J Steroid Biochem Mol Biol, 99: 59-66 . 193240

Chen GH; Kong J; Reinhard K; Fechter LD (2001). NMDA receptor blockage protects against permanent noise-induced hearing loss but not its potentiation by carbon monoxide . Hear Res, 154: 108-115. 193985

Cheng C; Noordeloos AM; Jeney V; Soares MP; Moll F; Pasterkamp G; Serruys PW; Duckers HJ (2009). Heme oxygenase 1 determines atherosclerotic lesion progression into a vulnerable plaque. Circulation, 119: 3017-3027. 193775

Chung Y; Huang SJ; Glabe A; Jue T (2006). Implication of CO inactivation on myoglobin function. Am J Physiol Lung Cell Mol Physiol, 290: 1616-1624. 193987

Cronje FJ; Carraway MS; Freiberger JJ; Suliman HB; Piantadosi CA (2004). Carbon monoxide actuates O2-limited heme degradation in the rat brain. Free Radic Biol Med, 37: 1802-1812. 180440

Cudmore M; Ahmad S; Al-Ani B; Fujisawa T; Coxall H; Chudasama K; Devey LR; Wigmore SJ; Abbas A; Hewett PW; Ahmed A (2007). Negative regulation of soluble Flt-1 and soluble endoglin release by heme oxygenase-1. Circulation, 36: 2973-2979. 193991

D'Amico G; Lam F; Hagen T; Moncada S (2006). Inhibition of cellular respiration by endogenously produced carbon monoxide. J Cell Sci, 119: 2291-2298. 193992

Dani C; Giannini L; Bertini G; Pratesi S; Corsini I; Longini M; Buonocore G; Masini E; Rubaltelli FF (2007). Changes of nitric oxide, carbon monoxide and oxidative stress in term infants at birth. Free Radic Res, 41: 1358-1363. 193994

Denschlag D; Marculescu R; Unfried G; Hefler LA; Exner M; Hashemi A; Riener EK; Keck C; Tempfer CB; Wagner O (2004). The size of a microsatellite polymorphism of the haem oxygenase 1 gene is associated with idiopathic recurrent miscarriage. Mol Hum Reprod, 10: 211-4. 193894

Dewilde S; Kiger L; Burmester T; Hankeln T; Baudin-Creuza V; Aerts T; Marden MC; Caubergs R; Moens L (2001). Biochemical characterization and ligand binding properties of neuroglobin, a novel member of the globin family. J Biol Chem, 276: 38949-38955. 019318

De Luca A; Pierno S; Tricarico D; Carratu MR; Cagiano R; Cuomo V; Camerino DC (1996). Developmental changes of membrane electrical properties of rat skeletal muscle fibers produced by prenatal exposure to carbon monoxide. Environ Toxicol Pharmacol, 2: 213-221. 080911

De Salvia MA; Cagiano R; Carratu MR; Di Giovanni V; Trabace L; Cuomo V (1995). Irreversible impairment of active avoidance behavior in rats prenatally exposed to mild concentrations of carbon monoxide. Psychopharmacology, 122: 66-71. 079441

Di Giovanni V; Cagiano R; De Salvia MA; Giustino A; Lacomba C; Renna G; Cuomo V (1993). Neurobehavioral changes produced in rats by prenatal exposure to carbon monoxide. Brain Res, 616: 126-131. 013822

Dubuis E; Gautier M; Melin A; Rebocho M; Girardin C; Bonnet P; Vandier C (2002). Chronic carbon monoxide enhanced IbTx-sensitive currents in rat resistance pulmonary artery smooth muscle cells. Am J Physiol Lung Cell Mol Physiol, 283: L120-L129. 193911

Dubuis E; Gautier M; Melin A; Rebocho M; Girardin C; Bonnet P; Vandier C (2003). Chronic carbon monoxide exposure of hypoxic rats increases in vitro sensitivity of pulmonary artery smooth muscle. Can J Physiol Pharmacol, 81: 711-719. 180439

Dubuis E; Potier M; Wang R; Vandier C (2005). Continuous inhalation of carbon monoxide attenuates hypoxic pulmonary hypertension development presumably through activation of BKCa channels. Cardiovasc Res, 65: 751-761. 180435

Durante W; Johnson FK; Johnson RA (2006). Role of carbon monoxide in cardiovascular function. J Cell Mol Med, 10: 672-686. 193778

Favory R; Lancel S; Tissier S; Mathieu D; Decoster B; Neviere R (2006). Myocardial dysfunction and potential cardiac hypoxia in rats induced by carbon monoxide inhalation. Am J Respir Crit Care Med, 174: 320-325. 184462

Fechter LD; Annau Z (1977). Toxicity of mild prenatal carbon monoxide exposure. Science, 197: 680-682. 010688

Fechter LD; Annau Z (1980). Prenatal carbon monoxide exposure alters behavioral development. Neurotoxicol Teratol, 2: 7-11. 011295

Fechter LD; Karpa MD; Proctor B; Lee AG; Storm JE (1987). Disruption of neostriatal development in rats following perinatal exposure to mild, but chronic carbon monoxide. Neurotoxicol Teratol, 9: 277-281. 012259

Fechter LD; Liu Y; Pearce TA (1997). Cochlear protection from carbon monoxide exposure by free radical blockers in the guinea pig. Toxicol Appl Pharmacol, 142: 47-55. 081322

Fechter LD; Mactutus CF; Storm JE (1986). Carbon monoxide and brain development. Neurotoxicology, 7: 463-473. 012030

Fechter LD; Thakur M; Miller B; Annau Z; Srivastava U (1980). Effects of prenatal carbon monoxide exposure on cardiac development. Toxicol Appl Pharmacol, 56: 370-375. 011294

Fechter LD; Thorne PR; Nuttall AL (1987). Effects of carbon monoxide on cochlear electrophysiology and blood flow. Hear Res, 27: 37-45. 012194

Garofolo MC; Seidler FJ; Auman JT; Slotkin TA (2002). beta-Adrenergic modulation of muscarinic cholinergic receptor expression and function in developing heart. Am J Physiol Regul Integr Comp Physiol, 282: R1356-1363. 193930

Gautier M; Antier D; Bonnet P; Le Net JL; Hanton G; Eder V (2007). Continuous inhalation of carbon monoxide induces right ventricle ischemia and dysfunction in rats with hypoxic pulmonary hypertension. Am J Physiol Heart Circ Physiol, 293: H1046-52. 096471

Gaworski CL; Carmines EL; Faqi AS; Rajendran N (2004). In utero and lactation exposure of rats to 1R4F reference cigarette mainstream smoke: Effect on prenatal and postnatal development. Toxicol Sci, 79: 157-169. 193933

Ghio AJ; Stonehuerner JG; Dailey LA; Richards JH; Madden MD; Deng Z; Nguyen NB; Callaghan KD; Yang F; Piantadosi CA (2008). Carbon monoxide reversibly alters iron homeostasis and respiratory epithelial cell function. Am J Respir Cell Mol Biol, 38: 715-723. 096321

Giustino A; Cagiano R; Carratu MR; Cassano T; Tattoli M; Cuomo V (1999). Prenatal exposure to low concentrations of carbon monoxide alters habituation and non-spatial working memory in rat offspring. Brain Res, 844: 201-205. 011538

Giustino A; Cagiano R; Carratu MR; De Salvia MA; Panaro MA; Jirillo E; Cuomo V (1993). Immunological changes produced in rats by prenatal exposure to carbon monoxide. Basic Clin Pharmacol Toxicol, 73: 274-278. 013833

Giustino A; Carratu MR; Brigiani GS; De Salvia MA; Pellegrino NM; Steardo L; Jirillo E; Cuomo V (1994). Changes in the frequency of splenic immunocompetent cells in rats exposed to carbon monoxide during gestation. Immunopharmacol Immunotoxicol, 16: 281-292. 076343

Glabe A; Chung Y; Xu D; Jue T (1998). Carbon monoxide inhibition of regulatory pathways in myocardium. Am J Physiol, 274: H2143-2151. 086704

Grover TR; Rairigh RL; Zenge JP; Abman SH; Kinsella JP (2000). Inhaled carbon monoxide does not cause pulmonary vasodilation in the late-gestation fetal limb. Am J Physiol, 278: L779-L784. 010465

Hara S; Mukai T; Kurosaki K; Kuriiwa F; Endo T (2002). Modification of the striatal dopaminergic neuron system by carbon monoxide exposure in free-moving rats, as determined by in vivo brain microdialysis. Arch Toxicol, 76: 596-605. 037497

Harada T; Koi H; Kubota T; Aso T (2004). Haem oxygenase augments porcine granulosa cell apoptosis in vitro. J Endocrinol, 181: 191-205. 193920

Hendler I; Baum M; Kreiser D; Schiff E; Druzin M; Stevenson DK; Seidman DS (2004). End-tidal breath carbon monoxide measurements are lower in pregnant women with uterine contractions. J Perinatol, 24: 275-278. 193925

Hofmann OM; Brittain T (1998). Partitioning of oxygen and carbon monoxide in the three human embryonic hemoglobins. Hemoglobin, 22: 313-319. 052019

Iheagwara KN; Thom SR; Deutschman CS; Levy RJ (2007). Myocardial cytochrome oxidase activity is decreased following carbon monoxide exposure. Biochim Biophys Acta, 1772: 1112-1116. 193861

Imai T; Morita T; Shindo T; Nagai R; Yazaki Y; Kurihara H; Suematsu M; Katayama S (2001). Vascular smooth muscle cell-directed overexpression of heme oxygenase-1 elevates blood pressure through attenuation of nitric oxide-induced vasodilation in mice. Circ Res, 89: 55-62. 193864

Ischiropoulos H; Beers MF; Ohnishi ST; Fisher D; Garner SE; Thom SR (1996). Nitric oxide production and perivascular tyrosine nitration in brain after carbon monoxide poisoning in the rat. J Clin Invest, 97: 2260-2267. 079491

Johnson FK; Durante W; Peyton KJ; Johnson RA (2003). Heme oxygenase inhibitor restores arteriolar nitric oxide function in Dahl rats. Hypertension, 41: 149-155. 193868

Johnson FK; Durante W; Peyton KJ; Johnson RA (2004). Heme oxygenase-mediated endothelial dysfunction in DOCA-salt, but not in spontaneously hypertensive, rat arterioles. Am J Physiol Heart Circ Physiol, 286: 1681-1687. 193870

Johnson FK; Johnson RA (2003). Carbon monoxide promotes endothelium-dependent constriction of isolated gracilis muscle arterioles. Am J Physiol, 285: R536-R541. 053611

Johnson FK; Johnson RA; Durante W; Jackson KE; Stevenson BK; Peyton KJ (2006). Metabolic syndrome increases endogenous carbon monoxide production to promote hypertension and endothelial dysfunction in obese Zucker rats. Am J Physiol Regul Integr Comp Physiol, 290: 601-608. 193874

Katoue MG; Khan I; Oriowo MA (2005). Increased expression and activity of heme oxygenase-2 in pregnant rat aorta is not involved in attenuated vasopressin-induced contraction. Naunyn Schmiedebergs Arch Pharmacol, 372: 220-7. 193896

Katoue MG; Khan I; Oriowo MA (2006). Pregnancy-induced modulation of calcium mobilization and down-regulation of Rho-kinase expression contribute to attenuated vassopressin-induced contraction of the rat aorta. Vascul Pharmacol, 44: 170-176. 193954

Khan AA; Wang Y; Sun Y; Mao XO; Xie L; Miles E; Graboski J; Chen S; Ellerby LM; Jin K; Greenberg DA (2006). Neuroglobin-overexpressing transgenic mice are resistant to cerebral and myocardial ischemia. PNAS, 103: 17944-17948. 193955

Kim HP; Wang X; Nakao A; Kim SI; Murase N; Choi ME; Ryter SW; Choi AM (2005). Caveolin-1 expression by means of p38beta mitogen-activated protein kinase mediates the antiproliferative effect of carbon monoxide. PNAS, 102: 11319-11324. 193959

Kim HS; Loughran PA; Rao J; Billar TR; Zuckerbraun BS (2008). Carbon monoxide activates NF-kappaB via ROS generation and Akt pathways to protect against cell death of hepatocytes. Am J Physiol Gastrointest Liver Physiol, 295: G146-G152. 193961

Kinobe R; Vlahakis J; Soong J; Szarek W; Brien J; Longo L; Nakatsu K (2006). Heme oxygenase activity in fetal and adult sheep is not altered by acclimatization to high altitude hypoxia. Can J Physiol Pharmacol, 84: 893 - 901. 188447

Knuckles TL; Lund AK; Lucas SN; Campen MJ (2008). Diesel exhaust exposure enhances venoconstriction via uncoupling of eNOS. Toxicol Appl Pharmacol, 230: 346-351. 191987

Korres S; Riga M; Balatsouras D; Papadakis C; Kanellos P; Ferekidis E (2007). Influence of smoking on developing cochlea: Does smoking during pregnancy affect the amplitudes of transient evoked otoacoustic emissions in newborns? Int J Pediatr Otorhinolaryngol, 71: 781-786. 190908

Kreiser D; Baum M; Seidman DS; Fanaroff A; Shah D; Hendler I; Stevenson DK; Schiff E; Druzin ML (2004). End tidal carbon monoxide levels are lower in women with gestational hypertension and pre-eclampsia. J Perinatol, 24: 213-217. 193948

Lash GE; McLaughlin BE; MacDonald-Goodfellow SK; Smith GN; Brien JF; Marks GS; Nakatsu K; Graham CH (2003). Relationship between tissue damage and heme oxygenase expression in chorionic villi of term human placenta. Am J Physiol Heart Circ Physiol, 284: H160-H167. 193849

Li X; Zhang C; Wang S; Ji Y; Wang H; Zhao L; Xu D (2008). Maternally administered lipopolysaccharide (LPS) upregulates the expression of heme oxygenase-1 in fetal liver: The role of reactive oxygen species. Toxicol Lett, 176: 169-177. 187003

Liu Y; Fechter LD (1995). MK-801 protects against carbon monoxide-induced hearing loss. Toxicol Appl Pharmacol, 132: 196-202. 076524

Loennechen JP; Beisvag V; Arbo I; Waldum HL; Sandvik AK; Knardahl S; Ellingsen O (1999). Chronic carbon monoxide exposure in vivo induces myocardial endothelin-1 expression and hypertrophy in rat. Pharmacol Toxicol, 85: 192-197. 011549

Longo M; Jain V; Vedernikov YP; Saade GR; Goodrum L; Facchinetti F; Garfield RE (1999). Effect of nitric oxide and carbon monoxide on uterine contractility during human and rat pregnancy. Am J Obstet Gynecol, 181: 981-988. 011548

Lopez I; Acuna D; Webber DS; Korsak RA; Edmond J (2003). Mild carbon monoxide exposure diminishes selectively the integrity of the cochlea of the developing rat. J Neurosci Res, 74: 666-75. 193901

Lopez IA; Acuna D; Beltran-Parrazal L; Espinosa-Jeffrey A; Edmond J (2008). Oxidative stress and the deleterious consequences to the rat cochlea after prenatal chronic mild exposure to carbon monoxide in air. Neuroscience, 151: 854-867. 097343

Lund AK; Knuckles TL; Obot Akata C; Shohet R; McDonald JD; Gigliotti A; Seagrave JC; Campen MJ (2007). Gasoline exhaust emissions induce vascular remodeling pathways involved in atherosclerosis. Toxicol Sci, 95: 485-94. 125741

Lund AK; Lucero J; Lucas S; Madden MC; McDonald JD; Seagrave JC; Knuckles TL; Campen MJ (2009). Vehicular emissions induce vascular MMP-9 expression and activity associated with endothelin-1 mediated pathways. Arterioscler Thromb Vasc Biol, 29: 511-517. 180257

Lyall F; Barber A; Myatt L; Bulmer JN; Robson SC (2000). Hemeoxygenase expression in human placenta and placental bed implies a role in regulation of trophoblast invasion and placental function. FASEB J, 14: 208-19. 193902

Lyall F; Myatt L (2002). The role of the placenta in pre-eclampsia -- a workshop report. Placenta, 23: S142-145. 193971

Mactutus CF; Fechter LD (1984). Prenatal exposure to carbon monoxide: learning and memory deficits. Science, 223: 409-411. 011355

McGregor HP; Westcott K; Walker DW (1998). The effect of prenatal exposure to carbon monoxide on breathing and growth of the newborn guinea pig. Pediatr Res, 43: 126-131. 085342

McLaughlin BE; Hutchinson JM; Graham CH; Smith GN; Marks GS; Nakatsu K; Brien JF (2000). Heme oxygenase activity in term human placenta. Placenta, 21: 870-873. 015815

McLaughlin BE; Lash GE; Graham CH; Smith GN; Vreman HJ; Stevenson DK; Marks GS; Nakatsu K; Brien JF (2001). Endogenous carbon monoxide formation by chorionic villi of term human placenta. Placenta, 22: 886-888. 193823

McLaughlin BE; Lash GE; Smith GN; Marks GS; Nakatsu K; Graham CH; Brien JF (2003). Heme oxygenase expression in selected regions of term human placenta. Exp Biol Med, 228: 564-567. 193827

McLean M; Bowman M; Clifton V; Smith R; Grossman AB (2000). Expression of the heme oxygenase - carbon monoxide signalling system in human placenta. J Clin Endocrinol Metab, 85: 2345-2349. 016269

Melin A; Bonnet P; Eder V; Antier D; Obert P; Fauchier L (2005). Direct implication of carbon monoxide in the development of heart failure in rats with cardiac hypertrophy subjected to air pollution. Cardiovasc Toxicol, 5: 311-320. 193833

Melin A; Obert P; Rebocho M; Bonnet P (2002). Cardiac morphology and function following long-term exposure to carbon monoxide at high altitude in rats. J Toxicol Environ Health A Curr Iss, 65: 1981-1998. 037502

Mereu G; Cammalleri M; Fà M; Francesconi W; Saba P; Tattoli M; Trabace L; Vaccari A; Cuomo V (2000). Prenatal exposure to a low concentration of carbon monoxide disrupts hippocampal long-term potentiation in rat offspring. J Pharmacol Exp Ther, 294: 728-734. 193838

Middendorff R; Kumm M; Davidoff MS; Holstein AF; Muller D (2000). Generation of cyclic guanosine monophosphate by heme oxygenases in the human testis--a regulatory role for carbon monoxide in Sertoli cells? Biol Reprod, 63: 651-657. 015842

Montagnani M; Serio M; Potenza MA; Mansi G; De Salvia MA; Cagiano R; Cuomo V; Mitolo-Chieppa D (1996). Prenatal exposure to carbon monoxide and vascular responsiveness of rat resistance vessels. Life Sci, 59: 1553-1561. 080902

Naik JS; Walker BR (2003). Heme oxygenase-mediated vasodilation involves vascular smooth muscle cell hyperpolarization. Am J Physiol Heart Circ Physiol, 285: 220-228. 193852

Ndisang JF; Tabien HE; Wang R (2004). Carbon monoxide and hypertension. Am J Hypertens, 22: 1057-1074. 180425

Neggers YH; Singh J (2006). Zinc supplementation to protein-deficient diet in CO-exposed mice decreased fetal mortality and malformation. Biol Trace Elem Res, 114: 269-279. 193964

Newby D; Cousins F; Myatt L; Lyall F (2005). Heme oxygenase expression in cultured human trophoblast cells during in vitro differentiation: Effects of hypoxia. Placenta, 26: 201-209. 193966

Odrcich MJ; Graham CH; Kimura KA; McLaughlin BE; Marks GS; Nakatsu K; Brien JF (1998). Heme oxygenase and nitric oxide synthase in the placenta of the guinea-pig during gestation. Placenta, 19: 509-516. 193958

Ozawa N; Goda N; Makino N; Yamaguchi T; Yoshimura Y; Suematsu M (2002). Leydig cell-derived heme oxygenase-1 regulates apoptosis of premeiotic germ cells in response to stress. J Clin Invest, 109: 457-467. 193841

Patel AP; Moody JA; Handy RD; Sneyd JR (2003). Carbon monoxide exposure in rat heart: glutathione depletion is prevented by antioxidants. Biochem Biophys Res Commun, 302: 392-396. 043155

Penney DG; Baylerian MS; Thill JE; Fanning CM; Yedavally S (1982). Postnatal carbon monoxide exposure: immediate and lasting effects in the rat. Am J Physiol, 243: H328-H339. 011387

Penney DG; Baylerian MS; Thill JE; Yedavally S; Fanning CM (1983). Cardiac response of the fetal rat to carbon monoxide exposure. Am J Physiol, 244: H289-H297. 011385

Piantadosi CA (2002). Biological chemistry of carbon monoxide. Antioxid Redox Signal, 4: 259-270. 037463

Piantadosi CA (2008). Carbon monoxide, reactive oxygen signaling, and oxidative stress. Free Radic Biol Med, 45: 562-569. 180423

Piantadosi CA; Carraway MS; Suliman HB (2006). Carbon monoxide, oxidative stress, and mitochondrial permeability pore transition. Free Radic Biol Med, 40: 1332-1339. 180424

Prigge E; Hochrainer D (1977). Effects of carbon monoxide inhalation on erythropoiesis and cardiac hypertrophy in fetal rats. Toxicol Appl Pharmacol, 42: 225-228. 012326

Raub JA; Benignus VA (2002). Carbon monoxide and the nervous system. Neurosci Biobehav Rev, 26: 925-940. 041616

Richardson RS; Noyszewski EA; Saltin B; Gonzalez-Alonso J (2002). Effect of mild carboxy-hemoglobin on exercising skeletal muscle: Intravascular and intracellular evidence. Am J Physiol, 283: R1131-R1139. 037513

Ryter SW; Alam J; Choi AMK (2006). Heme oxygenase-1/carbon monoxide: From basic science to therapeutic applications. Physiol Rev, 86: 583-650. 193765

Sartiani L; Cerbai E; Lonardo G; DePaoli P; Tattoli M; Cagiano R; Carratu M; Cuomo V; Mugelli A (2004). Prenatal exposure to carbon monoxide affects postnatal cellular electrophysiological maturation of the rat heart: a potential substrate for arrhythmogenesis in infancy. Circulation, 109-: 419-423. 190898

Schwetz BA; Smith FA; Leong BKJ; Staples RE (1979). Teratogenic potential of inhaled carbon monoxide in mice and rabbits. Teratology, 19: 385-391. 011855

Shaoqing Y; Ruxin Z; Yinjian C; Jianqiu C; Chunsheng Z; Jiangfeng T; Genhong L (2008). Possible contribution of endogenous carbon monoxide to the development of allergic rhinitis in guinea pigs. J Inflamm, 5: 23. 192384

Singh J (1986). Early behavioral alterations in mice following prenatal carbon monoxide exposure. Neurotoxicology, 7: 475-481. 012827

Singh J (2003). Gastroschisis is caused by the combination of carbon monoxide and protein-zinc deficiencies in mice. Birth Defects Res B Dev Reprod Toxicol, 68: 355-362. 053624

Singh J (2006). Interaction of maternal protein and carbon monoxide on pup mortality in mice: implications for global infant mortality. Birth Defects Res B Dev Reprod Toxicol, 77: 216-26. 190512

Singh J; Aggison L Jr; Moore-Cheatum L (1993). Teratogenicity and developmental toxicity of carbon monoxide in protein-deficient mice. Teratology, 48: 149-159. 013892

Singh J; Scott LH (1984). Threshold for carbon monoxide induced fetotoxicity. Teratology, 30: 253-257. 011409

Singh J; Smith CB; Moore-Cheatum L (1992). Additivity of protein deficiency and carbon monoxide on placental carboxyhemoglobin in mice. Am J Obstet Gynecol, 167: 843-846. 013759

Sitdikova GF; Islamov RR; Mukhamedyarov MA; Permyakova VV; Zefirov AL; Palotas A (2007). Modulation of neurotransmitter release by carbon monoxide at the frog neuro-muscular junction. Curr Drug Metab, 8: 177-184. 180417

Song R; Mahidhara RS; Liu F; Ning W; Otterbein LE; Choi AMK (2002). Carbon monoxide inhibits human airway smooth muscle cell proliferation via mitogen-activated protein kinase pathway. Am J Respir Cell Mol Biol, 27: 603-610. 037531

Sorhaug S; Steinshamn S; Nilsen OG; Waldum HL (2006). Chronic inhalation of carbon monoxide: Effects on the respiratory and cardiovascular system at doses corresponding to tobacco smoking. Toxicology, 228: 280-290. 180414

Stevens CF; Wang Y (1993). Reversal of long-term potentiation by inhibitors of haem oxygenase. Nature, 364: 147-149. 188458

Stockard-Sullivan JE; Korsak RA; Webber DS; Edmond J (2003). Mild carbon monoxide exposure and auditory function in the developing rat. J Neurosci Res, 74: 644-654. 190947

Storm JE; Fechter LD (1985). Alteration in the postnatal ontogeny of cerebellar norepinephrine content following chronic prenatal carbon monoxide. J Neurochem, 45: 965-969. 011653

Storm JE; Fechter LD (1985). Prenatal carbon monoxide exposure differentially affects postnatal weight and monoamine concentration of rat brain regions. Toxicol Appl Pharmacol, 81: 139-146. 011652

Storm JE; Valdes JJ; Fechter LD (1986). Postnatal alterations in cerebellar GABA content, GABA uptake and morphology following exposure to carbon monoxide early in development. Dev Neurosci, 8: 251-261. 012136

Styka PE; Penney DG (1978). Regression of carbon monoxide-induced cardiomegaly. Am J Physiol, 235: H516-H522. 011166

Suliman HB; Carraway MS; Tatro LG; Piantadosi CA (2007). A new activating role for CO in cardiac mitochondrial biogenesis. J Cell Sci, 120: 299-308. 193768

Sun Y; Jin K; Mao XO; Zhu Y; Greenberg DA (2001). Neuroglobin is up-regulated by and protects neurons from hypoxic-ischemic injury. PNAS, 98: 15,306-15,311. 026022

Tattoli M; Carratu MR; Cassano T; Cortese I; Di Giovanni V; Elia G; Renna G; Cagiano R (1999). Effects of early postnatal exposure to low concentrations of carbon monoxide on cognitive functions in rats. Pharmacol Res, 40: 271-274. 011557

Telfer JF; Itoh H; Thomson AJ; Norman JE; Nakao K; Campa JS; Poston L; Tribe RM; Magness RR (2001). Activity and expression of soluble and particulate guanylate cyclases in myometrium from nonpregnant and pregnant women: down-regulation of soluble guanylate cyclase at term. J Clin Endocrinol Metab, 86: 5934-5943. 193769

Teran FJ; Johnson RA; Stevenson BK; Peyton KJ; Jackson KE; Appleton SD; Durante W; Johnson FK (2005). Heme oxygenase-derived carbon monoxide promotes arteriolar endothelial dysfunction and contributes to salt-induced hypertension in Dahl salt-sensitive rats. Am J Physiol Regul Integr Comp Physiol, 288: 615-622. 193770

Thom SR; Bhopale VM; Han ST; Clark JM; Hardy KR (2006). Intravascular neutrophil activation due to carbon monoxide poisoning. Am J Respir Crit Care Med, 174: 1239-1248. 098418

Thom SR; Fisher D; Manevich Y (2001). Roles for platelet-activating factor and NO-derived oxidants causing neutrophil adherence after CO poisoning. Am J Physiol Heart Circ Physiol, 281: H923-H930. 193779

Thom SR; Fisher D; Xu YA; Garner S; Ischiropoulos H (1999). Role of nitric oxide-derived oxidants in vascular injury from carbon monoxide in the rat. Am J Physiol, 276: H984-H992. 016753

Thom SR; Fisher D; Xu YA; Notarfrancesco K; Ischiropoulos H (2000). Adaptive responses and apoptosis in endothelial cells exposed to carbon monoxide. PNAS, 97: 1305-1310. 011574

Thom SR; Ischiropoulos H (1997). Mechanism of oxidative stress from low levels of carbon monoxide. Health Effects Institute. Boston, MA. 085644

Thom SR; Ohnishi ST; Fisher D; Xu YA; Ischiropoulos H (1999). Pulmonary vascular stress from carbon monoxide. Toxicol Appl Pharmacol, 154: 12-19. 016757

Thom SR; Ohnishi ST; Ischiropoulos H (1994). Nitric oxide released by platelets inhibits neutrophil B2 integrin function following acute carbon monoxide poisoning. Toxicol Appl Pharmacol, 128: 105-110. 076459

Thom SR; Xu YA; Ischiropoulos H (1997). Vascular endothelial cells generate peroxynitrite in response to carbon monoxide exposure. Chem Res Toxicol, 10: 1023-1031. 084337

Thorup C; Jones CL; Gross SS; Moore LC; Goligorsky MS (1999). Carbon monoxide induces vasodilation and nitric oxide release but suppresses endothelial NOS. Am J Physiol, 277: F882-F889. 193782

Tolcos M; Mallard C; McGregor H; Walker D; Rees S (2000). Exposure to prenatal carbon monoxide and postnatal hyperthermia: short and long-term effects on neurochemicals and neuroglia in the developing brain. Exp Neurol, 162: 235-246. 010468

Tolcos M; McGregor H; Walker D; Rees S (2000). Chronic prenatal exposure to carbon monoxide results in a reduction in tyrosine hydroxylase-immunoreactivity and an increase in choline acetyltransferase-immunoreactivity in the fetal medulla: implications for sudden infant death syndrome. J Neuropathol Exp Neurol, 59: 218-228. 015997

Toyoda M; Saito H; Matsuki N (1996). Nitric oxide but not carbon monoxide is involved in spatial learning of mice. J Pharmacol Sci, 71: 205-211. 079945

Tschugguel W; Stonek F; Zhegu Z; Dietrich W; Schneeberger C; Stimpfl T; Waldhoer T; Vycudilik W; Huber JC (2001). Estrogen increases endothelial carbon monoxide, heme oxygenase 2, and carbon monoxide-derived cGMP by a receptor-mediated system. J Clin Endocrinol Metab, 86: 3833-3839. 193785

Vallone B; Nienhaus K; Matthes A; Brunori M; Nienhaus GU (2004). The structure of carbonmonoxy neuroglobin reveals a heme-sliding mechanism for control of ligand affinity. PNAS, 101: 17351-17356. 193993

Villamor E; Perez-Vizcaino F; Cogolludo AL; Conde-Oviedo J; Zaragoza-Arnaez F; Lopez-Lopez JG; Tamargo J (2000). Relaxant effects of carbon monoxide compared with nitric oxide in pulmonary and systemic vessels of newborn piglets. Pediatr Res, 48: 546-553. 015838

Vreman HJ; Wong RJ; Kadotani T; Stevenson DK (2005). Determination of carbon monoxide (CO) in rodent tissue: effect of heme administration and environmental CO exposure. Anal Biochem, 341: 280-289. 193786

Vreman HJ; Wong RJ; Kim EC; Nabseth DC; Marks GS; Stevenson DK (2000). Haem oxygenase activity in human umbilical cord and rat vascular tissues. Placenta, 21: 337-44. 096915

Weaver LK; Valentine KJ; Hopkins RO (2007). Carbon monoxide poisoning: risk factors for cognitive sequelae and the role of hyperbaric oxygen. Am J Respir Crit Care Med, 176: 491 - 497. 193939

Webber D; Lopez I; Korsak R; Hirota S; Acuna D; Edmond J (2005). Limiting iron availability confers neuroprotection from chronic mild carbon monoxide exposure in the developing auditory system of the rat. J Neurosci Res, 80: 620-633. 190514

Webber DS; Korsak RA; Sininger LK; Sampogna SL; Edmond J (2003). Mild carbon monoxide exposure impairs the developing auditory system of the rat. J Neurosci Res, 74: 655-665. 190515

Wellenius GA; Batalha JRF; Diaz EA; Lawrence J; Coull BA; Katz T; Verrier RL; Godleski JJ (2004). Cardiac effects of carbon monoxide and ambient particles in a rat model of myocardial infarction. Toxicol Sci, 80: 367-376. 087874

Wellenius GA; Coull BA; Batalha JRF; Diaz EA; Lawrence J; Godleski JJ (2006). Effects of ambient particles and carbon monoxide on supraventricular arrhythmias in a rat model of myocardial infarction. Inhal Toxicol, 18: 1077-1082. 156152

Yoshiki N; Kubota T; Aso T (2001). Identification of heme oxygenase in human endometrium. J Clin Endocrinol Metab, 86: 5033-5038. 193790

Zamudio S; Palmer SK; Dahms TE; Berman JC; Young DA; Moore LG (1995). Alterations in uteroplacental blood flow precede hypertension in preeclampsia at high altitude. J Appl Physiol, 79: 15-22. 193908

Zenclussen ML; Anegon I; Bertoja AZ; Chauveau C; Vogt K; Gerlof K; Sollwedel A; Volk HD; Ritter T; Zenclussen AC (2006). Over-expression of heme oxygenase-1 by adenoviral gene transfer improves pregnancy outcome in a murine model of abortion. Am J Reprod Immunol, 69: 35-52. 193873

Zhang C; Li XY; Zhao L; Wang H; Xu DX (2007). Lipopolysaccharide (LPS) up-regulates the expression of haem oxygenase-1 in mouse placenta. Placenta, 28: 951-957. 193879

Zhang X; Shan P; Alam J; Fu XY; Lee PJ (2005). Carbon monoxide differentially modulates STAT1 and STAT3 and inhibits apoptosis via a phosphatidylinositol 3-kinase/akt and p38 kinase-dependent STAT3 pathway during anoxia-reoxygenation injury. J Biol Chem, 280: 8714-8721. 184460

Zhao H; Wong RJ; Doyle TC; Nayak N; Vreman HJ; Contag CH; Stevenson DK (2008). Regulation of maternal and fetal hemodynamics by heme oxygenase in mice. Biol Reprod, 78: 744-751. 193883

Zhuo M; Small SA; Kandel ER; Hawkins RD (1993). Nitric oxide and carbon monoxide produce activity-dependent long-term synaptic enhancement in hippocampus. Science, 260: 1946-1950. 013905

Zuckerbraun BS; Chin BY; Bilban M; d'Avila JC; Rao J; Billiar TR; Otterbein LE (2007). Carbon monoxide signals via inhibition of cytochrome c oxidase and generation of mitochondrial reactive oxygen species. FASEB J, 21: 1099-1106. 193884